[Slide.]

I am going to put some overheads up but I think I will probably save you three minutes of time because, kindly, most of the presenters earlier did talk about the GeneLabs blot and I think the blot has been used, certainly, in other parts of the world as well as in the U.S. So I am not going to go into detail on the performance of the product but just give you an overview of some of the issues that we have faced.

[Slide.]

Just to reiterate, the product is available in the United States for research use only. The labeling has been approved both by CDRH and CBER as a research-use-only product and is offered as such. We do sell this product, as Dr. Busch pointed out, widely throughout Europe. It is approved by the French Agence de Medicament as well as the Portuguese Inframed. We sell the product additionally in Latin America and it is registered in various parts of Asia as well.

[Slide.]

We have faced two major issues hindering the submission of a license application. Both of these were pointed out earlier so I will just go briefly through. We certainly value the importance of having a research-use-only product used the way it is designated to be used.

One of the problems we had in 1997 when the product was first held and relabled is the length of time it took to go through that process. There was a disconnect, we felt, between CBER and the local compliance office. It actually took six months to go through the relabling effort and cost us significantly both in the relabling process and in the loss of revenues. So that was an issue that we worked through but that did cause a significant delay for us.

[Slide.]

And then, as already pointed out, the economic feasibility is questionable. I was very pleased to hear the presentations just now by Susan and Patricia and I am sure you will be hearing from us next week. But, because of the population, and going through internally the development costs that would be needed to meet the current regulatory criteria, the potential revenue just doesn't justify the expense.

[Slide.]

We have considered options internally. Some of these were just mentioned. The orphan products grants I think is something we do want to pursue at this point. Individual investigator INDs have been discussed but we haven't taken any of these to the agency as of yet.

[Slide.]

Then, last, again as has been discussed earlier today, we would like to have assistance. We do realize and we believe that there is diagnostic significance and benefit to both the laboratory and the patient in having supplemental tests approved. So we would like to see more public awareness or contribution and commitment towards some of these additional sources of funding.

Thank you.

DR. HOLLINGER: Thank you, Birgit.

The next speaker was to be Dr. Bentley Moyer, but I think Dr. William Andrews is going to speak in his behalf for Chiron.

DR. ANDREWS: Hi. My name is Dr. Bill Andrews and I am currently a development scientist in the Blood Testing Division at Chiron Corporation. I would to thank the committee for the opportunity to provide a statement regarding the availability of the supplemental tests for the detection of anti-HTLV I, II.

Several years ago, Chiron Corporation, through its joint business with Ortho Clinical Diagnostics, began development of the supplemental test for the detection of anti-HTLV I, II. This test, which is based upon Chiron's RIBA strip immunoblot assay technology utilizes both recombinant antigens and synthetic peptides encoded by the specific strains of HTLV I and HTLV viruses.

Our early development data indicated that the performance of the tests could provide accurate and meaningful results to blood bankers and clinicians in the counseling of donors and patients who are repeatedly reactive by an anti-HTLV I, II screening test. However, further development of this RIBA EIA test for HTLV I, II as well as an automated system for completing RIBA SIA tests was halted due to our limited resources and the concurrent need to complete development and bring to market our supplemental test to serve a greater public-health need, that is HCV.

While it is now possible to turn our attention to developing new products that fulfill other public-health concerns, we are obligated as a business to understand both the scientific and economic feasibility of fully developing a product which meets the requirements of the healthcare community and the FDA.

With respect to our anti-HTLV I, II supplemental tests in development, a recent collaborative study with Dr. Michael Busch of the Blood Centers of the Pacific and Dr. Sue Stramer of the American Red Cross has indicated that the specificity of the test is a significant improvement over a current means of supplemental testing such as secondary EIA, IFA or research western blots.

Even so, we believe that further development of

the test may be required to fully meet the needs of the blood banking and healthcare communities. Our difficulty has been to further justify any continuing product development or licensing efforts through the allocation of resources given two very significant factors.

First, the anticipated need for such a product in terms of numbers of tests required per year at an expected cost per test is such that our costs for product develop in clinical study would not likely be fully recouped within a reasonable time period.

Associated with this is the lengthy and arduous regulatory approval process. While we believe that the regulatory requirements, themselves, are, in principle, appropriate for blood-screening products, the reality of this process is such that it adds a significant additional cost to the development of the product.

Unfortunately, the combination of a low anticipated market need and a lengthy regulatory approval process has put Chiron in the position of making a difficult decision moving forward. As it stands today, the Chiron Ortho joint business is capable of fulfilling this public-health need.

However, the above-mentioned factors effectively preclude us from moving forward into an environment of both greater public health and business needs. In spite of this,

Chiron would be willing to have further discussions with the FDA in order to understand and further evaluate any creative pathways for streamlining the regulatory approval process.

Furthermore, in consideration of the circumstances surrounding the need for supplemental anti-HTLV I, II tests, we believe that it would be important for some federal funding to be made available to help offset the costs of product development and clinical study similar to what has been done with the development of nucleic-acid tests for blood screening through the grants from the National Heart, Lung and Blood Institute.

Assuming that a suitable product could be made available, Chiron believes that it would also be appropriate to grant some extent of market exclusivity following FDA approval of the supplemental anti-HTLV I, II product through a program such as or similar to the Orphan Drug Act.

Through these mechanisms, we believe that there may be a sufficient incentive for potential manufacturers to pursue the complete development and FDA approval of a supplemental anti-HTLV I, II test and, thus, fulfil the identified public-health need.

Thank you.

DR. HOLLINGER: Thank you.

The next speaker is Dr. Tony DeMarco from Abbott Laboratories.

DR. DEMARCO: Good afternoon. I am going to actually talk about more of a follow up to Dr. Sue Stramer's presentation on the dual EIA algorithm.

[Slide.]

Consistent with the two EIA testing algorithm presented by Dr. Stramer, we would like to present data obtained using the two-test algorithm that utilizes the Abbott PRISM HTLV I, HTLV II test following its approval in the United States and the currently licensed HTLV I, HTLV II EIA.

[Slide.]

A description of these two tests is shown on this slide. The Abbott PRISM HTLV I, HTLV II test is a viral-lysate-based direct chemiluninescent immunoassay with a repeat-reactive rate from U.S. clinical trials of 0.07 percent. The Abbott HTLV I, HTLV II EIA is an indirect enzyme immunoassay with a repeat-reactive rate of 0.16 percent from reporting sites in the United States, year to date 1999.

We believe that these tests fulfil the criteria established for different tests as defined in the recent FDA guidance document for HTLV testing.

[Slide.]

The evaluation of this two-test algorithm is performed by testing approximately 2200 random donor blood

specimens at four geographically distinct testing sites around the United States and one site in Canada. Specimens that were repeat-reactive by the PRISM HTLV I, II test were tested by the Abbott HTLV I, II EIA and, according to the algorithm, concordant reactive specimens were evaluated by western blot.

The results of the testing algorithm are shown on the next slide.

[Slide.]

In this evaluation, there were sixteen specimens or 0.07 percent of the total number of donors tested that were repeatedly reactive by the Abbott PRISM HTLV I assay. Twelve of those specimens were nonreactive in the HTLV I EIA test and no further testing would be required according to the algorithm.

Four of the specimens, or 25 percent, or 0.02 percent of the overall number, were repeat-reactive by the Abbott HTLV I EIA and those went on for further western blot testing. Two of those were negative and two were indeterminate.

Although the data are not shown here, the reverse algorithm was also evaluated where we tested the same set of specimens by the EIA first followed by the PRISM HTLV test. In that case, all of the discordant specimens--that is, the specimens that were repeat-reactive on either of the tests

were evaluated by western blot and by the RIPA. None of those samples were found to be positive.

Because there were no true positive specimens among this set of donors, we evaluated a large set of previously identified positive specimens using this algorithm.

[Slide.]

In this study, we took 601 specimens that were identified previously to be positive for HTLV I or HTLV II. It was actually approximately an even mix of the two types. 100 percent of the specimens were repeat-reactive by the PRISM test and by the EIA test. Of course, all were positive upon western blot testing.

[Slide.]

In summary, the PRISM HTLV I, HTLV II test shows high specificity at 99.93 percent. When used in conjunction with the Abbott HTLV I, HTLV II EIA as a second screening test, only 0.02 percent of donor specimens would require testing by western blot.

This dual-test strategy, employing the PRISM and the EIA test, will reduce the overall number of samples requiring western blot, thereby reducing the number of samples with indeterminate results.

So, in conclusion, the data are similar to those presented by Dr. Stramer except that the number of specimens

requiring supplemental testing is expected to be lower with the introduction of the PRISM HTLV test.

Thank you.

DR. HOLLINGER: Thank you.

The final person who asked to speak today is Dr. Busch who is going to talk from the AABB viewpoint.

DR. BUSCH: Let me just go to the bottom line here. I think you were all distributed the statement which basically Steve Kleinman developed and walks through all the issues we have heard today.

Just to go to kind of the bottom line, I think the unavailabity of appropriate confirmatory tests has not only precluded appropriate donor notification but it has also hindered epidemiologic surveillance of HTLV in the donor base. The AABB encourages FDA to consider the following options.

First, to encourage manufacturers to improve the specificity of FDA-licensed screening tests. The downside of that, as you have just heard, is these alternative EIA strategies and better specific tests leads to an even smaller market for the supplementals, so it is even more problematic issue around bringing the confirmatory tests forward; license screening tests that improve specificity as compared to those available today; encourage manufacturers to develop supplemental test strategies such as those used

in their clinical trials for FDA approval; continue to allow the use of alternative supplemental testing strategies such as the dual EIA testing algorithm; and provide regulatory pathways that both encourage manufacturers to develop supplemental-test kits for use under IND and then provide streamlined mechanisms for their widespread availability to the marketplace.

This must include simplified approaches to clinical trials, systems validation and FDA licensure mechanisms. If FDA considers that issues of donor reentry or consignee notification would interfere with the development of a streamlined approval mechanism, then we recommend that FDA consider using such mechanisms to approve the use of supplemental-test results for donor counseling and not for regulated manufacturing function.

DR. HOLLINGER: Thank you, Michael.

Committee Discussion

DR. HOLLINGER: I am going to open this up for committee discussion at this time. I am going to close the public hearing. Any discussion from the committee? Any issues.

I have some difficulties with these assays. What is often done is an EIA or a regular test is done. You get some repeat-reactives. Then, the non-reactives, you sort of ignore as if the gold standard has been the EIA test. Then

you go down this group over here and you find that some are positive and some are negative, and so on.

Really, I guess if you are setting something up like this, you would want all positive western blot. If you say the western blot or RIBA or whatever the assay is, any of the strip assays and so on, if they are the gold standard of what is a true positive assay, you would think that you would start with those and then go and look and see how the regular tests come out, because this idea, often, of using a couple of different EIA tests saying, "Well, one is good and the other one is maybe not so good. Which one are we going to count on? Which one is going to be our gold standard?"

Can somebody go over this with me, help me to understand this a little bit?

DR. BUSCH: I think you are referring mostly to this concept of trying to use an alternative EIA strategy. Indeed, I think Sue Stramer remarked on that with first showing that the two EIAs seemed to be head-to-head sensitivewise. So if you took two positives that were kind of borderline reactive on your screening test and then you tested them with the alternative licensed HTLV test, they were reactive on that test, too.

But then she actually started to use it and, in fact, was uncomfortable doing further testing on the discordant EIA nonreactives out of concern that if some of

those were found to be positive, and suspect that many of them might be false positive because of the supplemental test, that it would be a regulatory problem.

So it is for that reason that the study should describe we actually did, as an unlinked study, and we did take on to confirmatory testing both the RIBA and the western blots, even the samples that were alternative EIA nonreactive to ask that question of was this alternative EIA actually missing some true infections.

What we found was a handful of false positives on some of these supplemental tests but we further took them on to IFA and RIPA and the new GeneLabs antigen and showed that they were false positives. So those are the kinds of studies that do need to be done but they have to be done with caution because there are regulatory implications in the donor setting.

But I am convinced, at this point, that the alternative EIA strategies are sensitive meaning that the true infections are being sorted into the dual reactive group. In the donor setting, only about 20 percent of those dual reactives are real. And that is why we need, beyond that, a supplemental--

DR. HOLLINGER: I guess that is what I wanted somebody to--I guess, again, maybe, Sue, you can straighten it out for me again. Let's just take the two that are

positive, the ones that are concordant, and what their response is on the strip assays and so on and then the ones that are discordant with either one, in either direction, and what theirs were on the strip assays, how they came out in terms of positives and negatives.

Were there positives in some of the groups that were discordant?

DR. STRAMER: Yes.

DR. HOLLINGER: And were there positives in the ones--and what are the percentage of positives in the ones that were concordant?

DR. STRAMER: For concordance, what I showed is about 24 percent whether it was from the 7 million donors that I showed or the smaller study we did with blood systems. It was pretty consistent between 10 and 25 percent of concordant EIA repeat-reactives were western blot or RIBA-positive.

So whether we use the recombinant immunoblot or western blot, between 10 and 25 percent confirmed positive which we believe is still an overinflated number. So, if you look at the discordant category, the only ones that we did further supplemental testing were for the 200 BSL samples and the 128 Red Cross samples.

For the samples on supplemental testing that were discordant from BSL, there were 150 samples. Of those 150

samples, none--zero--were RIBA-positive, were Chiron RIBA-positive. None. So all of the discordants were either negative or indeterminate, and indeterminate is something that you would expect. So, zero out of 200.

For the Red Cross part of that equation, there were 128 samples. 93 were discordant. Of those 93--that is, reactive only by one EIA and not another--three, we found as RIBA-positive. When we found those as RIBA-positive, I called Mike and I said, "Why did you get me involved in this stuff?"

And Mike says, "Well, maybe they are true positives." And I said--I won't repeat what I said. I said, "We need to investigate these further." So then, what we did, is we know that p21--first of all, we did a western blot on them. On western blot, they all showed incredibly strong p21e reactivity which is what drives the positivity even on the RIBA test.

So we knew that there was something in common, which was p21e. Because p21e has historically been associated with false positivity, that is why we tested it then on the GD21 which is the GeneLabs construct that has eliminated this area of p21e that has been associated with false positivity.

So all three samples we found to be GD21-negative. Because I was still concerned that p21e is not the only

criteria we should use, we further sent them to what I still consider the gold standard for HTLV which is radioimmunoprecipitation assay. The only person on the planet that I know who still does this testing is California State.

So we sent them to Janice Diggs at California State and she did a viral lysate HTLV I and HTLV II immunofluorescence assay and also did RIPA. And they were negative on those.

So all we had, basically, was isolated p21e reactivity in the discordant EIA-reactive samples. Really, if you look at the donor demographics of these individuals, these are normal, routine blood donors who have absolutely no risk of HTLV. In fact, most of our confirmed positives fall in that category as well. So even if I showed prevalence of 10 per 100,000, if I go further back into the Red Cross history, that is really where Mike started.

Mike started showing the Red Cross data where, in the beginning, when HTLV tests were first licensed, we used two supplemental tests, either western blot or RIPA, and then we substituted the western blot for a single p21e test which is also used in combination with RIPA. HTLV is a very difficult agent to get a good supplemental test for.

There just has not been--well, it is the same thing. There hasn't been good development and

commercialization of that.

So I hope I answered your question.

DR. HOLLINGER: I appreciate it.

DR. NELSON: Have all of these assays been evaluated in populations that have higher prevalence and that is known, like Japanese populations for HTLV I or the Indian--the places where HTLV II is endemic? Is anything known about the population where the rate of true infections is higher, all of these assays? How do they perform there?

DR. BUSCH: The published papers that there are on each of these tests have looked at large numbers of endemic pedigreed, PCR-pedigreed, infected people from all these different geographic settings. So they seem to have very good sensitivity, to my read.

DR. HOLLINGER: I think something has come out here from some of the people who have spoken is this idea of what is available from the government standpoint in terms of funds. I think that is an important issue that has been brought here and, hopefully, they will be utilized.

Anyone else have any comments? I am not sure, Jay, other than to get this issue out in the open, what you want from the group here.

DR. EPSTEIN: We have been frustrated for some time, really since 1988, about the lack of development of commercial supplemental tests for HTLV I and now HTLV II.

We wanted to bring forward our best thinking on the dimensions of the problem trying to illuminate what the apparent obstacles are and what the apparent remedies might be.

We are really just looking to A, make this public and B, to see if there are any additional suggestions from the committee members. My own view of the situation is that the remedy that is needed is really economic. FDA historically does not deal directly in that area. I think what is needed is to find a way to subsidize the tests under GMP manufacturing.

One dimension that really didn't come out today--a lot was said about the cost of trials, but that is a one-time, up-front cost. It gets amortized over a period of years. The real problem is that the GMP manufacturing can't be paid for by the sales. So the question is how do you subsidize continued manufacturing under GMP.

I don't know the full answer but, to my way of thinking, one possible answer is to figure out a way for screening to subsidize supplemental testing. There are many ways that one could try to do that whether those would be fund transfers from organizations, surcharges at the blood unit, vertical integration of screening companies.

You can think of ideas, but the bottom line is that the money lies in screening but there is a need for

confirmation. The demand lies with the blood community. There should be a way to figure out how to link these things up.

The other thing that I would say is that FDA can show flexibility in terms of the trial requirements based on what data we can accept for review. What I am hearing is that there is lots of clinical data. It just hasn't been gathered under INDs. That doesn't preclude the agency from examining it if it does meet standards; in other words, if the human subjects of investigation were treated in accordance with Helsinki accords, if there are evaluable records, if the product can be shown to have been consistent during the course of the trial, et cetera, et cetera, et cetera.

So one shouldn't assume that because the data that exists weren't already obtained under IND or they were foreign data that we can't look at those data. We potentially can but it still has to meet U.S. standards. So I think there is a set of issues and I think it is very encouraging that there is continued development in the industry. We just have to figure out a way for the products to be developed under U.S. law.

DR. NELSON: Could the FDA somehow require that a screening instrument go beyond the purpose of just excluding potentially high-risk donors to the point of not only

excluding them but also notifying them of their health status, therefore requiring some sort of a supplemental evaluation of a positive screening test.

In other words, the approval would not be only the initial screening test but some sort of a process that would affectively deal with the potential false positives in that screening.

DR. EPSTEIN: Again, we took that approach in the mid-80's. We were successful initially with the HIV test in that the companies offering the EIAs offered in-house testing services for supplemental testing. The quality of those tests was highly variable and there was a lot of criticism over false-positive results and false-negative results of those tests that had not been evaluated as rigorously as the screen.

We then attempted to do the same thing in the arena of HTLV but we were heavily criticized for holding up HTLV screening. So we allowed them to go their own way, partly with this result. And then, also, as you see, there is the problem that when we have taken the compliance posture on unapproved tests being marketed that were approved for research-use-only and then were commercialized for clinical use, the market then dried up.

So the problem is that we need to figure out a way for companies to play by the rules. But we can continue to

encourage the companies that have screening tests to provide supplemental-test services. I am not sure that the best mechanism is FDA regulation. I think the consumers should demand it.

If they didn't sign contracts with test-kit providers of the screening tests unless they offered supplemental testing, this environment would change. I think that there is a lot of power in that kind of market leverage. It doesn't mean that the screening-test manufacturers have to manufacturer it. They could create business partnerships with other manufacturers that know how to manufacturer it.

So I just think that all the possible options haven't been exercised and that not everything needs an FDA regulatory solution.

DR. HOLLINGER: When you have something like an orphan drug or something like this where you finally license to one company and you sort of prevent, basically, competition from others so that they can actually get a toe hold--if you have several companies there, then that creates a little problem, particularly if you are looking at this where I think the last one I saw was you take 20,000 and you get 16 positives, so that would be what, out of 2 million? It was be 1600 positives, and so that would be maybe 8,000 positives maybe out of the blood supply.

If you have to separate that out into four or five different companies, it is going to be tough. It seems to me that if you are going to do this, then you are going to almost have to do, like the orphan drugs sometimes. You say, "We are going to license this to one company." And that's it, to me if you are going to have anything that is commercially feasible.

Or the government is going to have to make their own test which is something you haven't gotten into. But for something like this, that would be the other thing, that the government do this.

Any other thoughts?

DR. FITZPATRICK: Since Organon is not here and Abbott is, I just had one question since, obviously, Organon and Abbott won't qualify for an SBIR or an STTR, are you partnering or involved in providing research money to a small company to develop a partnership for this to help offset it?

MR. KLAMRZYNSKI: Matt Klamrzynski from Abbott. We continually have collaborations with firms but to give you any specifics right now, no; we don't have any.

DR. HOLLINGER: But that is a possibility, I suspect. Wouldn't it be?

MR. KLAMRZYNSKI: Yes. It would be a good way to work, a large company work with a small company, get the

SBIR money and provide them their expertise in helping develop the assay.

DR. STRAMER: Just to address some of Dr. Epstein's comments. Having been with industry now in the blood banks, kind of you do see both sides of the equation. I have called all of the companies. It has been very impossible to tie these to contracts because neither large manufacturer doesn't have supplemental assays for all markers. Some may have for one, and some may have for the other, so it is very difficult to get a full plate of exactly what you need.

The companies are moot as far as answering the questions. Whether the companies partner with small companies to provide, as the comment was just made, additional incentive, well, we at the screening test wanted partner either with RIBA or with Innogenetics--we have tried that route as well. It has not been successful.

So then, as Mike said, in the AABB comment, well, now we think maybe if do partner INDs like we do for NAT, we can take some of these small companies and show them that the FDA obstacles are not insurmountable and, with good data, we can get the job done.

So we are trying, now, to pursue the dual IND strategies. But all the small companies are so fearful of what manufacturing costs they have to do, the cost of

clinical trials, and what happens if we get a false negative in our clinical trials? So what I have responded to them is, so you put it in your labeling. That is what you have got. And then, "Buyer beware."

We just have to deal with it from that. At least something would be available. But there is a tremendous amount of inertia because of the fear that is involved in moving forward. I don't really know what that is there, but it is.

DR. HOLLINGER: Any other comments? You can see that this is, obviously, Jay, a real problem, as she has just spoken to, the fact that the small companies are concerned about not being able to make it. A large company could probably do it and write it off, possibly write it off on these small areas of things like this. You buy things in the supermarket that are writeoffs--with small stuff like this.

A lot of money is made in other parts of their products and one has to consider that, too. Sometimes, you have to step up to the plate, do the right thing.

DR. OHENE-FREMPONG: What is the precedent for the CDC establishing a test that may not be available commercially but which could serve blood banks, in this case.

DR. HOLLINGER: Sort of as a reference lab?

DR. OHENE-FREMPONG: Like a reference lab.

DR. HOLLINGER: With that small number, it could be like a reference lab.

DR. KHABBAZ: I really have no comment. There are a number of other examples of areas of orphan diagnostics and orphan vaccines and others that we struggle with. There are no easy answers.

DR. HOLLINGER: You don't have an answer.

DR. KHABBAZ: No.

DR. NELSON: They do for parasitic diseases. That has been one area--or unusual diseases.

DR. KHABBAZ: But they are rare. You are talking about--we heard the screen results and we heard the numbers. This is larger than any other disease or agents that we have offered reference to. There is no precedence, given the numbers and the size of this, for offering reference confirmatory--

DR. HOLLINGER: If there are no further comments, then I am going to close the meeting at this time. The next meeting of the BPAC is September 16 and 17. We will let you know where it is going to be.

[Whereupon, at 3:10 p.m., the meeting was adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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