rural, a large major resort.

Clearly, when you probe on the phone, there must be some general characteristics of these resorts that you are asking about, be it size, how long they have been in existence, are they in the middle of a forest, something like that. So I just would wonder if that is something that might be helpful and would ask my CDC colleagues if that is something that is practical or doable.

DR. PARISE: I think that we could work on that somewhat. Our main criteria there is that some of these resorts are really cities. They have built a lot of hotels in them. But they really are urban areas. Whereas, others are resorts that have been pretty much plunked down in a rural area.

The problem there is that when a resort is plunked down in a rural area, we consider that the rural resort. If it has been there for years and becomes very urbanized, until the map changes, we don't know. We play it conservative and we defer. Maybe if we went and inspected that resort and saw it, we wouldn't defer. But, again, we don't have any data and so we do the best we can.

But we probably could come up with large urbanized resorts that have come in urban areas.

DR. NELSON: The urban versus rural only applies to Latin America, not to Africa.

DR. PARISE: Largely. There are a few African cities that don't have transmission, but there are very few. And Southeast Asia. Southeast Asia and the Americas; yes.

DR. NELSON: So Africa is pretty easy. SubSaharan Africa is a problem.

DR. KOERPER: I am just curious how long this process takes. Does the prospective donor sit and wait in Seattle or San Francisco while the medical director calls the CDC?

DR. PARISE: That you would have to ask the blood banks.

DR. KOERPER: Or do they ever walk out the door and never come back again.

DR. HOLLINGER: The answer is yes from several of the blood-banking people here.

DR. PARISE: We place it as a priority. If we have chemoprophylaxis calls and the person there isn't right in her office, we will take a message. For cases of malaria and for blood-bank calls, if the person is not right there, they will page somebody. So we do, on our end, try to do them as fast as possible and interrupt what we are doing to go look at the atlas. But I am sure there can be many delays in the process.

DR. HOLLINGER: On the other hand, what I am hearing here, if this is an issue, here, in this computer

world, not to have this computerized--the same questions you are going to be asked, you obviously have answer for right now. To put that on a website that is computerized and could be changed in an instant would allow them, and the blood bank, to then pull that information or put that issue in there and receive a piece of information back. I can't understand that.

DR. PARISE: The Yellow Book is on the Web.

DR. HOLLINGER: And it has those sites on it.

DR. PARISE: Right, but at a mobile site, you don't even have an atlas so the Web isn't going to help you at a mobile site. Many of the calls we get are at mobile sites that don't have an atlas in front of them and they can't look. So they are relying on us.

We are amenable to dialogue on what else we could put on the Web besides the Yellow Book. That is all we use.

DR. KOERPER: Can't you put the atlas on the Web?

DR. PARISE: We didn't publish that, but I guess we can look into that.

DR. KOERPER: Color code the atlas on the Web.

DR. PARISE: We can look into that.

DR. HEINTZELMAN: Since we have this opportunity, we are talking about dusk-to-dawn. If that is implemented, or at least one scenario for implementation would be anywhere in the world. I want to make sure that people

aren't thinking just about Mexico or Caribbean. We are talking about global when we talk about dusk-to-dawn.

That is the sense of this. With the emphasis on Mexican resorts, because of the number of travelers, that's fine. But a change in policy would be all over Africa, all over Asia, any of the really, truly highly endemic areas.

Monica did a great job of presenting the malaria number of cases that have been reported. When you think about that, you may have noticed that there is an increase in '95 which is the last report. There is a 15 percent increase, according to the CDC's reports. That is imported malaria. It is important to consider the number of malaria cases coming into the United States and then to also think about transfusion-transmitted malaria because the donor base comes from the base population which includes the imported cases.

The fact that transfusion-transmitted malaria is running at a very low percentage--it is about 1 in 4 million donations--reflects a certain trend in screening and distribution and disease infectivity. But when you look at the amount of malaria that is coming into the country, you see that that is really a fairly significant number, very different from what you are seeing in the transfusion cases.

If you open up the door, I believe, to a broad proposal of allowing donors that have traveled anywhere in

the world, to the best of their recollection, during broad daylight hours, to donate, we may find that there is a potential for a change in that distribution.

DR. HOLLINGER: Do you view the dusk-to-dawn question as compared to what is currently being done now as something that will keep more donors eligible or lose more donors, at least for a period of time?

DR. HEINTZELMAN: We know where we are right now. While they may get approximately a dozen calls a day at CDC, if you look at 14 million units of blood collected in the United States over a year, roughly that is 40,000 units a day. I am not sure that everybody calls CDC when they have a gray area and are unsure about somebody's travel.

I think that the conservative issue is usually they just defer these people. I believe that if we go to a dusk-to-dawn, we may not decrease the donor base. We may increase the donor base. Increasing that donor base would be from within the population where imported malaria is evident. In that group, the trends have been roughly consistent but within the Americas there was 100 percent increase in 1995 for imported malaria.

DR. OHENE-FREMPONG: Just a couple of things. One, the dusk-to-dawn question, I can't see that applying to Africa, for instance. I can't see anybody traveling on a day trip to any part of Africa and being out to a non-

endemic area before nighttime.

The second question, though, just for clarification, the transmission through platelet transfusion, is that believed to be from red-cell contamination of the platelet pool and not from plasmodium in the platelets?

DR. PARISE: That's correct. It is felt to be from red-cell contamination in the platelet pool. The question in Africa--you're right. There might be a few selected areas such as taking a day trip out of Nairobi and Kenya or a day trip out of one of the cities in South Africa to a game park and coming back. But it would be unusual.

The other thing is, when we look at the vectors, the African vectors tend to bite very late. So if you say there was a fuzzy area, it is probably going to hit you more in the Americas when it is an early-biting vector in general than these Anopheles gambia which bites at 2:00 a.m.

DR. EPSTEIN: First, to clarify the issue of impacts, I think we are hearing two contradictory things and I want to try to sort that out. Current policy does not provide an exemption from deferral for daylight exposure or for being at a resort. So if the current guidance were to be followed, the donors would be deferred.

What I am hearing several blood-bank organizations say is that they have been querying the CDC and they have

been advised on many occasions that they can exempt daylight exposure and that they can exempt travel to specific resorts. I don't have a problem with that where it has been based on good science, but that is not the current FDA recommendation.

The current FDA recommendation would be to defer based on those exposures because we do not make those distinctions in our guidance. So we see the proposal to the advisory committee as a relaxation of the stringency of deferral.

The second point I would like to make is that that relaxation either does or does not add risk whether you believe that the history you get about the nature of the exposure is accurate. There is a distinction to be made about the accuracy of the history, and I would like Dr. Parise to comment on this.

In the case of chemoprophylaxis, you are dealing with the traveler just at the time of travel. You are not asking them a year later or three years later whether they ought to have been prophylaxed. They are telling you their travel plan and you are advising them based on current information.

The problem that we have in the donor selection process is that you may be asking that donor that question as much as three years after the travel where it would

affect their deferral. So the FDA's concern is how accurate is that information going to be. You are potentially asking a donor who was in a malarious area whether they were exposed only during hours of bright daylight and you are, in essence, asking them did they go jogging shortly before or after dawn? Did the cruise boat dock before dawn? Do they remember whether they stayed over that night?

You are asking that as much as three years later. That is part of what is concerning the FDA. So, you see, we are really not begging the question of the underlying science. If Drs. Ruebush and Parise tell me that mosquitos don't bite, well, I believe that. But the question is the accuracy of the histories.

So that is why I have suggested that a way out is we could accept the scientific principle but put the burden of proof on the medical director to basically decide how confident they can be in that history.

DR. HOLLINGER: But, Jay, just to clarify something. Although the question is asked for three years out, in essence, for travelers from the U.S., it is really one year that you are really looking at the history and that is the only thing that they are going to have to remember.

If I traveled three years ago, that would not exclude me.

DR. EPSTEIN: You are correct. I am being

technically precise because we have the semi-immune traveler where we are changing the policy to recognize that some of the delayed cases of malaria have been in semi-immune individuals who have, then, briefly traveled. So yes, the majority of travelers would only have an applicable history of one year.

But, even so, w donor you recollect nine months later was it broad daylight. Did you take that sunset walk?

DR. NELSON: Given the nature of the risk and the geographic distribution and real risk of malaria of a Caribbean resort versus Africa or some places in Asia and the much greater likelihood of falciparum, a potentially fatal infection, being acquired from Africa, could we limit this dusk-to-dawn recommendation or could the vote be on the Americas rather than the world.

DR. HOLLINGER: Or anything except Africa?

DR. NELSON: Right. Well, there are certain places in India that I think have a high risk, and certainly New Guinea. I would say limit it to the Americas.

DR. HOLLINGER: Dr. Ruebush or Dr. Parise, can you tell me a little bit about--since, we are talking about dusk-to-dawn, where do the anopheles rest during the daytime? The reason for asking that, in my previous life, I was an arbovirologist so I am very well aware of mosquitos and the issues.

I remember when we were looking for a site of Culex quinquefasciatis in Corpus Christi and couldn't determine why these cases were occurring until we went down in the storm sewers and found the mosquitos all resting down in the storm sewers during the day. Of course, anyone working in the storm sewers clearly ran the risk of being bitten by a female mosquito.

So the issue has to do with where they are resting and some of their feeding habits and so on. Could you enlighten us a little bit about that.

DR. RUEBUSH: During the day, most anopheles mosquitos rest inside houses, inside some sort of buildings, in relatively humid, dark, quiet, undisturbed environments. Some may rest outdoors under bridges or things like that, perhaps under leaves of bushes where it is shaded and they are not disturbed.

But most of them, at least the ones that the mosquito collectors find, are generally within buildings.

DR. HOLLINGER: Thank you.

DR. FITZPATRICK: I have two questions and, for your discretion, I have what might be construed as a statement. First, for CDC, how often is the Yellow Book updated and how do you update the world that the Yellow Book has been updated. The other one, you mentioned a river cruise in a shaded area. So are we going to have to ask our

donors if they left the beach and took a walk in the tropical forest in the dark shade?

DR. PARISE: In answer to your first question, the Yellow Book is updated every one to two years. Previously, it had been every year. The last update was two years ago and I believe the Division of Quarantine, who is responsible for the Yellow Book at CDC, is planning to do it on an every-two-year basis. The changes that we make in the Yellow Book, we put on the Web. They are based on the WHO.

The second question about the mosquitos in the forest, that's true. It is possible that, in a dark forest, that person could be more at risk if they went there during the day than somebody who went to somewhere that is not shaded. I actually think Jay's idea to--because this will increase donor availability. I don't have an idea of how many donors it is going to be because we don't measure that here, but I think that allowing for this exposure criteria, it is the blood bank director's discretion to prove that that really was a day trip is a very reasonable cause.

I agree that the recall bias that is present in what we do with travelers versus blood donors who would mainly fall into your category is a problem. But there are some people that we talk to that are just very clear about the timing of their trip.

DR. HOLLINGER: You said you had a statement?

DR. FITZPATRICK: Whenever you--

DR. HOLLINGER: Oh; okay. Why don't you go ahead and answer this.

DR. HEINTZELMAN: I will be very quick. Everyone is interested in having clear, concise guidance. I had posed this to our field investigators, one of the biologics experts, who does blood banks and asked her how she felt about this. And it is intriguing to note that she reflects the same concerns that everyone else has here. They want clear, implementable guidance that can be documented so that they can inspect for compliance with the regulations and do so in a fashion that doesn't lead to confusion.

It is the same wish that the blood banks have and I am sure that it is the same that the government agencies have. Trying to get to that point so it can be inspected and verified is a bit of a challenge.

DR. KHABBAZ: I want to get back to a suggestion or the question from Dr. Nelson, and that question is to the FDA. Is it possible to make a distinction between the Americas and either Asia and Africa or Africa with regard to the dusk-to-dawn question?

DR. NELSON: I think there is really a risk, quantitative--qualitative, almost--difference in the risk between travel to Africa and Asia. I have seen students, et cetera, that have gone to visit their home town in Africa

and have come back with malaria. It is a real risk and the risk is falciparum.

I wouldn't feel comfortable taking blood from a donor who said that he can't remember when he got back to Nairobi from the game park. To me, I think that that is a different kind of a risk than a cruise ship.

DR. OHENE-FREMPONG: I just want to say, as a frequent visitor to Africa, that the ultimate solution to this problem is to eradicate malaria.

DR. PARISE: I would just speak that we would not favor a distinction between the Americas and Africa for a few reasons. One is, as I mentioned, the vector biology doesn't really support the need although there is much more malaria transmission in Africa. The vector doesn't support it as well as the fact that--the bottom line, here, is when you look at our data, the problem is really not in the cases that are coming from these travelers.

It has mainly been in the immigrants or the people that go to visit. There hasn't been a case due to one of these U.S. travelers who would mainly be the people doing these day trips for the last over fifteen years.

So my impression is that it will add a level of complexity that we are already trying to simplify things and make clear.

DR. HEINTZELMAN: Are you referring to

transfusion-transmitted malaria or imported malaria, when you say there hasn't been a case in the last fifteen years.

DR. PARISE: Transfusion.

DR. HEINTZELMAN: Not all of the reported malaria cases.

DR. PARISE: In a person who was one--I mean, it is typically going to be your U.S. resident who lives in the United States that goes somewhere and takes one of these day trips. That is mainly the population that we are talking about that is going to be affected by the dusk-to-dawn. There hasn't been a case in one of those people for many years.

DR. MACIK: I guess is my confusion a little bit. What are the numbers we are talking about? What real impact is this on people who donate if you defer--outside the military, say, if you have traveled outside the states in a year and if you have, then it falls to the discretion of the blood bank director to apply certain rules to those people.

It seems like we are spending a lot of time talking about stuff that--what is really the magnitude of people that this is involving. I know that I have donated blood recently and I know that it is quite irritating to sit through all of these questions and go on and do these things that keep getting asked to you.

It seems like there should be some bright points

that fairly easily break out. So what is really the magnitude. And then the second point would be isn't there a way to educate the public beforehand about some of this because what we are talking about is asking the public to remember, a year later, did you go out for this or that.

Shouldn't there be some kind of thing that if you know that you are going to Africa, if you are going even to South America, you get all this information you can possibly get about where to go and what to do. One little stand should say, "Just remember for the next year, when you get back, you need to know whether you went to this place or that place and you may not be able to donate blood," so that those people have some education of the public beforehand and not just when they are sitting down at the time of answering out a blood-donation form.

DR. VERTER: I wonder if you could just clarify for me the review you made. You said there were 91 cases that were reviewed from '63 to '95 or '98 and you had data on 58. Of the 58, if I recall correctly, 36, if the current guidelines would have been followed, would have been deferred and the other 22, the current guidelines were irrelevant because the period of exposure was more than three years.

So, using the current system, if I can use the phrase, we had GMP, there would have been no change. This

addition or modification would not have changed anything for the cases that you could follow, the 58 of the 19.

DR. PARISE: I didn't quite understand. I'm sorry.

DR. VERTER: I am just asking if I am correct in what I just presumed.

DR. PARISE: About two thirds are because the process that we already have didn't work. Those questions, although we think--I mean, even in this very last case, "Were you outside of the U.S. or Canada in the last three years," to me, that is a very straightforward question. But it doesn't always work and in the '98 case, that specific question didn't work.

And then, in the other one-third, it is basically because the parasite lasted longer than we have set up in those criteria.

DR. VERTER: Therefore, any modification in the current guidelines wouldn't have changed anything for those 58 cases.

DR. PARISE: The questions, if we talk about the questions, those could potentially impact on those two-thirds that failed in that screening process.

DR. VERTER: Then I misunderstood how you were interpreting the screening process. I thought you meant that if the screening process, as it now stands, had been

accurately followed completely, that those two-thirds would have been deferred.

DR. PARISE: That's right.

DR. VERTER: Which means that this question wouldn't have added anything to it.

DR. PARISE: This dusk-to-dawn.

DR. VERTER: Right.

DR. PARISE: That's right. The dusk-to-dawn; right. Sorry.

DR. NELSON: But put the current recommendation as a relaxation, not a stringent thing.

DR. RUEBUSH: I just wanted to respond to the comment that was made about perhaps doing a better job from our standpoint at CDC when we answer a phone call from a physician or someone who is travelling overseas, something like that in the materials that we produce to remind people about the fact that yes, they would need to be deferred for a year.

We don't routinely do that and yes, we could do a better job in that both in terms of our direct-voice communications with travelers or physicians and what we publish.

DR. HOLLINGER: Also, just to state the obvious, the donors are lost for one year. That is not, as with so many other things, where they are lost indefinitely. So we

are talking about, basically, a year deferral. Many people will not return to these areas.

Dr. Ohene-Frempong I don't think would ever be able to donate, but so many of them will be coming back.

DR. KHABBAZ: I have a question and a comment. Actually I have two questions, maybe. One, the question that we are dealing is one of relaxation based on how long they have stayed in the area. There is also a proposed addition in the FDA guidance which deals with the partial acquired immunity, basically, which proposes adding three years after a visit for people who were born or have lived an extensive period of time.

My question is what is the impact of that addition in terms of numbers that might be additionally deferred. That was the first one. Do we know? We don't?

DR. HEINTZELMAN: We have no hard numbers, if you are looking for number of donors that would be deferred. There are no hard numbers for that.

DR. KHABBAZ: The other comment or question; I note that the FDA is proposing a change of order of questions starting with, "Were you born in the United States?" and then querying about the last three years. The AABB statement brought to my attention basically these questions.

If somebody who was born outside of the United

States, I can see a point of asking that question. I cannot donate blood for other reasons, but just saying, "Forget it; you don't want my blood." So, the sensitivity of how the question--if there is a reason to ask this question ahead of recent travel, fine. But I am missing the rationale for changing this order.

DR. PARISE: Actually, there was one point from before that I had forgotten. That is what I wanted to clarify and didn't. In terms of relaxation, this is a relaxation in terms of dusk-to-dawn. But, from our standpoint, this isn't a relaxation in terms of the resorts because the previous 1994 memo referred to what we define in our Yellow Book as malarious areas.

We have always said, in the Yellow Book, that the major resorts are okay. So that is not going to change.

I think the issue that I can respond to from my perspective and then, if anyone from FDA or anyone else wants to comment on the questions, where we failed in some of these recent cases--we don't have hard data on what happens in that interview. Sometimes, it is a "he said, she said," situation where the donor can say one thing and the blood-collection agency says another and we really don't know.

But it is our impression that one problem that might be happening is that, although the question is in the

last three years, people who have moved here within the last three years don't consider that if they--no, they haven't gone anywhere because, since they came, they haven't gone. But they came within three years.

Because most of the recent cases have been in people from other countries, we are trying to get at a way to know about that up front and then probe more. There may be better ways to word that and I think FDA is open to that.

DR. KHABBAZ: I think that is fine, but I would support piloting these questions and field testing and seeing how they work.

DR. OHENE-FREMPONG: It is really not a question of where you were born. It is where you lived. I just wonder if the question could be, "Were you born outside of the United States or have you lived outside of the United States."

DR. MITCHELL: I did want some more information about the impact of this and particularly the post-donation information. We had asked before, there are 1200 cases of post-donation information. I still don't have a good sense of what percentage of those are due to what kinds of answers and I was wondering if there was someone who can provide that.

DR. HOLLINGER: I don't think so, Mark. I don't think anyone could provide that information for you.

DR. MITCHELL: As to what those questions are?

DR. HOLLINGER: Yes.

DR. MITCHELL: Then, getting back to the discussion that is under way right now, I think that it would be more sensitive to ask whether someone has traveled or lived outside of the U.S. within the last three years and just leave that as a question.

DR. HOLLINGER: I saw someone start to stand up out there, maybe to answer. Do you have an answer to the question?

MS. JETT: Anecdotally, I know that some of the cases I have looked at in my own center are, the donor comes in at one visit and says, "I traveled here and there." And then the next time, when they come in, they have a slightly different take on where they have been and what they did. So it is the donor giving different information on the next interview that would be a post-donation information report.

DR. MITCHELL: So the information is more on where they went.

MS. JETT: Yes. One time, they will report a visit and it may be the details of if it was rural or urban or maybe just having to mention this country or not that they visited on the trip.

DR. MITCHELL: The reason I am asking that, then, is because a day trip may make a big difference. It is my

impression that people are less likely to remember if they didn't spend the night there. If they went on a cruise ship and they stopped at two places at day, it is hard to remember all of those places.

MS. JETT: My subjective impression is when you are sitting in the donor chair, whether you are going to give enough detail to make a good judgment on them just depends on how they feel that day or who is interviewing or if they feel like being chatty or not.

DR. BUSCH: Comments on two issues; in terms of country of birth, we do, in the REDS group, ask donors--it is not a required question but we have been eliciting country of birth along with other special questions of donors. I think about 3 percent of donors sort of refuse or don't answer that question.

We have looked extensively at predictors of risk, particularly incidence of infections. Country of birth is not an independent predictor of risk of HIV or other seroconversion so there is no evidence, perhaps independent of this malaria issue, that would justify deferring. So I would agree with the comments about residents in as opposed to country of birth probably being a more sensitive approach to that issue.

The other general point--I wasn't here yesterday but I heard feedback in terms of all of the implications of

post-donation reports. Many, certainly, of these post-donation information reports are these subtle deferral issues such as visiting areas or things like tatoos or piercing and things like that.

You can argue whether or not those deferrals are very effective and justified in the first place. Certainly, I would suggest that it might be appropriate to make a distinction as to whether such deferrals warrant investigation after the fact. For example, I think my understanding is FDA is not going to require, if you have lived in Britain during the period that is now being implicated as potential risk for new-variant CJD, you may be deferred prospectively but that will not be a basis for a post-donation report.

You will not have to retrieve product or investigate product donations. So the same kind of distinction, I think, should be considered for many of these soft, if you will, deferrals, that so many of these recalls and potential investigations are driven by donors acknowledging later that they maybe had a body piercing or tatoo or something. It may be a basis for prospective deferral, but I think it shouldn't be a basis for post-donation information investigation.

DR. HOLLINGER: I think one of the more important things that you have provided us with, as I look at this

information, was the fact that, at least recently, if you are a U.S.-born traveler, there is little danger of transfusion-transmitted malaria if the guidelines are followed or if they answer the proper questions. Is that a correct statement basically, that most of the cases of transfusion-transmitteds are occurring in individuals who have lived in an endemic area or immigrants or refugees that, perhaps, have P. malariae or something else or perhaps, even, falciparum that might be persisting longer than the time limit.

DR. PARISE: Let me tell you the data because I am not sure--if the guidelines were not followed, actually, about half of those are U.S. travelers. Even our U.S. travelers are not answering the questions right all the time, and half of them are in the immigrant category, refugee, et cetera.

Of the other cases that happen because of these long exclusionary periods, those, there are very few in U.S. travelers. That is sort of our aggregate data. When we look at our sort of analysis in recent years, the U.S. traveler falls way down in, say, the '80s and the '90s.

DR. HOLLINGER: For transfusion-transmitted malaria.

DR. PARISE: That's right.

DR. HOLLINGER: Which is what we are really

dealing with here today.

Dr. Linden, do you have any comments?

DR. LINDEN: I guess I am a little concerned with what appears to be a discordance of the information that CDC has been giving to people that isn't really consistent with the FDA recommendations. I think that situation needs to be reconciled so that all of the federal agencies are giving uniform information. So, whichever way we go, I think we should get together.

But, otherwise, it seems that this change is reasonable. It sounds like, in part, it is sort of have been implemented already. But I agree with Dr. Epstein that it should be only if you can fully document that you know this is the case and if there is any question, you certainly defer.

DR. BOYLE: The travel exclusion questions that we are talking about are among the very few items, I believe, in terms of risk factors that are relatively easy to validate because you can get samples of people by destinations very easily and you can test your questionnaire to see what the error rates are, whether or not they are reporting what we suppose them to be.

The question is has been done?

DR. HOLLINGER: I would guess not.

DR. BOYLE: Then I will make my statement. Since

it is one of the few things that is relatively easy to find out what the error rate is in terms of reporting, particularly because you can pre-identify pretty much, and then those are discordant, obviously, you can follow up with, that it would be a good first step of learning a little bit about how good these screening questionnaires are.

DR. HOLLINGER: Dr. Fitzpatrick, you had a statement.

DR. FITZPATRICK: I will make this brief. Jay already brought up that the current policy is to defer and that there is no dusk-to-dawn exclusion. And I am not sure what percentage of donor centers are making exceptions or calling CDC.

In twenty-one years, I have managed six major and minor Army facilities that are donor centers and I was responsible for policy in all of Europe. I don't disagree with the science at all. The science is valid. The science is sound. But we have an implementation problem. We discussed last meeting the problem between the interviewer, the screener and the donor and perceptions and understanding and the need for better questions and questionnaires.

We have data that says 62 percent of the transmissions were due to a failure in the screening process. AABB and the ABC have, in both their statements,

said that the donor history interview is critical and very complex.

I think adding complexity to the interview will increase the error-accident rate. I believe that we are adding complexity to the interview. In order to not add complexity to the interview and if current policy, as dictated by the FDA is being followed, we are not impacting the donor supply. If we enact this, you are loosening the restrictions and increasing the donor supply. But, if current policy is being followed, you are not decreasing the donor supply.

And I have a problem with what Jay initially told us in his interview. In the IOM study, he stated that the precautionary paradigm is the one the FDA is following. What we are going to hear about at TSE and British donor deferral is an enactment of the precautionary paradigm. Yet this, to me, is in conflict with enacting the precautionary paradigm.

So Jay's suggestion of a blanket deferral with possible exceptions by the medical director may be the best approach.

So, in short, I would say that I think the dusk-to-dawn exclusion, while valid scientifically, increases the complexity of implementation, increases an already very complex difficult interviewer-donor situation, perception,

understanding, communication area and I don't see that the gain is worth what we are talking about.

DR. HOLLINGER: Thank you.

I think I am going to call for the question. If somebody could put it up.

DR. NELSON: The current policy allows the medical director of the blood bank to make an interpretation based on CDC advice? What is the current recommendation? What is it that we are going to change or vote to change?

DR. STRONCEK: Practically speaking, if you are going to make exceptions, you really have to have your SOPs written very carefully. You don't want to make a lot of exceptions. You want it well documented. That is not practical. As a medical director, I would want something, at this level of detail, that is very well spelled out.

DR. EPSTEIN: The current guidance makes no distinction regarding risk exposure based on time of day. We do not recommend that that issue be further explored with the CDC, although we have always respected the need and value to consult CDC when there were questions about geographic exposures because the FDA does not monitor areas for risk of transmission. The CDC does.

But, really, what has happened is that blood centers have gone beyond the existing guidance and asked more subtle questions such as resorts, such as time of day.

But it is not in the current FDA guidance.

DR. BUCHHOLZ: Jay, if I look at the current guidance and I have a donor that answers that question, and I call CDC and, based on being educated or based on something I know, I say, "Okay; you are in an urban area," or, "You were only in the daylight." And FDA inspectors come in. Do I get a GIG then if I let that donor donate, because I got advice from CDC or things I knew such as the basis of science that have said, no problem. Yet, I would guess that represents a compliance situation in terms of an inspector coming in and reviewing my records.

DR. HOLLINGER: Dr. Chamberland?

DR. CHAMBERLAND: I will ask Monica or Trent to comment or correct me but I think, and perhaps we are well aware of feedback that we have gotten that there has been disparity in information that CDC and FDA have advised on. I think, from henceforth and maybe it has already been your practice, the appropriate technical question to CDC is is this person-donor, non-donor, traveler at risk for acquisition of malaria and does this require institution of chemoprophylaxis.

I don't think, at all, that, as an agency, we should be making decisions for medical directors of blood banks determining donor suitability. Clearly, we don't want to be in conflict with FDA guidance or regulation in this

area, so I think, as an agency, we have to be very careful as to our responses in this area, that it is probably not appropriate for us to be making decisions about donor suitability.

I think this is what is going to be the problem is that CDC, as a public-health agency will be telling individuals or medical directors, "No; this person is not at risk for acquisition of malaria. Prophylaxis is not needed." Blood bankers and CDC will then be faced with confusion and complexity. That is not to say we can't work through it but, in talking with some of the blood bankers who also work as travel-clinic directors, they are going to be giving two sets of information out to people when the traveler shows up in their travel clinic, "You are not at risk for malaria based on what you told me. You don't need to take prophylaxis. But when you show up in my blood bank, I am not going to let you donate. You will be deferred because you pose a risk of malaria transmission to a potential recipient."

So Trent and Monica, again, I just wanted to make sure that you were in agreement with what I just said and after the vote today and the subsequent guidance, that was probably a better way to cast our role.

DR. RUEBUSH: We agree wholeheartedly. I think, many times, the question comes to us from a blood bank or

something like that, "Is there a risk of malaria in this area or in this situation?" And we have based our response on the scientific knowledge and we feel a daylight trip to a malarious area when you are spending the night in a non-malarious area, doesn't represent a risk.

I think if the FDA guidance is different, we need to be very careful in the future to make a distinction when we talk with someone on the phone that, for prophylaxis purposes, we would not consider a risk, we would not recommend chemoprophylaxis, but you are calling us from a blood bank, in which case, the guidance is to do the following. And we are prepared to do that.

DR. EPSTEIN: Speaking to Dr. Buchholz' question what the compliance approach would be if a medical director exempted a donor when that was not in the FDA guidance. I guess the answer is a little bit complex. The field investigators do recognize the role of enforcement discretion.

They generally would give a fair amount of consideration to exercise of good medical judgment, especially if it was well-documented what the basis of the decision was.

Generally, we look askance at exceptions other than those that are provided in the regulations based on medical need. So, outside of the documented medical need

which is, of course, particularized to a patient, we sort of look very carefully. These kinds of inconsistencies, when they are noticed by the field, usually would surface back to the center as a policy question, which is exactly how we get here.

So I think it is not so straightforward as that they would simply take enforcement action or cite on a 483. More often than not, they would then call us and say, "What do you expect us to do. Your guidance is unclear."

DR. HOLLINGER: I am going to have just two more comments and then we are going to call for the question.

DR. CHAMBERLAND: Before the question is called, I wondered--Jay, you had mentioned the possibility of potentially allowing for some flexibility in override or whatever for medical directors to have some discretion about deferral. I wondered if you had crafted that in language that could be voted upon because I am also keeping in mind the statement from America's Blood Centers which represents half of the blood collectors in the United States which are also asking for that flexibility.

Yes; we all have heard comments on both sides of the question that there are people that want us to be very black and white with no flexibility, but there are others that would like that discretionary flexibility. So I will leave it to the chairman, certainly, to decide on how the

voting should proceed, but you did raise this as an option and I was just curious as how that translates into a statement that could be considered by the committee.

DR. McCURDY: I have got a little bit of confusion that I thought had been cleared up but I am not sure that it has, now. first, I think that difference between whether a traveler should take prophylaxis or not or whether a traveler should be a donor or not when they come back are different.

I don't think they can be answered by the same--I think you have to differentiate between those two. The risk of transfusion malaria appears to be of the order of two to three cases per year. This is the same order of magnitude, not quite as large, but it is the same order of magnitude as the likely transmission of HIV infection by blood transfusion in the present milieu.

I think transfusion-transmitted malaria is frequently fatal. It is probably fatal because there is a delay in diagnosis because nobody thinks about it. It is probably fatal because transfusions are given to sick people who will not tolerate an additional illness.

I think it is likely under-reported so the two to three cases per year probably doesn't represent the total cases. I want to be sure that CDC is differentiating in their advice between the risk of being a donor and the risk

of chemoprophylaxis where you must balance the potential problems of the drug versus the risk of malaria.

I think those are vastly different.

DR. HOLLINGER: I think Dr. Ruebush did comment about that. I think you are right, Paul. They need to be distinguished.

I am going to call for a vote on the question. The question is written up there. "Do the committee members support a change in the current blood-donor policy to allow for travel to areas endemic for malaria when travel exposure was limited to hours of bright daylight?"

As we said before, a vote of yes means to allow travelers to malarious areas during daylight hours to serve as blood donors and a vote of no means to stay with the current proposals for deferral of travelers to malarious areas regardless of the time of day. It is fairly straightforward.

All those in favor of this change in the current blood policy raise your hands.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Anyone abstaining?

[No response.]

DR. HOLLINGER: Dr. Buchholz?

DR. BUCHHOLZ: I vote no.

DR. HOLLINGER: Ms. Knowles?

MS. KNOWLES: No.

DR. SMALLWOOD: The results of voting are as follows: there were 5 "yes" votes, and that includes the vote left by Dr. Koerper. There were 9 "no" votes. No abstentions. The consumer representative agreed with the "no" vote. And the industry representative agreed with the "no" vote. There are 14 members eligible to vote including the vote that was left by Dr. Koerper.

DR. HOLLINGER: I think the issue that Dr. Chamberland brought up is very important regarding what one has in the guidance regarding the role of the medical director or others to make some decisions regarding this and what the ABC had indicated. I don't know how we are going to deal with that, or if we should deal with it or anything. I think the comments were made.

We have got a few minutes here before we break here for lunch. But does anybody have any comments about what Dr. Chamberland mentioned or any thoughts about it?

DR. ELLISON: I would have preferred to see some kind of a discretion. It would have certainly have influenced by vote. I agree with Dr. Fitzpatrick's comments as far as that question which we are asked. I don't think the question allowed the leeway, the medical-director

discretion, that I think is essential.

DR. HOLLINGER: Right now, I think it is pretty clear. It has clarified the issue, I think, for both the concerns that they have.

MS. KNOWLES: I do have a suggestion in terms of maybe a tool to help with the Yellow Book being on the Web and that is that there is a really good computer program via the Internet called Mapquest. If the two of those could be integrated, that probably would help solve a lot of those questions.

DR. HOLLINGER: Thank you.

DR. NELSON: I know there are a lot of travel clinics that advise people on, often, malaria prophylaxis and vaccines. I think they rarely mention the issue of deferral from blood donation afterwards based on travel and how the risk that would lead to prophylaxis might be different from the lower risk but much greater consequence of a transfusion-transmitted infection.

I think of travel clinics, and there is now an organization of travel clinics. They have meetings, et cetera--I think that there should be an effort to educate travel clinics about this issue. My sense is that it has not been done very much to date.

DR. HOLLINGER: I think we will take a break now until 1 o'clock. We will return here at 1 o'clock for the

next meeting which will be on HTLV.

[Whereupon, at 12 o'clock p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

AFTERNOON PROCEEDINGS

[1:05 p.m.]

DR. HOLLINGER: We will begin the afternoon session on Development of HTLV Supplemental Tests. Those speaking, we will keep you to your assigned times. If you were not assigned a time, then we will assign you one.

This is an important issue, the development of HTLV supplemental tests so we want to have plenty of time to have some discussion if we need to. We are going to start out with an introduction and background by Dr. Cowan, Senior Staff Scientist, Laboratory of Molecular Virology, DTTD.

Development of HTLV Supplemental Tests

Introduction and Background

DR. COWAN: Thank you very much.

[Slide.]

I would like to begin by presenting to you the goal for this last session of the meeting which is HTLV supplemental testing.

[Slide.]

That goal is, to promote to the best of our ability, the submission of INDS for HTLV supplemental tests. There are currently no licensed supplemental tests for HTLV to follow up specimens that are repeatedly reactive on HTLV screening tests.

It is our intention to work with manufacturers of

research-used tests to remedy that situation. To that end, you will hear the following presentations.

[Slide.]

You will first hear a series of presentations on HTLV testing of U.S. blood donors. I will present an overview addressing some of the issues related to HTLV supplemental testing. Next, Dr. Susan Stramer will speak about the resolution of reactive HTLV screening test results with estimates on the number of specimens that would require supplemental testing. Dr. Michael Busch will then speak about clinical experience with HTLV supplemental tests.

After this discussion of clinical HTLV testing, you will hear two presentations that may offer funding opportunities to support licensure of HTLV supplemental tests by Susan Pucie from NHLBI and Pat Robuck from the Office of Orphan Products Development at FDA.

[Slide.]

To begin with the overview, why are we concerned about HTLV. There are two reasons. First, HTLV is associated with disease. By HTLV, of course, I am referring to HTLV I and HTLV II, retroviruses that are closely related to one another. HTLV I is known to be the etiologic agent of primarily two diseases, adult T-cell leukemia and HTLV-I-associated myelopathy, tropical spastic paraparesis, although other disease associations have been described as

well.

HTLV II also appears to be associated with a HAM/TSP-like disease. The second reason that we are concerned about HTLV I and HTLV II is that they are transmitted very efficiently by transfusion with the rate of approximately 63 percent for HTLV I.

As a result, on November 29, 1988, FDA issued a memorandum to blood establishments recommending testing of donations of whole blood and cellular components for transfusion for antibodies to HTLV I with licensed FDA tests.

[Slide.]

Subsequently, on August 15, 1997, FDA issued the guidance to industry on donor screening for antibodies to HTLV II recommending that blood establishments implement donor screening for antibodies to HTLV II using licensed tests.

[Slide.]

The testing algorithm for donor screening for antibodies to HTLV introduced in the 1988 document is shown here characterized colloquially as a "two strikes and you're out" algorithm. Primary screening of blood donors is performed using an EIA. A donation that tests repeatedly reactive by EIA is destroyed but the donor is not notified of the test result.

The donor is also eligible for future donations and non-reactive donations may be used until another repeatedly reactive test result is obtained on a subsequent donation even if there had been a series of intervening non-reactive test results.

At this point--that is, the second repeatedly reactive test result, the donor is indefinitely deferred from donating blood.

[Slide.]

An additional testing algorithm was introduced in the August 1997 guidance document to industry on donor screening for antibodies to HTLV II. In this case, a specimen from a single donation that tests repeatedly reactive using the primary screening test may be tested by a second licensed screening test of a different type for HTLV II and HTLV II antibodies.

However, if the specimen tests repeatedly reactive using the second screening test, then the donation is destroyed and the donor is indefinitely deferred and counseled on the basis of test results on this single donation.

If, on the other hand, there is a non-reactive result using the second screening test, then the unit is destroyed but the donor remains eligible for future donations as in the single EIA testing algorithm.

[Slide.]

However, there is an important piece of the testing algorithm that is missing. As stated in the August 1997 document as well as an earlier statement from FDA, donors with repeatedly reactive donations should be permanently deferred whenever additional, more specific tests confirm that the donor has antibodies to HTLV I or HTLV II and utilization of investigational additional more specific tests may be useful in notification and counseling of donors with repeatedly reactive screening tests for antibodies to HTLV I or II.

Having said that, we are now at the issue of the matter at hand, and that is, at the present time, there are no FDA-licensed additional more specific tests for antibodies to HTLV I or HTLV II. This statement is taken as a quote from the 1997 guidance to industry on donor screening for antibodies for HTLV II and it still holds true today.

[Slide.]

As you are aware, supplemental tests provide more specific information about EIA reactivity, defining that reactivity in terms of antibodies to particular viral proteins as opposed to general reactivity to various populations of antibodies or false positive reactions.

These tests are typically immunoblots such as

Western Blots or strips continuing viral peptides or recombinant antigens. The lack of availability of licensed HTLV I-II supplemental tests impacts at least two sectors which you will hear more about later.

First, blood banks are suffering the indefinite loss of valuable donors who cannot be reentered into the donor pool. Second, blood donors cannot be counseled appropriately following a repeatedly reactive screening test. Dr. Stramer and Dr. Busch will speak directly to this issue. The impact of a false-positive test result on a blood donor cannot be ignored.

[Slide.]

Why are there no licensed supplemental tests for HTLV I and HTLV II? One historical reason is that research use, or only RUO tests, have been used for donor counseling. However, I must emphasize here, as I have in a previous presentation before this committee, that RUO tests should not be used for donor or patient-testing or counseling except under the terms of an IND exemption, this according to the Code of Federal Regulations.

Another reason for the absence of licensed HTLV I-II supplemental tests is communicated to me by a number of individuals in industry on numerous occasions is that the number of samples that would require supplemental testing may simply be too small to justify the expense of licensure.

This is due to both a low incidence of HTLV I and HTLV II in the U.S. and to the specificity of the currently licensed HTLV I-II screening tests. Dr. Stramer will be addressing this point next.

[Slide.]

I would like to end with the following request from the committee; as you listen to the various presentations in this session, I would ask that you please provide us with general comments on strategies to promote the development of licensed supplemental tests for HTLV.

Thank you very much.

DR. HOLLINGER: Thank you.

The next presentation is going to be Dr. Stramer from the American Red Cross.

Presentation

DR. STRAMER: Thank you.

[Slide.]

This is the topic that I was asked to cover today, resolution testing of HTLV screening tests repeatedly reactive blood donor samples. I will take you through an evolution of a process leading to where we are today with the dual EIA algorithm.

[Slide.]

As far as background, as Elliott Cowan just reported, currently there are no routinely available

supplemental tests for anti-HTLV I-II confirmation. Data I will show you shows that those that are available under IND, which includes one test, has indeterminate rates greater than 70 percent.

As Dr. Cowan also mentioned, an HTLV I-II algorithm is proposed in which repeat-reactive donations from the primary screen are then tested using a second licensed EIA of a different type and the use of this dual EIA algorithm was coincident with the implementation of HTLV I-II screening in February, actually February 15, of 1998.

According to this dual EIA algorithm, concordant repeat reactives are then tested by an investigational Western blot and the investigational Western blot is manufactured by Cambridge Biotech.

[Slide.]

The American Red Cross notified FDA of its intent to perform this algorithm on February 10, 1998 and, again, I said it was meant to be coincident with the implementation of HTLV I-II screening. We received verbal approval and then received written approval on March 15 of this year but, within our approval letter and relevant, as you will see, to some of the results I will show you, is FDA asked us to change the interpretation, the interpretive criteria, recommended by the manufacturer of the IND reagent.

The IND reagent states that you need to have two

gene products of HTLV reactive; that is, one from core, p24, and one from envelope which can be recombinant GP21e which is a recombinant protein or the viral lysate protein directly which is gp46.

This is relevant because p21e has high rates of nonspecific reactivity and that will come through in the data. But what FDA requested is that we maintain the Public Health Service criteria which is not what the IND requires but what uses a positive interpretation requiring p24 and gp46.

[Slide.]

For the dual EIA data that I will show you--that is, data subjected to the dual EIA algorithm--approximately $7 whole-blood donations were screened using an anti-HTLV I-II kit and we used Organon Teknika as our primary kit. Repeat reactives were then tested by a second licensed HTLV I-II kit, Abbott. Concordant repeat reactives were tested by the investigational Cambridge blot, as I stated.

When we initially implemented this test, we worked with Community Blood Center of Greater Kansas City to also qualify the reverse of this algorithm; that is, for blood centers who begin with Abbott and then would use, as their reflex test, Organon. So I will show you a small amount of data showing how the reverse algorithm looks.

Then, in a larger study that we just completed,

looking at what is the supplemental test reactivity of discordant EIAs, we have looked at that in the presence of both directions of the algorithm; that is, we took 200 samples from blood-systems laboratories in collaboration with Mike Busch and Sally Caglioti and they were tested first by Abbott and then by Organon.

With Red Cross samples, we took 128 Organon repeat reactives and then tested them by Abbott. All samples were tested, whether they were concordant EIA-reactive or discordant EIA-reactive, by both the Cambridge investigational western blot and also by a research test-kit referred to as a strip immunoassay or recombinant immunoblot assay RIBA, which is the same technology that was recently licensed for hepatitis C.

[Slide.]

To give you first some historical perspective on what our expectations are for HTLV, this shows you Red Cross data that I have shown at BPAC committees previously. It covers the year-and-a-half period of time between 1996 and 1997 before the Red Cross made some changes in their screening test methodology.

Here you can see what the prevalence of HTLV that we would expect in a blood-donor population is relative to 10,000 donations. So our expectation is 10 per 100,000 donations. You can see here how that fits relative to other

viral markers we screen for.

[Slide.]

When we made a switch from the Abbott HTLV I kit to the Cambridge HTLV I kit, we noticed a dramatic change. Now, we changed vendors in June of 1997 and both algorithms involved a screening test followed by the Cambridge Biotech western blot. The issue with our change was the Cambridge EIA contained the exact same antigens as the western blot. Therefore, one would infer that what is repeat-reactive by the antigens of I would still be repeat-reactive by the antigens of the second test.

In fact, that is exactly what happened. So, if you compare two three-month periods of time, the three months just before we stopped the test and the three months when we introduced the new test, what is really compelling here are two points; one, that no matter what we do on western blot, we always see high rates of indeterminate.

Secondly, when we went from the Abbott test to the Cambridge test, all of a sudden, the number of positives we were reporting doubled. So that is a significant problem because we can't ignore a positive test result.

[Slide.]

Looking at the quality of the blot, you can see why the indeterminate rate is so high. What I am going to show you are manufacturing defects in the blot that occur

during the electropheresis in construction of a western blot.

Here you can see what is referred to as smiling. That is when the glass plates generally aren't clean and we see antigens not electrophoresing completely linearly. The other thing you see on this blot are a tremendous number of viral bands that indicate not true positivity in these cases but, in fact, false positivity. There are HLA bands here. There is just background on the blot. Generally, they are poor quality.

[Slide.]

Here you can see another blot batch. Here you actually see a hole in the gel so this is on the positive control although it doesn't affect the area that you read. Again, non-specific viral bands--this is probably the only true positive of all the strips that I have shown you. Here is the p21e recombinant reactivity.

[Slide.]

The next three graphs are the ones that have the line that is very important to see. It is in pink. This shows you historically what has now happened when we switched EIAs. One would expect, under CGMP testing, using an FDA-licensed product on a relatively stable population, that, week-to-week, lot-to-lot, our numbers should be consistent and should be not fluctuating.

With the Abbott product, during each fall, we would see a rise in initial and repeat reactivity due to cross-reactivity of flu-shot vacinees so that would occur in the fall. Then, when we switched to the Cambridge EIA, our repeat-reactive rates skyrocketed as well as the initial rates. We were pleased when we switched, then, to Organon because, on the first two months, the rates went down.

But then what happened, in response to a request from FDA to increase the sensitivity of the kit based on a lot-release number, we saw a tremendous increase in repeat reactivity here. You can see a mean during these weeks of greater than 0.2 percent. As Elliott said, without supplemental testing, we have to tell donors something about these results.

Then they were allowed to recalibrate their kit to not exceed the levels that FDA requested it to on the lot-release panel and we saw a decrease. But now, what is happening, is we are seeing another increase. So the point in showing you this graph is that the screening repeat-reactive rates are not stable product-to-product.

[Slide.]

When we switched to the Organon HTLV I-II kit, we wanted to make sure that the sensitivity of our primary screen and the reflex screen, the second EIA, were comparable. So we asked the manufacturer for some

assistance. What the manufacturer did was provide us their most weekly reactive samples out of their clinical trial.

You can see this from S/COs of 1 to 2. Then, when tested on the Abbott kit, they showed very comparable sensitivities so we could see out of the FDA validated clinical trials the most weekly reactive confirmed-positive samples had equal strengths on both kits. So we felt confident that we could proceed forward.

[Slide.]

The data to date, for 7 million whole-blood donations is as follows with the dual EIA. I will now show you its stability over time. The Organon Teknika; again, we screened 7 million blood donations with a repeat-reactive rate of 0.12 percent. So this is the number that we start with.

Over this period of time, which is over a year, that includes 8,661 blood donors, we then tested those donor samples by Abbott. Only 35 percent were concordant repeat-reactive. So, just by doing the second EIA, we eliminated over half and, in this study, 65 percent of samples from unnecessarily being tested by western blot.

If you look at this as a concordant repeat-reactive rate, that is about a 0.94 percent repeat-reactive rate which is really what we would like to see for the reactivity of the primary screen. Those samples were then

taken on to western blot and here you see, if you look at the percent concordant repeat-reactive, what the outcome of the blot results were.

Again, 73 percent indeterminate. So it is this blot that is generating a lot of problems regarding high numbers of indeterminate. The non-reactives, as Elliott also said, are not tested further by the second EIA and those donors remain eligible for a second donation, although their repeat-reactive donation is destroyed.

[Slide.]

I wish this were clearer because this slide speaks a thousand words. These represent samples per week that are required for confirmatory testing. That sample, incoming samples into my lab--I run a confirmatory lab to the Red Cross--represents the fluctuation that we see week-to-week from product-to-product with HTLV.

This represents, initially, what we started with with Abbott. This represented the increase with Cambridge. Then we went to Organon. We saw a dip. Then we saw the increase and then another dip and now another increase.

[Slide.]

To look at the impact of the second EIA--and, again, I apologize regarding the colors--the blue, again, represents the number of incoming samples. The green line represents those samples that are non-reactive by the second

ELISA or ones that we do not have to do supplemental testing on. So, again, this represents 65 percent and it represents probably false positives from the primary screen.

The red or pink line down here represents the total number of concordant repeat reactives that go on to western blot. You can see that this line is relatively stable and that is because we are screening out most of the false positives with the second EIA.

[Slide.]

Looking at true positives following western blot, just western blot positives, this is what we see over the three tests. You will see the impact of the false positives on the supplemental or Cambridge western blot. With the Abbott test, over time, we generally saw, as I said, 10 per 100,000 donations as confirmed positive.

When we converted to Cambridge, that number skyrocketed to 23 per 100,000. Again, we believe that is an artifact using the same kit for screening and confirmatory. Now that we are back with Organon using the dual EIA algorithm and the western blot, we are back now to 10 per 100,000. You can see that relatively stable over the Organon product.

[Slide.]

As I said when we first started this testing, we also qualified the reverse algorithm. These are the data

from Community Blood Center of Greater Kansas City in collaboration with Gary Tegmire. These were the Red Cross data from the first five months.

We initially saw a primary screening repeat-reactive rate of 0.10. Then, at that time, only 45 percent of those were repeat-reactive on the second EIA for an overall repeat-reactive rate of 0.05 percent. This is a little bit lower than what I have shown you on the previous slide of 35 percent.

But, going from Abbott to Organon, in the beginning when Abbott was first licensed, the specificity wasn't so good. So the importance of the second EIA was very, very needed because it eliminated 90 percent of the false positives, a much higher number than here, and yielded an overall repeat-reactive rate by both directions of the algorithm that was relatively comparable.

[Slide.]

Looking at this now in a more recent study, also qualifying both sides of the algorithm, it is going from Abbott to Organon and Organon to Abbott, what we tested were 200 samples from BSL, Blood Systems Laboratory. They were Abbott repeat-reactive, Organon nonreactive. We actually tested all of the discordant EIAs by supplemental testing so we could see if there were any positives not detected.

Of 150 that were discordant, or 75 percent, none

of them were Western blot positive.

[Slide.]

Looking at a similar study from the Red Cross, we had three samples here out of 128 total screened that included 93 that were discordant EIA-reactive. We, unfortunately, had three that were RIBA positive. This is the RUO test. A certain explanation of this is that they are false positives so we investigated further. These samples, actually, by western blot had only very strong p21 reactivity according to PHS criteria but extremely strong p21 reactivity.

We tested them by another construct of p21e that has a piece of the recombinant protein truncated that is supposed to represent the non-specific region. All three samples were nonreactive with the more specific 21e construct. They also were negative by immunofluorescence and by RIPA in the state of California.

[Slide.]

So if you put all the data together for BSI and Red Cross in this first study of 200 screened in 128, only about 25 percent were concordant repeat-reactive similar to the overall Red Cross number I showed you of 35 percent. Similar results were obtained by RIBA and western blot for confirmatory testing also similar to those that I showed you from Red Cross experience total, which included about

24 percent being positive.

Now, when we looked at the Red Cross samples, there was one sample here that was western blot indeterminate and RIBA positive. Is that a false negative or a false positive. That sample is undergoing further study.

[Slide.]

This now combines a larger dataset of 200 Red Cross samples and 200 BSI samples, just to look at a two-by-two table comparing the performance of western blot to RIBA. When we did a statistical analysis to say, are these methods similar?" the statistics said no, they were significantly different.

The reason that these were significantly different was because of this cell that represented 47 percent of the data that is western-blot indeterminate, those problem samples that I showed you that were all RIBA negative. This would all be well and good if we had concordance on positivity for both assays, but, on this testing, we have 12 western-blot-positive samples that were RIBA negative and we also had one western-blot-indeterminate sample that was RIBA positive.

So, in order for us to assess the sensitivity of these methods, further testing needs to be done because there appears to be some discordance. But the methods were

primarily not related because of the high numbers of western-blot indeterminates.

[Slide.]

So, summary and conclusions; the unavailability of HTLV supplemental tests having validated sensitivity and specificity have forced alternate strategies to be examined. Fluctuating repeat-reactive rates and screening test-kit performance have placed further pressure on the need for HTLV supplemental tests.

Screening and supplemental tests should not contain the same manufacturer antigens. The dual EIA strategy reduces the number of samples requiring western blot by at least 65 to 75 percent, consequently greatly reducing indeterminate rates.

[Slide.]

And even with the use of the dual EIA algorithm, high numbers of samples require further supplemental testing. The availability of HTLV I supplemental tests is limited and the quality of the one available is poor and RIBA may offer a more specific alternative to western blot once sensitivity has been fully qualified.

Thank you.

DR. HOLLINGER: Thank you, Dr. Stramer. Any questions for Dr. Stramer regarding the information she presented? So the percentage of positives that are EIA--I

mean, with a different test, the number that you are left with, finally, how does that make. How many donors? What percent of the donors would, therefore, under this circumstance, be ineligible?

DR. STRAMER: From the small study we just did with BSI and with our small number of samples, that was 25 percent. So it is 25 percent of the repeat reactives which is 0.12 percent. 25 percent is 0.12 percent of 0.04 percent.

DR. HOLLINGER: Okay; so the 0.04 percent.

DR. STRAMER: Which is really what I reported for the concordant repeat-reactive rate. So it is about 0.04 percent is the total demand for supplemental testing.

DR. HOLLINGER: If you had supplemental tests, how many would that further reduce?

DR. STRAMER: The supplemental test would then divide the samples into negative indeterminate and positive and the answer to your question would be it would depend on the performance of the supplemental test. We would hope that all of them would be negative with very few positives, but we know that is unrealistic.

DR. HOLLINGER: Thank you.

DR. KHABBAZ: I have a question for Sue. Clearly, from the time that I knew HTLV better than now, and was involved with HTLV, things seem to have deteriorated with

regard to supplemental tests.

My question is what happened with the western blot that had I- and II-specific glycoproteins whose performance, as I recall, and I don't have the numbers, was much better than what you have now.

DR. STRAMER: You are referring to the Diagnostic Biotechnology blot which is now referred to as the GeneLabs blot. In your era of HTLV, there was the version 2.3 which is now the 2.4 soon to be the 3.0. But, anyway, that product was distributed in the United States under RUO labeling and it was being used for blood-donor counseling which is against the CFR that Dr. Cowan replied, so the product had to be removed from circulation.

They weren't following the guidelines as Cambridge was. They never filed an IND.

DR. NELSON: Will these supplemental tests--will the western blot or RIBA differentiate HTLV I and II?

DR. STRAMER: The one problem with the Cambridge blot and actually reported in the U.S. Public Health Service guidelines is it says that one guide to differentiate HTLV I from HTLV II is p19 or p24 reactivity. That is really not the way to do it.

The RIBA does have, and I should have mentioned this but didn't, HTLV I and, separate, HTLV 2 enveloped glycoproteins. So you can confirm and distinguish HTLV I

from HTLV II by specific peptide which the blot does not have. The blot that Rima referred to did differentiate but that is no longer available in the United States.

This western blot that I showed you is probably absolutely first-generation.

DR. KHABBAZ: The other one had a I- and II-specific glycoprotein recombinant or peptide--

DR. STRAMER: Right.

DR. OHENE-FREMPONG: Is there a nucleic-acid test in development?

DR. STRAMER: HTLV is a cellular-associated virus. It doesn't circulate freely in a viremic phase the way HIV does or HCV, so we can't do a plasma-based PCR. You can do cellular-based PCR but that requires cells and it is not something that is conducive to routine supplemental testing

There have been reports of serum-based HTLV PCR, but that has not been very well reproduced.

DR. NELSON: Have the donors been followed? Are most of the HTLV donors from endemic areas and the IIs are drug users?

DR. STRAMER: I think the epidemiology of HTLV has been pretty consistent. We see a predominance--and I don't want to use Red Cross data because that is based on p19 and p24 and I have zero confidence in that reporting methods. But, from REDS data, and I think Michael may hit on this, we

believe most of them are HTLV IIs still and risk factors, drug use. I think the epidemiology for HTLV has been pretty consistent.

DR. HOLLINGER: The next presentation will be by Dr. Busch on the clinical experience with HTLV supplemental testing. Dr. Busch represents Blood Centers of the Pacific, Irwin Center.

Clinical Experience with HTLV Supplemental Testing

DR. BUSCH: Thank you.

[Slide.]

I am glad to be able to address this topic. It has been one that has really been a problem for ten years or more and it is a more general problem than just HTLV. The issue of adequate supplemental assays for donor infectivity screening tests has continued to be a problem for all of the markers where, basically, as the companies bring forward more sensitive screening tests, there is not much incentive financially or from a regulatory perspective for them to invest in the appropriate supplemental test to complement the screening test.

So we have really been handcuffed in terms of the donor notification site of this for a number of years for all of the viruses.

[Slide.]

So I am going to slightly more generalize my

comments and, unfortunately, I had distributed some papers to FDA that I thought would be distributed and they weren't.

But, in any event, I would refer you to an editorial I wrote several years ago that really tried to focus on the adverse impact of the lack of adequate supplemental tests on our blood donors. As you can imagine, from all these tests put together, well over a percent of blood donations are detected as reactive on one or more of these screening assays and the donors are usually deferred and have to be notified and counseled and, often, in the absence of adequate--and, certainly, adequate FDA-approved supplemental assays.

A couple of just general, fundamental problems. One is that as the companies, again, bring forward enhanced screening EIAs, the lack of capacity to bring forward complementary enhanced supplemental tests to adequately notify these donors.

What we have been documenting over the last few years is a fairly high rate of false-positive supplemental-test results. This have been well-documented now in the context of HIV where, in the range of about 10 percent of all donors who were being notified that they are HIV western blot-positive in fact have patterns that are indicative, and a high proportion of those represent non-infected donors who have non-specific patterns on HIV western blot.

On HTLV western blot, again, in the range of probably 10 to 20 of donors who are scoring positive on the Cambridge biotechnology blot are actually false-positive blots. I will get into that as well.

On both HIV and HTLV immunofluorescence assay, false positivity has now been well documented. For hepatitis B surface antigen and p24 antigen neutralization assays, there is a fairly high rate of false positivity. For HIV, there are probably 20 false neutralization tests for every true neutralization positive that has been reported.

Even with some of the earlier recombinant tests, like HCV RIBAs, there was interpretive criteria that resulted in false-positive notifications and, indeed, as we have begun to evaluate the new-generation HTLV supplementals such as the Biotechnology blot or the HCV HTLV I-II RIBA, those do have much lower rates but still have some problems with false-positive results.

You can just imagine the impact on donors, many of whom are told they are false positive and only years later do we really understand this issue and the dilemma of going back to these donors who were told they were infected with these viruses and coming back, years later, and trying to tell them that we made a mistake, if we ever get to the point of retesting all those samples and sorting it out.

Another big area that has been just a chronic problem is, as Sue alluded to, the very high rates of indeterminate results using these viral lysate-based assays. So we are running in the range of 30 to 50 percent of blood donors who are repeat-reactive for HIV are reported out as indeterminate on the FDA-licensed western blots and, using, again, viral-lysate assays such as the Cambridge or the spiked blots from Biotechnology GeneLabs, we see 70 to 80 percent of these donations are reactive on one band or another and the donors are being notified that they have an indeterminate test result.

Then, in terms of discrimination of viral subtypes, for none of the viruses, HIV, HTLV or hepatitis C are there approved methods for detecting subtypes which, in some cases, have great clinical relevance.

Now, the problem here really has to do with sort of the economics and regulatory issues around supplemental assays. There is a fundamental problem simply economically in that the market for supplemental tests is much, much lower than for screening assays.

So the companies focused their resources on getting better competitive screening tests developed, manufactured and licensed and tend to minimize the focus just enough to get them through the trials. And test like HTLV, where the market is relatively low, where the whole

world doesn't screen, the numbers of screened donations that require supplemental testing are so low that the companies basically are not willing to go through the continued developmental and regulatory channels.

As a result, in addition, the FDA's policies, I think, have been somewhat misguided in this area. Usually, the FDA looks at licensing a supplemental test in concert with approving a donor reinstatement protocol. So they are very critical of the assays requiring that they have head-to-head or improved sensitivity compared to the screening assays and, also, obviously, good specificity.

So that has resulted in very intense scrutiny of the assay sensitivity during the regulatory process which takes years and during the time that a company is trying to get approval for a supplemental test, there is a new screening test that comes along that has to build in type O or has slightly better window-phase sensitivity.

So a supplemental test that really was excellent and still is a great improvement over what we have is not able to get through the regulatory hoop. So we are basically, at this point, in terms of many of these agents--really, there are, to my knowledge, no really state-of-the-art supplemental tests going to FDA for HIV, HTLV, even though these assays are being widely used elsewhere in the world and they have been developed and are much better than

the current viral lysate or no approved assays that we are dealing with today.

So I think, to my mind, one important consideration to FDA would be to look at approving these assays for donor notification and counseling as an initial step independent of the issues around donor reinstatement that have implications for blood safety because what we really need--in fact, none of the large blood programs reinstate donors because it is such a regulatory risk that, if the FDA comes in and you reinstated a donor inappropriately, you really get nailed.

So most of the blood programs are not reinstating even though there may be an acceptable algorithm. So we would rather see the focus on getting methods for donor notification and counseling and potentially, downstream, through later validation studies, could the reinstatement issues be addressed.

The other issue, again, is that the supplemental tests become obsolete as a type-O antigen detection or other improvements in the screening test come forward. This leads FDA to put reinstatement programs on hold and so a test that might have been approved for donor reinstatement is no longer adequate. So FDA cancels the reinstatement program.

The other issue is that blood banks, as a consequence, some of them have taken a very, I think, donor-

adverse approach to the notification and are not even doing confirmatory testing for some agents although, as Jay said, there has been somewhat of a mandate and I think we are waiting for an FDA regulation to require supplemental testing.

At this point, it is not required and, given the absence of FDA-approved assays, some blood banks are actually notifying donors based on repeat reactivity which I think is totally unacceptable.

[Slide.]

Specific to HTLV, actually we did a study early on in the REDS group that looked at a very large number, I think around 500 or 600 HTLV repeat-reactive donors by PCR and a number of other assays. In fact, what we discovered was that the routing supplemental algorithms that were kind of built when the tests were first licensed, by Abbott in particular, were really extraordinarily accurate.

What they were doing is they were actually doing parallel western blot and radioimmunoprecipitation which is a labor-intensive sort of research-mode assay. And then many blood banks were supplementing that with early available peptide-typing assays.

What this study showed was that those methods were 99.9 percent sensitive to detecting true infection. A small fraction of indeterminates were really infected and none of

the negatives were infected. So, really, the early supplemental-test algorithms that were available through the company reference lab channels were very accurate.

Over the subsequent years, companies did begin to develop and market RUO tests that were improvements. I will show some examples of those. There were peptide and recombinant p21 EIAs available. There were very enhanced antigen spiked western blots as well as what we will see in a few minutes, both Chiron and Innogenetics have been built completely recombinant peptide-based strip immunoassays.

Roche, actually, for a three or four-year period did have an RUO HTLV I-II PCR assay out on the market. But what happened was that none of these companies were willing to pursue the regulatory channel because, again, of these cost issues downstream, that there simply wasn't enough recovery envisioned downstream and the regulatory issues were problematic, as I alluded to.

So this has led people to develop the strategies, such as Sue described, doing alternative EIA-type strategies or using these older, first-generation viral lysate western blots and trying to report type differentiation based on p19, p24 band intensity which we now know is very inaccurate.

[Slide.]

I will show you a little bit of data about how

these results have resulted in artifactual observations of false positivity. I just wanted to show you a few of these newer blots. This is the one that Rima was addressing, the GeneLabs Diagnostic Biotechnology western blot that was first developed and reported back in the early '90's and has since gone through a few generations of improvement.

[Slide.]

Let me show you a representative figure. This assay, in addition to a viral-lysate-type western blot and the recombinant p21e antigen, which is a very sensitive antigen that cross reacts with all the virus, they added type-specific antigens for a particular envelope region.

So this allows one to differentiate whether the donor harbors HTLV I or HTLV II in the same assay. In the early-generation studies, the antigen that was the p21e antigen actually had nonspecificity, the same as the Cambridge blot.

[Slide.]

So we and others reported on problems with that assay reporting out a low rate of false-positive western blots. And the GeneLabs group actually went on to identify within that HTLV I p21e antigen the immunodominant-specific epitope versus the non-specific region. And they later have modified the blot to include a new revised antigen that is called GD21e which is very specific and does not have false

positivity associated with it.

So, in the background, companies have improved and these assays are manufactured actually overseas and are widely distributed worldwide.

[Slide.]

A Belgian company has developed an assay called the INNO-LIA test which is a complete recombinant peptide base supplemental test for HTLV.

[Slide.]

It has control bands and then it has HTLV I-II generic antigen so a p19, p24 and several enveloped antigens that react with HTLV specifically but do not define the type.

But then there are three type-specific antigen, a gag and two types of specific enveloped antigens which give you the type of the donor, be that I or II, among the seropositives.

[Slide.]

There has been a series of recent papers. This is just one of them I won't go through but the critical value of these tests is really that they eliminate the indeterminate results that were such a problem.

They are very accurate in terms of sensitivity and typing and they reduce the rate of indeterminate results by 80 percent compared to what one sees with a lysate western

at

blot.

[Slide.]

This is the Chiron assay which we have been beginning to collaborate with them on that similarly to INNO-LIA assay has a series of strips. It is very similar to the HCV RIBA. There is also an HIV one to RIBA that has been in development. But basically it uses the same p21e antigen and then uses type-specific subsets of the p21e antigen to type the individuals or peptides and then a combined HTLV I-II gag test.

[Slide.]

So just to point out that these improved assays have been under development but they have not been implemented. In fact, if anything, we have gone backwards on HTLV. This became apparent to the REDS group as we were monitoring the epidemiology incidence prevalence of virus in the donor pool, all the other viruses, the incidence and prevalence has declined whereas what we observed for HTLV was an actual increase in the prevalence among first-time donors of HTLV over the period '93 to '95--

[Slide.]

--as well as a sudden increase in the point estimate of the incidence, although not significant.

[Slide.]

We wondered whether this was real or not. What we

did was to look back at the confirmatory assays and criteria. What we documented is what you have heard, that the Red Cross, in part because of some regulatory issues, moved away from using the p21e EIA and the RIPA assays going back to the only assay that has been submitted under IND, the Cambridge assay, in 1993, late '93, whereas the non-Red-Cross centers actually went the other way. We started to use this Diagnostic Biotechnology blot which has good specificity, supplemented by RIBA.

[Slide.]

So then we looked at the REDS data separating it by the Red Cross and non-Red-Cross centers. What we could see was that that increase in prevalence was limited to the three Red Cross regions and really probably coincided with this change to inferior, less specific supplemental tests.

[Slide.]

To further validate that, we did a study where we took 260 donations that the blood centers had called confirmed positive over this period of time. Those were tested by PCR, by peptide EIAs, and by the HTLV RIBA test. Using the very stringent criteria that all of these test had to be negative or the RIBA could be indeterminate, we identified 30 percent of these samples as false positive.

When we look at the frequency of false-positive results over time, we see that they really only began to be

reported by the blood centers in '94 and '95. Now, as I say, about 30 percent of what blood centers are reported out are false-positive results until the most recent change which is now the Red Cross is precluded from using the p21e antigen. So, now, nobody is being told they are positive. Everybody is an indeterminate.

So it is really a haywire situation.

[Slide.]

The last thing I wanted to mention is some comments about the impacts of false-positive and other test results on donors. This is an area that I think we have all kind of talked about and waved our hands about but REDS, over the last several years, has tried to do some formal surveys to try to quantitate the impact of false notifications and true notifications on donors.

We actually published a paper several years ago that looked at the psychological impact on notifying donors who truly were seropositive for HTLV I and II compared to normals and could document significant psychosocial impact on infected donors who were being told they had a virus that probably would never get them sick, that maybe they could transmit to others but we couldn't do anything about it, so kind of the problems about telling somebody they have one of these infections.

[Slide.]

But recently we have done another survey of about 4,000 donors who were told they had various test results including various false-positive patterns. I just want to share a few slides of preliminary data from that survey. These surveys are organized mostly by Allen Williams.

What this summarizes is for some of the more common false-positive patterns, HIV indeterminate, HTLV indeterminate, HCV indeterminate, HCV RIBA-negative and anti-core reactive donors who were notified that they were deferred due to anti-core reactivity, what the impact was on these donors in their answers to questions such as this: "Were you confused when you were informed of these test results?"

You can see that 80-plus percent of these donors were confused with about half of them being very confused and half somewhat confused.

[Slide.]

Are they still confused? These surveys were actually administered about a year after these donors were notified. You can see that, still, a high proportion of these donors remain confused over the test results a year or more after the notification event.

[Slide.]

Did the notification emotionally upset them? Again, about 80 percent of these donors who were told that

they had what we, in fact, think are mostly non-specific results and try to reassure the donors--and, of course, for many of these viruses, we really can't help them further, or their doctors don't know anything about HTLV, so these donors are basically anxious over these test results.

Again, this was a persistent finding in a high proportion of those donors.

[Slide.]

Many of them went on to seek--even though our counseling messages say, "You are not infected; it is okay," many of them on to see physician follow up after these notifications.

[Slide.]

Finally, within the REDS group, we have tried to address this problem and talk to FDA about potential strategies. So, over the last year, we have compiled some panels, large panels, of pedigreed samples from donors with well-characterized HTLV infection status.

We have begun to develop collaborations. We have been working recently with Chiron, one of the manufacturers of the peptide EIAs although this company has now decided to discontinue making that test so they are no longer interested in studying this, it seems.

And Innogenetics, we have now started to collaborate with them to try to do preliminary evaluations

of their tests and then, together with a company after we felt that the test that they have is adequate, try to file and IND because the companies are not willing to file this on their own accord or fund and pursue a clinical trial.

So we have pursued the strategy somewhat analogous to NAT to try and file and IND with the company and then continue to test under IND doing some additional clinical studies but with an understanding with FDA that realistically this may not evolve to a full application but will at least allow donor notification while testing under IND and the concept of probably broadening the testing to several of the larger testing labs to allow the availability of these results for all donors.

Thank you.

DR. HOLLINGER: Thank you, Mike. Any questions of Dr. Busch?

DR. TABOR: I really regret that I have to correct a number of very careless comments, or comments that appear to be very careless in the early part of your talk.

First of all, you gave the impression that confirmatory tests or supplemental tests for several of the viruses that are tested for in blood have a very high rate of nonspecificity quite apart from the indeterminate results. I don't believe that that is really connotatively verifiable.

Second of all, you gave the impression that companies are beating down the door at FDA to try to get us to approve supplemental tests that are new and improved. That is certainly not the case.

Third, you gave the impression--in fact, you stated--that the development of new screening assays for things like HIV group O, that was a specific example you gave, immediately invalidated confirmatory tests that had already been approved by FDA.

First of all, we are still not testing for group O because the companies have been slow to develop screening tests for group O and, even if you had a screening test for group O, it would certainly not invalidate a validated confirmatory test or supplemental test for the vast majority of the HIV that is detected in this country.

Finally, you made the careless mistake of referring to RUO tests that are "on the market." RUO, in case anybody missed it, stands for research use only and the companies are not supposed to have those on the market, even though they do, in fact, get cost reimbursement for them. They have to have an FDA license or approval in order to be on the market.

DR. BUSCH: I am sure my mother will disagree with you. The first point, I think I could share with you a series of manuscripts published from the REDS group and

others in terms of the false-positive problems with the current supplemental tests. Obviously, they are most serious in the donor setting. In any kind of high prevalence, high-incidence setting, they are fairly trivial.

But, in the blood-donor setting, I can show you published papers for HIV, HTLV, p24 antigen, surface antigen, that document what I think are unacceptable 5, 10, 15 percent rates of false-positive results coming off these assays in the blood-donor setting.

In terms of beating down the doors, I think what I said was that there are no tests in the pipeline or, if there are, they are stalled. I discussed these issues extensively with the companies and, basically, they won't bring tests in because they can't afford the cost of these trials to them get to the market that is so small and the unlikely regulatory path that is reasonably likely to be aborted because of the third issue which is that, although group O may not have invalidated the license status of the licensed western blots, any test for supplemental assays, it is my understanding, that would come forward now for supplementing donor screening would have to have group O represented.

So, if a company had a test well in development or through clinical trials, I think they would have to go back and, it is my understanding, incorporate group O into those

to get them licensed downstream. I am not certain about that.

The last issue, RUO; I guess it is the definition of market. We were able to purchase and run the biotechnology blot several years ago for research use only. The preclusion became that we were told, "Yeah; you can buy it and do research with it but you can't tell people the results." It is a definition of market.

DR. NELSON: Are these supplemental tests--would they classify as an orphan drug?

DR. BUSCH: I think you will about potentially that.

DR. NELSON: As I understand it, that category of drug was used to deal with the disincentives to develop important diagnostic and therapeutic reagents based upon only economic considerations. Here it seems to me to be pretty remarkable.

The other issue with some of the supplemental tests is that--and it may be based, and I guess it is, on economics--the costs of, for instance, the RIBA for the hepatitis C that the company cites make it impossible to use this for research. It is like $100 an assay or something ridiculous.

I don't know what the blood banks are paying or if this is part of the equation or part of the problem, but I

know for use in research in a non-blood-bank situation, it is just not feasible. They are important, obviously, because false positives in a research setting can generate data that is not--

DR. BUSCH: I agree. I think strategies such as Sue has developed of using alternative EIAs to save that cost on a large number of samples is great. I think FDA early on wasn't terribly supportive of using alternative EIA strategies, but I think recently they have been receptive to that.

DR. KHABBAZ: It is a comment and not a question, Mike, but if my memory serves me right, screening for HTLV I a decade ago, as I remember, was pushed because the tests were there. The manufacturers made them. They were there. We weren't sure about the disease and what we were preventing but they made these tests, screening tests, and pushed and we did.

It is easy for us to sit here in the era, as Jay eloquently defined, the precautionary paradigm and say it is good because we are preventing disease with one little bit and with two possibly very little. I won't get into that argument but, at the time when they pushed these tests, as I recall, they offered--part of the deal was to offer supplementary tests.

You mentioned that, Mike. That was done. To get

to the economic incentive, clearly the incentive--the screening assays is where the economics come into play. Somehow it seems that we have had, over the years, a separation whereas the screening tests--and you have improved tests--are there and where the money is to be made.

Yet, the manufacturers of these screening tests have kind of divorced themselves from the supplemental assays and you are left with what we are left with, talking about orphan tests. They are, in a way, but they are not if you link them to the bigger picture of screening.

DR. EPSTEIN: I agree with what Dr. Khabbaz just said. The agency, however, was criticized for, if you will, holding up the pace of development of screening tests by holding the companies to the standard of having available supplemental tests, at least as in-house services, at the time of approval of screening tests. So the arguments cut both ways.

On the question of whether we could change the approval standard to approve HTLV or other tests as diagnostics independent of the whole question of donor reentry, well, of course we could. But our approvals process is geared toward the product claim. The question is what is the intent to market?

The problem isn't that we couldn't approve them in their own right as diagnostic, it is that if they are being

used to follow up donor screening by EIA, then, in order to understand the false-negative rate, you have to compare it to the sensitivity of the EIA.

So it is more a scientific issue than a policy issue. In other words, we could approve with different labeling tests that had lower sensitivity than EIAs but what exactly do we say in the labeling claim if we don't have a requirement to know the answer?

And then I would make one other observation about trials which is that there is a paradox here because it has been stated repeatedly, well, we had these great RUO tests. But, if they were that great and people believed it-- presumably, they believed it because of data, and the question is why couldn't those data be brought before the agency. If they are so convincing as all that, why can't they be compiled?

So we always get into this conundrum where the test that is not studied through official mechanisms, legal routes, is always touted to be better than sliced bread. But somehow no one can show the agency the data. I think that we ought to ask that question, that if those tests are that good, what prevents them from that being demonstrated under IND or the data otherwise provided.

I think that is important issue. Then one last point about the economics. As you showed, the positive

rates of screening, the repeat-reactive rates, aren't all that different for some of the other markers compared with HTLV. But there is a big difference in the size of the market for the supplemental tests.

The reason for that is sort of external to the blood system. It is because there is a public-health testing role for the other screens whereas, for HTLV, there is no mandate for routine public-health screening in essentially any context for HTLV. That is why there is not a collateral market. It is not that the blood system better supports the economic profitability of the supplementals for some of the other agents, it is just that there is a larger global market that has very little to do with blood screening.

These are just additional observations. I am not really criticizing anything one way or the other, just that these are some of the factors that the committee needs to be aware of.

DR. KHABBAZ: Just for the record, my comments were not meant as criticism to FDA.

DR. HOLLINGER: Thank you, Mike.

The next speaker is Susan Pucie from NHLBI on funding opportunities for small business. That will be followed by Patricia Robuck.

Funding Opportunities for Small Business

Presentation

MS. PUCIE: Thank you. As I am getting the slides set up, I just to let you know this will be noncontroversial because I am here to show you the money.

[Slide.]

Thank you for inviting me to talk about the small-business funding opportunities at NIH. We appreciate every chance to publicize these programs. In the next few minutes, I am going to give you a lot of information but don't worry about taking notes because hard copies of the slides are available. I tried to hand them out and then there are some on the chair in the front.

The National Institutes of Health has two programs reserved for small business. They are the Small Business Innovation Research Program or, for short, the SBIR Program, and the Small Business Technology Transfer Program, or the STTR Program.

[Slide.]

Briefly, the SBIR Program sets aside 2.5 percent of the NIH extramural budget to support innovative research conducted by small business that has potential for commercialization. We do anticipate that that percentage will increase over the next year. The STTR Program sets aside 0.15 percent of the extramural budget to support innovation through cooperative R&D carried out between small

business and research institutions.

[Slide.]

In Fiscal Year 1999, the NIH expects to award $1,520 SBIR and STTR grants for approximately $325 million.

[Slide.]

To qualify for an SBIR or STTR award, the small business must meet these four criteria. You must be an independently owned, controlled and operated for profit U.S. business. You have to have a principal place of business in the U.S., the control of the research facilities where the research will be conducted and you must have 500 or fewer employees.

[Slide.]

In addition, to qualify for an STTR award, the small business must be a partner with a research institution and at least 40 percent of the STTR work must be performed by the small business and at least 30 percent by the research institution.

[Slide.]

Why pursue SBIR or STTR funding? Because over $300 million are available; because this is seed money to fund high-risk projects; and this is not a loan. There is no repayment of the awards. The company retains the intellectual property rights. You get recognition and visibility. This is a potential leveraging tool to attract

capital. And NIH is interested in doing business with you.

[Slide.]

Here is a little information about program mechanics. There are three phases to the SBIR and STTR programs. Phase 1 is to evaluate the scientific and technical merit and feasibility of an idea and the awards are for six months for up to $100,000. Phase 2 is to expand on the result of and further pursue the development of phase 1. SBIR awards are for two years for up to $750,000 and STTR awards are for two years for up to $500,000.

Phase 3 is for the commercialization of the results of phase 2 and it requires the use of private sector or non-SBIR federal funding. I just want to mention here that the numbers that I quoted, $100,000 for phase 1 and $750,000 and $500,000 for phase 2, NIH is flexible about those figures. If you need more time and dollars, if you justify that in your proposal, that will be considered.

[Slide.]

There are three receipt dates for each of these programs. Applications for the SBIR Program are due on April 15, August 15 or December 15. Applications for the STTR Program are due April 1, August 1 and December 1.

[Slide.]

For projects with a very clear development path that have already attracted outside interest, there is also

a fast-track parallel review option. This allows for concurrent submission and review of phase-1 and phase-2 proposals. The funding gap between phase 1 and phase 2 is eliminated or reduced.

The key requirements are that the phase-1 application contain clear measurable milestones and the phase-2 application contains a product-development plan.

[Slide.]

Now, I would like to say a few words about my institute which is the National Heart, Lung and Blood Institute and our SBIR Program. The NHLBI Program fosters research on pharmaceuticals, medical devices and implants, biologics, informatics and biotechnologies for the causes, prevention, diagnosis and treatment of heart, blood-vessel, lung, blood diseases and sleep disorders.

[Slide.]

In Fiscal Year 1998, the NHLBI awarded 162 SBIR and STTR grants for over $35 million.

[Slide.]

Now, more specifically, the NHLBI is very interested in receiving strong proposals from small business in technologies and methods to improve the safety of the nation's blood supply. The following four slides highlight some of these areas. But I will just mention, for example, our interest in assays or agents that cause transfusion-

transmitted disease.

[Slide.]

Equipment and procedures for the collection, separation, processing, preservation, storage, distribution of blood and blood components, computer-assisted systems to improve the blood-donor screening process, management and education systems for more effective and appropriate use of blood products, and methods and technologies for inactivation or removal or microorganisms from blood, blood components and plasma derivatives.

[Slide.]

If you are interested in learning more about the SBIR and STTR Programs, or if you would like to discuss a specific application, please call, fax or E-mail my office and I will be glad to help you or put you in touch with program staff with the right expertise to discuss your ideas.

[Slide.]

I would also like to encourage you to visit the NIH Small Business Funding Opportunities page which is on the Web. Let me mention there is also a model or a sample application there if you are new to writing one that is very helpful to new applicants.

[Slide.]

Finally, you can obtain hard copies of the

official solicitation documents for these programs at this address. The SBIR Program is sort of a fuchsia colored book and the STTR is a blue book. All of this is on the Web but it is easier to see in hard copy.

I hope this information has sparked your interest and I thank you for your attention.

DR. HOLLINGER: Thank you very much.

The next presentation, then, is by Patricia Robuck, Office of Orphan Drug Production.

Presentation

MS. ROBUCK: I have to say that Susan took one of my lines, but I have a couple more. The next one is, "I am here from the government and I am here to help you." That always gets a chuckle.

And Dr. Nelson, are you a plant?

DR. NELSON: No; I am an animal. [Laughter.]

MS. ROBUCK: Oh, no; as in planted in the audience.

[Slide.]

I am from the Office of Orphan Products Development. The one thing that I don't have on here that I should have put on here is my phone number, so any of you that are interested. You should have copies of this as well. My phone number is 301 827-0984. That will get you right to my phone. Or 301 827-3666. That will get you to

the office.

[Slide.]

As some of you, obviously, already know, we were brought into existence in 1983 to try and help industry and the academic community to make products available to persons with rare diseases and disorders. This was signed into law, as I said, in 1983.

[Slide.]

The definition of this; there are two definitions. The original definition was for products with little or no commercial value. It took less than a year for us to realize that that was a very difficult definition. And, therefore, the definition was amended to include disease or disorders that affect fewer than 200,000 persons in the United States.

This is a prevalence figure. It is not an incidence figure. But, for example, in the subject that we are talking about today, incidence would be appropriate use of this and we would be looking at yearly incidence in this particular case.

So we are not looking at the number of people that, perhaps, are HTLV-positive in the United States. What we are looking at is the population of intended us. So, if the population of intended use for this product is fewer than 200,000, then you would qualify.

[Slide.]

Of importance today--I hear people saying that you need some incentives and you need some help with money--is that our office supports only clinical trials. We can't help you, but the SBIR can, in the beginning stages. But we will give money for clinical trials only. These include studies of drugs, biologics, medical foods and medical devices.

The incentives, and there are other incentives under the Orphan Drug Act, are limited to drugs and biologics but the Grants Program goes further. They are to determine safety and efficacy. And the data that is derived from these clinical trials is intended for potential use by the agency.

So what that means is that they must be done under an IND or, in the case of a device, and IDE. We, unfortunately, do not fund basic research. I was intrigued by the amount of money that the SBIR Program has. We have about, I think, $11.1 million this year. But maybe it will be up next year.

[Slide.]

So, as I said, the goals of the Grants Program are to accelerate products getting to the marketplace. We want availability of products under the whole guise of the Orphan Drug Act, but we want to get these products to the market as

fast as we can. As I said devices and medical foods are part of this.

[Slide.]

So what is the process? The first thing we do is we put out a Federal Register Notice. I will tell you at the end, so you have to pay attention when that is coming up. Our office does a review of the application. One of the most important parts of the RFA and the application is the IND or the IDE. It will state very clearly in the RFA that your study must be clinical trial, it must be done under an IND or an IDE that has been submitted to the appropriate division of the FDA at least 30 days prior to the application deadline.

This is a change that has taken place over the last few years. The reason is that we need to make sure that you are ready to start your trial when the funding begins. We also need to make sure that when we review the application that it is a study that can go forward.

The 30 days is so that you are not calling the appropriate division of the FDA every day saying, "When is it going to be approved?"

Once we get the applications in, we get category-specific reviewers and we form ad hoc panels to review these grant applications. Typically, we get about 100 applications. Sometimes, we get a few more, but it

guarantees that the applications, for example, that have to do with blood and blood products will not be reviewed with applications that have to do with other disorders, orthopedics or neurology.

We will do literature searches and we will find the experts in these fields so that even if a product does not get funded that particular year, we will prepare a summary statement and tell you what you need to do to get it funded, perhaps, in the future, where your science is off.

Then we take it to a national advisory council and the grant is awarded.

[Slide.]

We award approximately 20 to 25 new studies a year. It really depends on how much money we have in a given year and where we are going with that, how much money has to go to continuing studies.

The program review criteria that we do, just so that you know exactly what we are looking for in the application is, of course, we have to be sure that your prevalence is under 200,000. We ask you to document that. I have already told you that you have to have an active IND or an IDE.

[Slide.]

And then, when it goes to ad hoc panel review, this is a scientific and technical-merit criteria that we

ask for. It is important to note that we get all of our reviewers from the academic community. We have no one from business on our committee. It is an anonymous process that we never reveal the names of our reviewers for any ad hoc panel.

We do this so that we get the best review and because, a lot of times, there are only a handful of experts in that field. We don't want to discourage anyone. If we are asked to reveal the names of our reviewers, we will give you the names of everybody in our reviewer database, which is presently about 600 reviewers. But it changes. Every year when we have a new panel, we make it up of new people. And we have a rule that we cannot have the same panel twice. So there will always be new members that will be added to this.

These are just the normal things that you would expect to see.

[Slide.]

We look for adequacy of the resources. This is where something like an SBIR other sources of funding take place. I haven't told you yet. The dollar amounts are not great for funding a clinical study. They are $200,000 per year for up to three years but you are also allowed indirect costs. So it can be substantially more than that.

So it is perfectly okay and it is very much

encouraged that you seek other sources of funding as well. Our grants can go to either for-profit or non-profit organizations. It makes no difference to us. We limit it to small businesses, however that is defined.

We want to make sure that you do have the product, that you have justified that budget and that, if you tell us that you need a million dollars and you have only asked us for $200,000, where are you going to get the rest of the money for the study.

Of course, you have to have informed consent and IRB approval.

[Slide.]

We anticipate that the FY 2000 RFA is going to be coming out sometime in July. Right before I left here, I got an E-mail saying that it had cleared general counsel. So I anticipate that it will be in the Federal Register in the very near future.

As soon as it gets up on the Federal Register, then we will also put it on our website. So if you are looking for it, you can call the office. You can E-mail us and we will send you a copy of that. We will have two due-dates. The first one is November 15 and the second one is April 1 of the Year 2000.

Our money is tied to fiscal year which means that we have to spend all of our money by September 29 of the

year 2000 when the money becomes available. We will do just that. So it really makes very little difference if you apply in November or whether you apply in April of any year. What it will do, if you have a stupendous score when you go to the ad hoc panel, you might get funded about two or three months before the grants that were submitted in April.

But we take all of the applications and we put them all together and we fund until the money goes out.

There is one other point that I would like to make and that is if you do get a grant or if you need any information about grants or if you have an orphan product, we have a staff of people--it is not a huge staff--but we have a staff of people that will help you walk through this whole process. We are delighted to have all comers and we would welcome applications or phone calls from anyone that is interested in developing these products.

Thank you.

DR. HOLLINGER: Will you write the grants, too?

MS. ROBUCK: No; but I might be able to tell you what to put in there and what not to put in there.

DR. HOLLINGER: Thank you very much. Appreciate it.

We are under a little time constraint here and I really must apologize to the committee and everyone here. But, apparently, there is something outside, a class reunion

or something, that is going to be barging in here before too long. We have got a little bit of extra time, but I do want to give everybody a chance to talk and then we will have to come back to this.

So if you will bear with me, let's go through--we have several speakers who have asked to speak on the HTLV supplemental test. They have five minutes, each one, no more than that. The first one is Dr. Michael Ussery from Innogenetics.

Open Public Hearing

DR. USSERY: I have slides for ten minutes, so I will cut it. Dr. Busch has actually already mentioned our product.

[Slide.]

This product was just approved on the 15th of June in France on the basis of three studies that I will mention and that are published. They are retrospective studies of multiply reactive samples.

[Slide.]

It is a line immunoblot assay for the confirmation of antibodies to HTLV. You can use either serum or plasma.

[Slide.]

There are control lines on the strip as well as the confirmatory lines that Dr. Busch mentioned to you and the discriminatory lines that allow a determination of a

HTLV I or II infection. I did provide handouts to the committee. It looks like most of you have them.

There are a few slides that are not in those handouts and I will be happy to E-mail anyone a powerpoint including those.

[Slide.]

This is a description of the controls. I think that might not be in the handout.

[Slide.]

There is a semiquantitation that is allowed by the strip but it is certainly not a quantitative assay. The different antigens, either recombinant proteins or synthetic peptides that go up to make the materials that are on the strips.

[Slide.]

The test procedure involves an overnight incubation with the sample. Often, that is started as soon as the reactive result is gained on the initial test. Once that result is there, the labs often put these on overnight and then a couple of steps the next morning.

[Slide.]

This is an example of a result on a strip that shows that HTLV I pattern. So it is positive in the confirmation lines in the middle, the last two, and in the first two, one specific discriminatory line in the bottom

panel.

[Slide.]

This is one of the studies that was used for approval in France--this is from the Rega Institute in Belgium--looking at a number of samples, comparing them with the GeneLabs 2.4 assay. In this case, you can see a negative that was called positive by the GeneLabs. This was confirmed negative by PCR. All of the discordant results that we have here were confirmed by PCR when we had cells.

There was a call of a 2 with the GeneLabs. That was determined to be a 1. And that was additionally confirmed by serotyping. We didn't have cells to do that.

[Slide.]

One of the big problems with the 2.4 western blot as well as the 2.3 is the number of indeterminates. We determined that 24 of those were negative and confirmed all of those by PCR. There are a few other differences in the chart that you have. Those were all confirmed.

[Slide.]

This western blot of indeterminate was confirmed to HTLV II both by the INNO-LIA and by PCR. A number of indeterminates, most of them fall out as negative.

[Slide.]

Obviously, the LIA is not a western blot. It is a plastic-bag strip. It can be automatically read as well as

manually read with our auto-LIA and our scanning procedures. There are control lines and antigen lines fixed on the membrane.

[Slide.]

Just some characteristics, semi-quantitative.

I think that is all the slides. In the interest of time, there are two other studies that were used and I only received the publication for one study on Monday that was from the Journal of Clinical Microbiology in May of this year. That study was in Brazil. There we had 18,000 donors that we looked at which 292 repeatedly reactive samples. And, by western blot, there were 172 indeterminates out of that 292. And we were able to show and confirm by PCR that 153 of those were actually negatives.

There were 54 samples that were nontypable but we were able to type. There were actually 69 typables. Our test could type 54 of those 60. There was one other study that was performed in France, and I have the reference for that as well, that was done on commercially available samples.

So I think, in the interest of time, I will stop.

DR. HOLLINGER: Thank you very much.

The next speaker is Ms. Birgit Fleurent from GeneLabs Technology.

MS. FLEURENT: Good afternoon, everyone.