DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE SIXTY-SIXTH MEETING

VOLUME I

Thursday, June 15, 2000

8:00 a.m.

Holiday Inn 8777
Georgia Avenue
Silver Spring, Maryland

P A R T I C I P A N T S

F. Blaine Hollinger, M.D., Chairman

Linda Smallwood, Ph.D., Executive Secretary

MEMBERS:
John M. Boyle, Ph.D.
Mary E. Chamberland, M.D.
G. Michael Fitzpatrick, Ph.D.
Richard J. Kagan. M.D.
Marion A. Koerper, M.D.
Jeanne V. Linden, M.D. B.
Gail Macik, M.D. Mark A.
Mitchell, M.D.
Kwaku Ohene-Frempong, M.D.
Terry V. Rice
Paul J. Schmidt, M.D.

NON-VOTING REPRESENTATIVES:

Katherine R. Knowles, Consumer Representative
Toby L. Simon, M.D., Industry Representative

TEMPORARY VOTING MEMBERS:

Paul R. McCurdy, M.D.
Kenrad E. Nelson, M.D. Carmelita U. Tuazon, M.D.

C O N T E N T S

T E N T S(Continued)

P R O C E E D I N G S

Conflict of Interest

DR. SMALLWOOD: The following announcement is made a part of the public record to preclude the appearance of a conflict of interest at this meeting. Pursuant to the authority granted under the Committee Charter, the Director of the FDA's Center for Biologics Evaluation and Research has appointed Dr. Kenrad Nelson as a temporary voting member, and the Senior Associate Commissioner for the Food and Drug Administration has appointed Dr. Carmelita Tuazon as a temporary voting member for the discussions on the development of rapid HIV tests.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all relevant financial interests reported by the meeting participants. In the event that the discussions involve other products or firms not already on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

With respect to all other meeting participants we ask in the interest of fairness that you state your name, affiliation and address any current or previous financial involvement with any firm whose products you wish to comment upon. If there are any declarations to be made at this

time, we will accept those. If not, then I will move forward with making a few announcements at this time.

First, I would like to introduce the members of the Blood Products Advisory Committee. When I call your name, members, would you please raise your hand? First we will begin with Dr. Blaine Hollinger who is the Chairperson, Dr. John Boyle, Dr. Jeanne Linden, Dr. Ohene-Frempong, Dr. Gail Macik, Dr. Paul Schmidt, Dr. Michael Fitzpatrick, Miss Kathy Knowles, Dr. Toby Simon, Dr. Mary Chamberland, Mr. Terry Rice, Dr. Marion Koerper, Dr. Richard Kagan, Dr. Paul McCurdy.

Absent from this meeting are Dr. Norig Ellison, Dr. Daniel McGee, Dr. David Stroncek and Dr. Sherri Stuver. We will have with us for this meeting, as temporary voting members, Dr. Carmelita Tuazon and Dr. Kenrad Nelson, and we will also have as a guest of the committee Dr. Raymond Koff.

I would just like to announce that out on the table there is information regarding a workshop on recruiting blood donors. It will occur July 6th and 7th. You may pick up that information at the table outside.

So that our proceedings will move smoothly, we are asking that cell phones preferably be turned off, however, if you must have them, that they be turned down low so that the ringing will not interfere with the proceedings. Also, if you would be mindful that we have a full agenda today so

that all speakers will be prepared to speak when called upon and that you will adhere to the time frames that we have allotted.

At this time I would like to turn over the proceedings of the meeting to the Chairperson, Dr. Blaine Hollinger.

DR. HOLLINGER: Thank you, Dr. Smallwood. Welcome, everybody. We have a very busy day and a half. The last meeting I attended was a few weeks ago, where Paul Brown was chairing the meeting. I noticed that he had a gavel and I told Linda that I needed a gavel up here.

[Laughter]

We do have a busy meeting today. We are going to have several updates, both to start off this morning as well as tomorrow morning. The two major topics today -- one is going to be on the potential for plasma pool screen by nucleic acid testing for HAV. There will be some questions about that, and potential recommendations from the committee. This afternoon will be pretty much devoted to HIV rapid testing, again with some recommendations and discussions from the committee. Then, tomorrow there will be a session on leukoreduction, again with the same format.

Since we do have a big morning, we are going to start off with the committee updates, and the first committee update will be a summary of the PHS Advisory

Committee on Blood Safety and Availability meeting which was held April 25th and 26th, and Dr. Nightingale is going to give us an update.

Committee Updates

Advisory Committee on Blood Safety and Availability

DR. NIGHTINGALE: Good morning and thank you. Dr. Hollinger, I don't think that you will need to use that gavel for me because as soon as my presentation is completed my vacation begins.

[Laughter]

The advisory committee did meet on April 24th and 25th, and it made five recommendations. When I spoke to you in March I indicated that our deliberations on error and accident management in transfusion medicine were continuing. The first of the five recommendations made by the advisory committee is lengthy but uncommonly literate for advisory committee recommendations. I will, nevertheless, refrain from reading it to you in its entirety but the meat of the issue is as follows:

The advisory committee recommended that error management systems should acknowledge the rights of patients to know of any risk or harm suffered as a consequence of any error or accident related to blood products received. At the same time, there should be statutory protection from disclosure for voluntarily reported information and quality

assurance activities that are not associated with potential or actual harm, provided that the information is also not associated with reckless or intentionally harmful acts.

These error management systems should complement and not replace current regulatory activities, notably but not exclusively, in the area of product safety. All analyses of collected data should be made available in a timely manner to regulatory agencies, national transfusion medicine surveyance programs and other participants in reporting systems.

While I think the god or the devil is in the details, the feeling within the advisory committee is that its immediate charge was accomplished to lay a framework for ways to support the implementation of more effective error management programs.

In a brief paragraph of this recommendation, the advisory committee recommended that Congress should appropriate sufficient funds to develop these systems and for infrastructure sufficient to support and maintain them. In the Fiscal Year 2001 budget, Congress should stipulate that these funds should not be reallocated for other purposes and that no other funding should be reduced because of the availability of these funds. Funds necessary to maintain these systems should be appropriated annually.

I know that Dr. Hollinger receives a copy of all

the mailings of the advisory committee, and I believe that they are, or certainly can be, distributed to the other BPAC members. For the public, these are available on our web site, which is www.dhhs.gov/bloodsafety. The web site is slightly less clunky than its predecessor.

The advisory committee made four other recommendations, and the second and third are also directed at Congress. Although I believe the advisory committee was aware that it is the Secretary of Health and Human Services and not Congress that it advises, nevertheless, the Congress is interested in the deliberations and these have been communicated to the Congress.

The second of these recommendations was that there is a small but non-zero risk associated with the use of blood products or plasma derivatives that cannot be eliminated with current technology. The advisory committee, therefore, supports the prior recommendation of the Institute of Medicine and of others that a prospective national system to compensate recipients for injuries or death caused by blood products or plasma derivatives, and not associated with reckless or intentionally harmful acts, should be enacted and funded by Congress.

This is clearly a complex issue. The Institute of Medicine and others have previously recommended it. Of course, the details here that the advisory committee did not

address are how to identify who should be compensated and what is just compensation. So, I don't anticipate immediate reaction to it but this is clearly, like the first issue, an issue that goes beyond the scope of either the advisory committee itself or, for that matter, we believe the Department. So, this at the moment was directed to Congress for further action and we will see, in an election year and afterwards, what becomes of it.

The third of the five recommendations is of substantial interest to the blood community. To summarize, there is a "whereas" at the beginning -- safety and availability is dedicated to ensuring patient access -- it goes on though -- the advisory committee, consistent with prior recommendations, recommends that the Secretary and Congress support legislation to ensure fair and accurate reimbursement for inpatient blood-related products and services. Such legislation should provide sufficient funding to account for increased blood-related costs, including those associated with new blood safety measures, and require that these costs be reflected in annual updates of inpatient diagnosis related groups.

Again, this is a complex recommendation. I think the advisory committee has stated its position and from this point on it is for the Congress and the Executive Branch to take further action.

The fourth of the five recommendations, the advisory committee recommended that HCFA promptly distribute guidelines for coding and billing for its outpatient prospective payment system. I believe that you will have seen in the papers that the implementation of that system has been delayed for 30 days so that recommendations, such as this one for appropriate implementation, can be effected before the outpatient PPD is implemented.

The final recommendation of the advisory committee in April was that, recognizing the significant economic issues currently affecting the blood system, the advisory committee seeks to review the role of various considerations and decision-making related to new and existing blood safety measures. Underneath that somewhat opaque language is a further discussion of the realities of the transfusion business -- using that word intentionally -- and what the government can do to provide relief not only for the business but for the people for whom that business is intended to help. We will meet for a single day on August 24th. I would be glad to answer any questions.

DR. HOLLINGER: Steve, there was a lot of discussion at this meeting on compensation of people who perhaps may develop some diseases from blood products and so on, as well as reimbursement for these very expensive items which we discuss frequently. In terms of the one about

compensation, was there any discussion about similar ideas as to what is done with vaccines where so much of a vaccine product goes into a pool to pay for that so that, for example, any blood product that is given a certain portion would go to make up some money available for problems that develop?

Secondly, how does this work? I mean, I know this goes to the Secretary of Health but what committee does this go to in terms of reimbursement and how does this finally get into the Congress where it perhaps can be acted upon?

DR. NIGHTINGALE: In response to the first question, the discussion about no fault was really lead by Mr. Justice Krever's presentation to the committee. When I spoke to you in March I noted that there would be a jurist. I didn't have in writing Horace Krever's acceptance and I just did not feel at liberty to say there is a 99 percent chance that Mr. Krever, now retired, would be there. So, I wasn't holding back from the committee; I just didn't have it on paper at the time.

The committee and those in attendance were very taken up by Mr. Justice Krever's presentation, in particular taken with his very clear demarcation of the line between what tort can accomplish and what tort cannot accomplish. Mr. Justice Krever was very clear and articulate in his views of the limitation of tort systems in his home country

to deal with the tragedies that can ensue in the course of attempts to make people better, and it was on the basis of the limitations of the tort system that he strongly advocated a no-fault system. He did note, however, that in his own country that had not by any means been completely implemented.

The second recommendation, which was for such a system in the States, can be seen in the transcripts to come fairly directly from the persuasiveness, at least to the committee, of his recommendations, but there are clearly political and real-world details to be worked out.

The answer to the second question as to where do these things go, our charter is fairly clear. We advise the senior management of the Department of Health and Human Services -- we, being the Advisory Committee on Blood Safety and Availability. In practice, both of these recommendations come to the blood safety director who takes that advice and makes his own recommendations to the secretary. That is what is on paper. In the real world, a lot of people are interested in blood safety. For example, the agenda item on errors and accidents was driven to some extent by interest in the House Commerce Committee in that issue, although we had separately been anticipating that issue for some time before the Commerce Committee or the Institute of Medicine got wind of it.

I think as a courtesy we distribute the transcripts and the summaries to anyone who is interested directly. We post them on the web. The interest right now is in the House Commerce Committee, the Subcommittee on Oversight Investigations which is chaired by Mr. Fred Upton, Republican, Michigan, is particularly interested in this issue. In this election year, it is unclear whether the presence of election will promote or slow down progress on these issues.

DR. HOLLINGER: Yes, Dr. Simon?

DR. SIMON: Just a couple of comments on this report. First, in my previous life I was involved with the issue of no-fault compensation for transfusion-related injury, first on behalf of AABB and then subsequently on behalf of ABC. And, in fact, all the blood banking organizations tried hard to get a model program in the State of Arizona, when I was with Blood Systems out there, and I think it never did finally come into being. But over the years this has been an issue that the blood banking organizations have been very interested in and have tried to push for progress.

From time to time the model of the vaccine injury program comes up, as you mentioned, and we bring this up on Capitol Hill. The two comments that are made by congressional staff people to dissuade us from moving in

this direction are, number one, when this was put into effect people like Congressman Waxman and Senator Kennedy made it very clear that this was a one-time exception to tort law that they were willing to make and take on the trial lawyers in this area, but it was clearly a one-time exception.

Secondly, it was explained to me that the logic behind the vaccine injury program and a special exception for this is that the parents vaccinate their children not so much for the benefit of that child but for herd immunity to protect society as a whole. So, it is reasonable for society, through a tax measure, to assure the parents when they vaccinate their children that, should anything happen, society will take care of that. But it wasn't felt that this same principle applies to transfusion where someone is being transfused for their own benefit, just like any other medical form of therapy. So, I just thought I would add that to this discussion.

The second point I just wanted to make on errors and accidents is that it seemed to me, in reviewing this, that that is kind of right down the middle of the plate for this committee and FDA. I think it is certainly an area where we would be interested in further progress and would hope that FDA, as they presumably evolve in their internal discussions on this, might at some point bring some

suggestions to the committee.

DR. NIGHTINGALE: Dr. Hollinger, could I make a response to that?

DR. HOLLINGER: Yes, please.

DR. NIGHTINGALE: I am aware of those previous discussions and, in fact, I have been in contact with Dr. Sherman, who is going to prepare for me a summary of those deliberations, and I have also spoken to the AABB about this and I anticipate that there will be further discussion of what the blood community had accomplished in the past and the question about what should be accomplished in the future.

One of the comments that has been made, and it is not a comment that I made and attribute to somebody else but is certainly one that I share, is that the legs of such an enterprise are vastly strengthened when they include active participation either by those who will be directly affected by that or their representatives. When you talked about errors and accidents being right down the plate of FDA, within FDA's current budget there is a proposal for funds to assist in the implementation of error and accident systems and, honestly, we will have to see what happens on or about September 30th of this year.

DR. HOLLINGER: Yes, Dr. Schmidt?

DR. SCHMIDT: I think for those on this committee

who are not involved in or keep up with these things, it is worthwhile mentioning -- you had Justice Krever from Canada, but the events over the last few years have forced the Canadian Red Cross to declare bankruptcy for its entire operation and a complete revision of the blood collection and distribution system in Canada. So, this is a mighty effect of this tort problem.

DR. HOLLINGER: Thank you, Dr. Nightingale. The second update is a summary of a workshop that was held on plasticizers: scientific issues in blood collection, storage, and transfusion, held on October 18, 1999, and Dr. Vostal will give us an update on that.

Summary of Worship on Plasticizers: Scientific Issues in Blood Collection, Storage and Transfusion

DR. VOSTAL: Good morning. Thank you very much for giving me the opportunity to review our workshop.

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We had a workshop last October, and it was entitled Plasticizers: Scientific Issues in Blood Collection, Storage and Transfusion. It was jointly sponsored by the Center for Biologics and the Center for Devices.

The objectives of the workshop were to provide an open forum for discussion of scientific data on the use of plasticizers in blood collection and storage, and to examine

the risks and benefits of currently used plasticizers and other available plasticizers and plastics for blood collection and storage.

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So as a little bit of a background, you are all well aware that blood components are collected and stored in soft, pliable and gas permeable plastic bags. Now, the characteristics that are given to these bags are that the plasticizers are actually dissolved in the plastics, the main plastic that the bags are made of. Plasticizers are not covalently bound to plastics, and can leach out into the stored blood and be transfused along with the blood components. One of the main plasticizers that has been debated over the years has been di(2-ethylhexyl) phthalate or DEHP. The problem with this plasticizer is that it has demonstrated toxicity in rodents. It has been a 30-year debate or longer than 30 years whether this type of toxicity can also be extended to humans.

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DEHP does have some demonstrated benefits. It actually incorporates into the red cell membrane as it leaches out of the plastic bags and extends the storage dating of red cells from 21 days to 42 days. This was actually demonstrated by Dr. Jim au Buchon at the NIH Blood Bank, in the early '80s.

However, these are some of the risks that have been demonstrated in animals. In rodents DEHP leads to carcinogenicity, and the mechanism of this is peroxisomal proliferation. There are also new data coming out showing that DEHP has negative effects on reproduction, and this is both in male and female adult rodents. There is new evidence coming out that shows that there is testicular toxicity in developing animals, and this was done in rodents. So, again, with these types of things the question is whether these effects could be taking place in human after they have been exposed to DEHP through transfusion.

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In the workshop there was a great deal of debate on alternatives to phthalate plasticizers. For platelets, manufacturers have actually moved away from phthalate plasticizers and they now use citrated plasticizers with PVC or polyolefin bags which don't require plasticizers. So the amount of plasticizers reaching out into platelet products has been greatly decreased.

For red cells, there has been a lot of research for plasticizers also and, actually, Baxter came out with citrated plasticizers in PVC for storage of red cells. That was cleared by the FDA and introduced to the market in the early '90s. However, it was not well received by the transfusion community. There were problems with labels not

sticking to the bags. There were reports of an unpleasant odor to the bags, and there was also an increased cost. So, after about two years these bags were taken off the market and we were back to using bags that have DEHP.

The major concern that was discussed in the workshop is that any new type of plasticizer that is introduced has to have adequate toxicological evaluation, and the recurring theme is are we switching from devil that we know to the devil that we don't know in terms of DEHP and phthalate plasticizers?

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About the time we were having this workshop, we were fortunate that there were three separate risk assessments being conducted and published. One was done by the American Council on Science and Health. This was an expert panel that was chaired by Dr. Koop. Their conclusion was that benefits of DEHP outweigh the risks to humans. So, they felt that use of DEHP in medical devices was safe.

Another group, Health Care Without Harm, commissioned the Lowell Center for Sustainable Production, University of Massachusetts, to look at the issue of DEHP toxicity in medical devices, and this was a report authored by Joel Tichner. Their conclusion was slightly different. They said that DEHP poses a potential risk that should not be ignored, and that alternatives should be sought.

There is also another risk assessment that is still going on, and this was done by the Center for Evaluation of Risk to Human Reproduction, which is part of the National Toxicology Program, headed by Michael Shelby. They have an expert panel of toxicologists and they have met twice to discuss DEHP toxicity in humans, and they haven't come to a conclusion yet. They have one more meeting coming up in July, 2000. I think this is going to be a very good report, based solely on science, and we are looking forward to that report coming out.

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At the end of the workshop we had a discussion panel, and this discussion panel was clinically oriented. We had transfusion experts, we had pediatricians, epidemiologists, and we were looking for a clinical debate on toxicity and use of DEHP in blood products.

These are some of the highlights that the panel was discussing: One of the points that they brought up is that DEHP has an extensive clinical record, 30-40 years of transfusions with DEHP plastic bags, and there is no clear-cut toxicity to humans that has been demonstrated.

They pointed out that immediate withdrawal of DEHP is not warranted because it would significantly affect the blood supply and alternatives to DEHP are not well studied.

An important point that they brought up is that

past studies of DEHP toxicity may not have looked at the appropriate endpoints. Most of the studies done in the past have looked at carcinogenicity and recent reports indicate that carcinogenicity in rodents doesn't have the same mechanism as would be found in humans. The more appropriate endpoints now would be reproductive toxicity.

They also pointed out that there are subpopulations of patients, such as pediatric patients, that may be more sensitive to DEHP or other plasticizers because of undeveloped metabolic pathways and higher per kilogram exposure. They suggested that new clinical trials should be set up to evaluate levels of DEHP that patients are being exposed to currently and corresponding toxicity in humans.

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Since the workshop, there have been a couple more interesting updates on the risk of DEHP. The International Agency for Research on Cancer has downgraded DEHP from what for many years was labeled as "possibly carcinogenic to humans," to "not classifiable as carcinogenic to humans." This is because it is now felt that the carcinogenicity in rodents is not applicable to humans.

The Center for Evaluation of Risk to Human Reproduction has had two out of the three meetings and they have released some preliminary conclusions. It sounds as if they will conclude that doses that cause testicular effects

in rodents are only about 10-fold higher than what may be reached in some medical procedures, such as dialysis or ECMO. So, they are concerned about this type of toxicity going on with the use of current medical devices.

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From our perspective, this is what we got out of the workshop. It again demonstrated that there are benefits to DEHP in red cell storage, and that to remove DEHP from use currently would significantly affect the supply of red cells.

It was also pointed out that human dose and toxicity from DEHP in blood products is not well defined but should be reinvestigated. Some of the things that were suggested in the workshop were studies of multiply transfused individuals such as sickle cell and thalassemia patients, and special subpopulations of patients such as infants exposed to extracorporeal membrane oxygenation. This is an interesting situation were there is IV application of DEHP exposure. Most of the studies that have been done in the past with animals are oral exposure because it is very difficult to do IV exposure in small rodents. So, this is an interesting colleague situation where we can look at effects of DEHP through IV infusion in humans.

The reproductive toxicity of DEHP should be an area of active research, and there are a couple of studies

ongoing right now that are international reproductive toxicity studies. This will show whether offsprings of treated animals do have any type of reproductive effects. We would also encourage development of alternative plasticizers to improve the efficacy in storage, as well as improve the toxicity as compared to DEHP. As with any other complicated issue, this may in the future become a Blood Product Advisory Committee issue. We will be looking for your advice. Thank you very much.

DR. HOLLINGER: Any questions for Dr. Vostal? Yes, Dr. Simon?

DR. SIMON: I guess the only comment is that, you know, this is such an old issue. When I was with NIH in 1972-74 there were several contracts let to look at toxicity, and the conclusion then was that it wasn't significant. I guess it just keeps rearing its head and people continue to be uncomfortable but it seems that with the passage of time it becomes sort of a non-issue.

DR. HOLLINGER: Yes, Dr. Mitchell?

DR. MITCHELL: I guess I am concerned about the reproductive health aspects of it. Do you know of any ongoing studies? You talked about recommendations for looking at the exposure in humans. Do you know if there are any studies looking at the exposure level in humans?

DR. VOSTAL: Right now, I am not aware of any

studies in humans that are looking at correlating DEHP exposure and reproductive function. There are studies going on in rodents. However, there is always going to be a problem with these types of studies because most of them are oral administration of DEHP and what we are concerned about is IV administration of DEHP, and there may be different metabolic pathways that act on DEHP by different routes.

DR. MITCHELL: And, what about epidemiological studies that may be linking DEHP to the decrease in sperm counts that are found in people?

DR. VOSTAL: I think those would be great studies to do. Right now there aren't any being conducted. You know, I think there is a lack of funding for that right now.

DR. HOLLINGER: Thank you. Our third topic is the report on blood supply monitoring, and Dr. McCurdy is going to give us an update on the monitoring.

Report on Blood Supply Monitoring

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DR. MCCURDY: As there were a number of new things that came along leading to increased blood donor deferral and increased loss due to testing, the Surgeon General asked the Public Health Service to determine how the blood supply was responding to these and to do some monitoring. That was a fairly high priority item that was put forth first by an internal advisory committee and accepted by the Surgeon

General.

The National Heart, Lung and Blood Institute arranged to contract with the National Blood Data Resource Center of the American Association of Blood Banks to collect and supply the data, and we made an attempt to overcome some of the problems in the past in selecting how we would collect the data.

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We opted to do a sample of blood centers, and beginning in the next one to three months we will do the same thing for hospital transfusion services. For blood centers, we utilized data from the national surveys that were originally conducted by Dr. Douglas Surgenor and are now being conducted periodically by the AABB blood data center to select, by region of the country, a number of centers that are within one standard deviation of the mean collection for that particular part of the country.

There were 27 selected. We had three kinds, as I recall, of samples. One was totally random, which generally is preferred. One was selected, not quite random but selected in slightly different fashion, and we opted to do this one because it was weighted to the cities and our major purpose was to determine whether there was a blood shortage and, if possible, to predict by trend analysis what is going to happen.

There were 27 selected, 6 were unable to comply with the data requirements and there were 6 substitutes, and there was 1 late dropout so that the final sample was 26 centers. The objective was to get data reported by the 10th of the month for the preceding month and have data supplied to the National Heart, Lung and Blood Institute for beginning analysis shortly thereafter. We are doing, I think, as well as might be expected with the timeliness, but we are not getting data from all 26 centers by the 10th of the month.

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The centers that were selected came online at various different times. We began to collect data in February for the month of January but we also asked the centers to go back three months and provide us with retrospective data for October, November and December. You can see that between 15 and 20 of the centers were able to do that, the others came online as time went on, with the last coming on in April, providing data in May.

The data is being collected, as you will see, by blood group as well as total because most of us in blood banking have long been aware that the groups O, O positive and negative were much more of a problem than groups A or particularly AB.

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Here you see the total number of red cells released for distribution. This is after testing losses. There was a little decrease in December and January and increase in February, March and a little drop-off in April and then a little climb back up in May. These are normalized, if you will, for 26 centers. That is, we are dividing by the number of centers that actually provided data and multiplying by 26. So, these are "independent" of the number of centers reporting. On this slide you see not only the total, in the top line, but also the O positive and O negative in the bottom line. We have data for the others but it is not on this slide.

[Slide]

This is looking at the monthly amount of blood released as a percent of the total that has been released in this period, here, of 8 months. So, between 12 and 12.5 percent of the blood released during this entire period was released for distribution in October, and so forth. The peak here occurs in March; the drop-off in April. Some of these figures, at least at this time, must be looked at with a bit of a jaundiced eye because there were I think between 15 and 20 centers involved here and the May data, which I got at the beginning of this week, only represents 10 centers of the 26.

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We are also asking for inventories taken on the first and third Wednesday of each month. These inventories represent considerably fewer than the 15 to 20 centers that reported at that time because many could not go back and look at inventory, either total or by individual blood group, several months before. Again, you can see that there may be a slight trend upward overall in this but, although I haven't analyzed it, I don't believe it is really particularly significant. These inventories are meant to be taken at a specific time of day on the first and third Wednesday, and ultimately I think we may be able to do some trend analysis on this.

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We are also able to look at inventories by region. We know which regions of the country the centers are in. We do not know what the individual centers are. They are reported to us under code. This was to remove any concern about Big Brother, Sister or whatever looking over the data and pointing fingers.

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This is the mid-Atlantic and southeast sections of the country -- eastern section of the country. This is the central section. Presumably, these are in mid-America where the blood supply has traditionally been more stable and less subject to fluctuation, whereas this is in the northeast,

mid-Atlantic and southeast where there is more fluctuation.

I also did this in part because I received a report from the America's Blood Centers that a number of their centers had gone out with appeals in the month of May, toward the end of May and early June. This was earlier than they usually did in the past. It wasn't clear whether this was increased utilization for which we now have no data or whether it was decreased collections. We are not able to detect decreased collections. On the other hand, ours is macro data and individual centers are dealing with their own individual micro information.

I think I can stop here. If there any questions, I would be glad to answer them.

DR. HOLLINGER: Any questions of Dr. McCurdy? Yes, Dr. Simon?

DR. SIMON: I think this information is extremely useful, and I am pleased that the effort is being made to collect it and take a look at it. I know that a lot of the focus is on the fallout in terms of donors from the exclusion from people who have been in the United Kingdom for six months, from 1980 to 1996.

I think one of the issues that we are dealing with in both plasma and the blood industry there is that the publicity caused many people to self-defer and not show up so that we can't get accurate data on just how many people

we are losing because that question was introduced. So, I think the kind of data that Dr. McCurdy is giving us is the kind of data on which we will have to rely, that is, what is the final impact on the blood supply.

I would also point out that we have tended not to monitor the supply of source plasma. At our last liaison meeting we discussed this with the FDA but there is now data showing a significant fall-off in source plasma donations, possibly in the range of, you know, 10-20 percent over the last couple of years, which has not yet impacted final product but could. So, I think there are a number of supply issues that may be of importance to this committee and the agency in the upcoming months.

DR. MCCURDY: It is hard for me to speak off the cuff on this, but I think that the Institute would be quite willing to listen to proposals that might have a similar type of approach to the plasma industry. I don't know whether there is anything collected in that which is universal but we would at least be willing to talk.

DR. SIMON: The main universal is that all new plasma donors are checked through the National Donor Deferral Registry. So, ABRA does have a running total of those checks and of the new plasma donors who have shown up at centers. There has been a bit of a problem getting other sources of data because they are proprietary in nature and

these centers do compete with each other in similar communities, but I think it is certainly something we need to pay more attention to.

DR. MCCURDY: In this, we tried to avoid some of the proprietary issues and so forth by having it go through a so-called neutral party and having us know by code and sections of the country but not by individual center what is going on.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: Paul, looking at the last graph, the drop in mid-Atlantic and southeast looks precipitous and large. I just wondered if you could comment on how accurate the data are on that graph and then, secondly, a response to Toby Simon, the Canadians have tried to look at the question of measuring the impact of the U.K. related exposure deferral by doing surveys of donors, including non-returned donors. If, in fact, most centers in the U.S. which have implemented U.K. deferral have only done so in late March and April, it may very well be the case that what we are seeing in May is correlated, but I wonder if there has been any thought in the blood community about doing a survey similar to what the Canadians did to actually find out if that is so. Of course, if the dip goes away we perhaps don't care but if it doesn't go away it might help to know why it is happening.

DR. MCCURDY: The sample for May which showed that is a sample that had six centers from the east area, northeast, mid-Atlantic and southeast, and four centers from the midwest. There were no centers from the west that have come in with reports yet. And, it is only ten. Ten are extrapolated for the whole 26 sample. I think the closer you get to the 26 the more comfortable I am with that extrapolation. So, I think we need more data and we will certainly share that within the PHS and we will probably ultimately, when we get enough to make it meaningful, try to arrange to share it much more widely.

DR. HOLLINGER: Paul, I like your metaphor but I don't think this committee ever wants to look at things with a jaundiced eye --

[Laughter]

-- but, you know, one of the issues with the apheresis donors -- I think Ron Gilcher commented that he was concerned about how that might make an impact. I know you looked at whole blood and a few other things, but what has happened with the apheresis donors, or have you talked to him? I am particularly interested in that because he said a lot of these people are people who have traveled a lot, extensively, and have been gone.

DR. MCCURDY: I have not talked with Ron specifically on this issue. About a week ago we made a

presentation in front of the TSE advisory committee, and that was focused primarily on what we could learn about the U.K. deferrals and timing.

Unfortunately, most of the centers came on fairly late, the largest number, and the others came on intermittently throughout which made analysis a real challenge. We could not detect anything that appeared to happen before and after centers that provided that kind of data came online with U.K. deferral. In that, we looked at the apheresis situation. We are collecting information on platelets and apheresis platelets, and we were unable to detect any real change in the availability of apheresis products in that period of time. But analysis is very difficult and this is macro data. We heard some anecdotes at the TSE advisory committee that there were problems in collections and they did, at least in some instances, seem to be related to U.K. deferral.

DR. HOLLINGER: Yes, Toby?

DR. SIMON: Just as an anecdotal addition, from our company with 64 centers, the thread that is most consistent is proximity to Air Force installations and a little bit of some of the other services, but it is those centers that draw from that population, either active or retired, that are located geographically in such a way where we have seen the biggest impact. That has been the only

consistent finding. There has been a little bit also in the plasma industry to correlate with Dr. Gilcher's observation that donors in specialty centers that tend to be higher socioeconomic individuals and travel more, there is a slight tendency to pick up a little more there, but the Air Force one has been the most consistent marker.

DR. HOLLINGER: Thank you. Thank you, Paul. I look forward to the next report. The final report is the summary of Transmissible Spongiform Encephalopathies Advisory Committee meeting, which was held June 1st and 2nd of this year, and Dr. Asher will give us an overview and comments about that meeting. Dr. Asher?

Summary of Transmissible Spongiform Encephalopathies Advisory Committee Meeting

DR. ASHER: Thank you. Good morning.

[Slide]

The TSE Advisory Committee met on June 1st and 2nd and addressed two issues. First, the issue of potential possible deferral of blood donors with a history of travel or residence in BSE countries other than the United Kingdom, as well as a look back, obviously, concerning the U.K. Second, the possible effects of leukoreduction on reducing the risk of transmitting CJD by blood.

As you may recall, although the risk of transmitting CJD via blood and blood products is entirely

theoretical, the FDA has taken a very conservative position on the issue as recently as November of 1996 recommending withdrawal not only of blood and components but also of plasma derivatives where a donor was belatedly recognized as having CJD or being at increased risk of CJD.

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However, by the end of 1997 it was clear that there was no demonstrated risk, detectable by epidemiological studies, of CJD in implicated plasma derivatives in transmitting disease. The withdrawals were recognized as not substantially reducing the theoretical risk, at least for recipients receiving multiple exposures when at least 25 percent of large plasma pools used to produce derivatives were likely to contain a contribution from at least one donor who would ultimately get sporadic CJD. There was no screening question that could defer such a donor and no laboratory test available to detect the risk. Withdrawals had failed to retrieve most CJD implicated products anyhow, and CJD withdrawals were contributing significantly to shortages of some plasma derivatives. So, in January of 1998 the PHS Advisory Committee on Blood Safety and Availability recommended that the FDA could relax policy sufficient to relieve those shortages without seriously endangering public health.

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In August of 1998 the Surgeon General, Dr. David Satcher, announced the new policy which was then elaborated in guidance issued by the FDA in September of 1998. The agency recommended continued deferral of donors with CJD or increased risk of CJD and continued quarantine and retrieval of blood and components, but no longer recommended withdrawal of plasma derivatives prepared from pools to which those donors with classical CJD or increased risk had contributed. However, withdrawal of plasma derivatives and quarantine of intermediates prepared from pools to which any donor who developed new variant CJD -- CJD attributable to infection with bovine a spongiform encephalopathy agent -- those derivatives would still be withdrawn.

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The reasons for increased concern about donors during the incubation period of CJD are as follows: First, less is known about the pathogenesis of new variant CJD than sporadic CJD.

Second, new variant CJD is an emerging infection not yet recognized in the United States and lymphoid tissues of patients with CJD, and even at the end of the incubation period of new variant CJD, contain detectable protease resistant prion protein while those in patients with sporadic CJD do not, which implies that the blood which contains lymphoid cells might be more infectious in patients

with new variant CJD than it is in sporadic CJD.

Finally, authorities in the United Kingdom decided not to source plasma for preparing derivatives from their own U.K. donors which implied a certain lack of confidence in the safety of the plasma. The FDA then felt compelled to consider the issue of donors who had been potentially exposed to the BSE agent while traveling or residing abroad.

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Following consideration by the TSE Advisory Committee in December of 1998 and June of 1999, the agency recommended deferral of donors who had resided in the United Kingdom for six months or more cumulative between January 1st, 1990 and end of December, 1996, and deferral of donors who had received injections of bovine insulin from the United Kingdom, but did not recommend withdrawal of plasma derivatives for U.K. residents at any period or for exposure to injectable bovine products.

Finally, there was a commitment made that the Public Health Service would monitor the effects of this revised broad policy on the blood supply, and as part of that commitment the TSE Advisory Committee meeting was held on June 1 and 2.

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There is reason to think that exposures to the BSE agent in the United Kingdom have been markedly reduced after

1996 and, in general, recent news from the United Kingdom is guardedly good. Perhaps it is fair to say that at least it is not bad news in that cases of BSE, after peaking at the end of 1992, have continued to decline although there were over 2200 cases diagnosed in cattle last year, and this year in the first third of the year there have been more than 300 cases of BSE recognized, but the various precautionary measures to reduce exposure are well in place and the rate of recognition in cattle continues to drop markedly. Cases of new variant CJD continue to increase but not at an accelerating rate and interim results of a survey of lymphoid tissue from normal, healthy, younger patients, 3000 of them, have not revealed any protease-resistant prion protein.

[Slide]

But concerns about BSE in some other European countries are increasing, and I just want to remind you that since January of 1998 the United States Department of Agriculture has considered all European countries to be suspect as BSE countries.

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During the past year diagnosed BSE cases have increased in several European countries and a new country, Denmark, has been recognized as having the disease in its native-born cattle. It has also been recognized that

substantial exports of U.K. cattle beef and beef products continued from the U.K. to several European countries during the high BSE years. France may have imported at least 5 percent of its meat and meat products from the U.K. during that period. The Netherlands also imported a significant amount of beef, and other countries did as well. Finally, cases of new variant CJD have increased. There are now three cases confirmed and others are under suspicion.

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So, on June 1, the TSE Advisory Committee was asked to evaluate new information concerning new variant CJD and BSE in the United Kingdom, France, as well as BSE in other European countries besides France and the U.K.

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And, to look at any effects that recent changes in blood deferral policy might have had on the blood supply and blood products in the United States, as well as effects to be anticipated if additional deferral of donors was to be recommended. Dr. McCurdy presented earlier information from the same survey that you heard this morning.

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The committee reviewed recent events concerning new variant CJD and BSE in the United Kingdom. They looked at projections of potential exposures to BSE and cases of new variant CJD recognized and expected to occur in France

and the Republic of Ireland, and CJD and BSE surveillance in Switzerland where there have been no cases of new variant CJD recognized. They also heard USDA estimates of BSE occurrence in various European countries.

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They looked at estimates of possible human exposure to the agent elsewhere in the European Union and heard results of a very interesting assessment by Canadian authorities of the risk of new variant CJD in Canadians who had traveled to the United Kingdom and to France, and finally reviewed the effects of recent policies on the supply of blood and blood products in the United States.

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When asked if the committee thought that the available scientific data on the risk of transmitting CJD and new variant CJD warranted a change in the current FDA policy regarding deferrals of blood and plasma donors and product retrievals based on their travel or residence in the United Kingdom, the committee members voted three in favor and 15 opposed. The members felt that insufficient time had passed since the implementation of the new policy to assess its effects on supply and they were, therefore, reluctant to advise any further changes at the moment. There were a couple of contingent questions concerning it. They felt comfortable staying with the current policy concerning

deferral of donors resident in the U.K.

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When asked if FDA should recommend deferral from blood or plasma donations for persons with a history of travel or residence in France, the vote was 17 against such deferral and only one in favor. The committee seemed impressed that both the assessments of exposure to U.K. beef and beef products in France and the rates of new variant CJD both suggested that the risk to residents of France was only about 5 percent of that in the U.K. The apparently concluded that such a risk was not sufficiently significant to recommend any deferral even for much longer periods of residence in France.

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Essentially the same advice was offered for donors resident in other BSE countries, although there was concern about the lack of information concerning potential exposures to BSE in some of those countries.

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The secondary issue of possible effects of leukoreduction on CJD risk was addressed. Since a large part of the infectivity in blood of rodents experimentally infected with TSE's is in the buffy coat, it has been proposed that leukofiltration might reduce the risk of blood-borne transmission of CJD, and several European

countries have decided to do that as a precautionary measure to reduce the risk of transmitting CJD. So, the committee was asked to consider evidence that leukoreduction might be expected to reduce the theoretical risk of transmitting CJD and new variant CJD by human blood, blood components and plasma derivatives and whether the reduction in risk is likely to be substantial enough to have practical value and, consequently, whether universal leukoreduction of blood and blood components should be recommended by the FDA for that purpose.

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The committee reviewed information on the work of this committee, that is, recent recommendations and prospects for the implementation of universal leukoreduction techniques and theoretical applications of leukoreduction to remove TSE agents from blood, and the possible role of leukocytes in experimental pathogenesis of TSEs in rodents and the implications for human blood, the main one being that since circulating cells of lymphoid origin seemed to be obligatory for pathogenesis of TSEs in rodents, it was to be expected that there would be infected cells in the blood of humans as well, although that has never been convincingly demonstrated. They also looked at TSE infectivity in the blood of experimentally infected rodents and that implementation for human disease as a model. The available

information was very limited and one small but troubling study even suggested that animals infected by the intravenous route cleared infected cells better than they did the same amount of infectivity presented in a cell free form.

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So, when asked if leukoreduction can be expected to reduce significantly the infectivity theoretically present in blood of persons during the course of CJD and new variant CJD, the committee concluded that available data were simply insufficient to decide and, with two dissenting votes, they advised that leukoreduction not be recommended as a precaution to reduce the risk of transmitting CJD until its potential effects are better understood. Thank you very much.

DR. HOLLINGER: Thank you, Dr. Asher. Any questions for Dr. Asher on the issues raised on TSE? If not, thank you. Are there any general comments from the committee before we move into the next major portion of our meeting today? If not, we are going to move into the next portion of our meeting. This is going to be a discussion on plasma pool screening by nucleic acid tests for HAV. Robin Biswas will give us an introduction and background to this issue. Robin?

Plasma Pool Screening by Nucleic Acid Tests

for Hepatitis A Virus

Introduction and Background

DR. BISWAS: Good morning. This will be music to your ears --

[Laughter]

[Slide]

The FDA has received a submission from a manufacturer for plasma derivatives for the plasma screening of minipools by using nucleic acid tests for hepatitis A virus and human parvovirus B19. Currently, the agency has articulated policies for NAT plasma pool testing for parvovirus B19, human immunodeficiency virus, hepatitis B virus and hepatitis C virus, but has not yet developed a policy in regard to HAV plasma pool testing, and that is what we will be discussing for the rest of this morning, namely, plasma pool screening by nucleic acid tests (NAT) for hepatitis A virus (HAV).

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The issues that will be discussed here stem from a manufacturer's intention to perform testing of minipools of samples from donated plasma units by HAV NAT and then discarding the HAV positive units, thereby withholding them from the manufacturing pool from which plasma derivatives are made. The intention is to lower the viral load in the manufacturing pool from which the plasma derivatives are

made. This should enhance the margin of safety for these plasma derivatives.

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While transmission of HAV by plasma derivatives is not a major clinical problem, plasma derived volume expanders and immunoglobulins have been historically safe, rare transmissions by coagulation Factors VIII and IX have been reported, and Dr. Farshid will go into this in a little more detail later on.

I should say at this point that there is a recommendation for persons receiving coagulation factors to receive vaccine hepatitis A. Stephen Feinstone will go into this in a little bit more detail later.

[Slide]

Solvent/detergents are widely used in the manufacture of coagulation factors, and immune globulins to inactivate lipid-enveloped HIV, HBV and HCV, and are very effective in doing this, but HAV is a non-lipid-enveloped virus and is not inactivated by these solvent/detergents.

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There is an underlying general plasma pool NAT testing assumption here: If a certain pool of samples from donated units is NAT positive, then a particular positive unit and donor can be identified.

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In the past, FDA has viewed plasma NAT pool testing of samples of units as either in-process control in which the donor is not identified or as donor screening where the donor is identified.

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In 1997 when NAT pool testing was under development for HIV, HBV and HCV, the Blood Products Advisory Committee endorsed FDA's position that NAT pool testing for these three viruses should be considered donor screening and that the donor should be identified. Clinical studies to validated the clinical efficacy of NAT for these viruses under IND is required.

In the case of parvovirus B19 NAT pool testing, in September last year the committee agreed with FDA that studies to validate clinical efficacy of B19 NAT under IND for plasma for further manufacture need not be required. This was considered then to be in-process control testing and the donor need not be identified. In this case, the NAT test requires validation as an analytical test only in regard to sensitivity, specificity and reproducibility, and Sheryl Kochman will be going into this a bit later. In regard to parvo B19 NAT testing, no clinical correlates need be established if no decisions regarding donor or recipient management are taken.

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I would now like to describe briefly, in a bit more detail, some of the decisions that need to be made when NAT pool testing of samples of donated units for a particular virus are introduced, and also the types of data and information that need to be considered to make those decisions.

[Slide]

The first decision -- do you go ahead an identify the individual donor?

[Slide]

Are you going to retrieve products from that donor?

[Slide]

Are you going to retrieve previously collected, non-pooled plasma units in the case of source plasma, over on the left of the slide? If it is recovered plasma that is under question from volunteer donor whole blood units, does one then retrieve transfusable components from the current donation? The previous donation?

[Slide]

Are you going to notify the donor that the donor has a positive test result?

[Slide]

Are you going to then defer that donor for a finite period, or perhaps I should also have added

indefinitely? These are questions.

[Slide]

Are you going to notify the recipients of the transfusable components?

[Slide]

These considerations used for deciding whether viral NAT pool testing for a particular virus is in-process control or donor screening can be broken down into these three items: Donor-related criteria, product-related criteria, and recipient-related criteria.

[Slide]

In regard to the donor-related criteria, decisions need to be based on the medical and technical feasibility of donor deferral from donation and donor counseling as to treatment and avoidance of transmitting infections to others.

[Slide]

In regard to product-related criteria, decisions should be based on the medical benefit and technical feasibility of quarantining or destroying the positive plasma unit, and that is actually what we are doing here; quarantining or destroying other transfusible components from whole blood donations from the same whole blood donation; and quarantining and destroying of unused, previously collected window period donations.

[Slide]

In regard to the recipient-related criteria, decisions should be based on the usefulness of notifying recipients of previously collected window period transfusible products in regard to recipient testing of diagnostic procedures, treatment if available and necessary, and counseling in avoidance of transmitting the infection to others.

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To provide a basis for decision-making, one needs to consider the relevant aspects of the particular viral infection. In the case of HBV, HCV and HIV and B19, here are the criteria that were examined to come to the two different ways of handling pool testing. I have left HAV blank.

The criteria that we used were severity of disease, window period and chronic infections. In the case of HBV, HCV and HIV, it can be fatal or causing significant morbidity. In the case, of B19 it is mild or asymptomatic in most cases.

The window period for the "big three" -- there can be a long period before seroconversion, and prior donations may be infectious despite negative tests. For B19, there is a short period before seroconversion, and there is a short duration of disease.

In regard to chronic infections, individuals may remain infectious for life. This is true for HIV; it is true for 85 percent of HCV cases and 5 percent of HBV cases. In regard to B19, the disease is usually self-limiting. Another consideration was that anti-B19 could be beneficial for IG products so if somebody has a NAT positive test and they are going to quickly seroconvert, then it may be beneficial actually to have their units in the pool. Symptomatic disease is rare but the infection and antibody prevalence is not rare. So, what we are saying there is that there is a high prevalence of immunity in the population. So, if somebody gets B19 they will most likely be immune to it.

[Slide]

In regard to donor-related criteria for HBV, HCV, HIV and B19 NAT pool testing, it was decided, because of the slide that I showed you earlier on the nature of the diseases, that deferral was appropriate for HIV, HBV and HCV and not really necessary for B19. We also took into account that treatment is generally available for HBV, HCV and HIV in this country and for B19 there is none usually indicated. In regard to avoidance of secondary infections, of course, people should be counseled to do that in case of HBV, HCV and HIV, and it can be done and should be done. In the case of B19 there is nothing really you can do about that.

[Slide]

In regard to product-related criteria and NAT pool testing for these viruses, the following decisions were made: Quarantine and destroy the positive plasma unit, yes in both of the cases. Quarantine and destroy components from the same donation when that is possible. It is being done. In regard to lookback, I should say that in regard to HBV, HCV in regard to components, they are not used and source plasma units, they aren't used. So, previous donations are not used. This is all being done under IND for HBV, HCV and HIV. In regard to notification, it does take place if the previous unit is undiluted, that is, if a single unit does have a NAT-positive test notification is apparently taking place. In regard to B19, there is no lookback.

[Slide]

In regard to recipient-related criteria for NAT pool testing, it would be appropriate to consider all of these criteria -- testing, treatment and avoidance of secondary infections, if a person received transfusible components from a NAT-positive collection. In the case of B19, this is really not necessary or not considered the thing to do.

[Slide]

I think at this stage, I will go through FDA's

current thinking. I will do this so that when you hear the other speakers you can put the information that they will give you into this framework.

Well, our current thinking is that validated HAV NAT minipool testing enhances the margin of safety for plasma derivatives. So, we do encourage that.

We believe that donors of HAV NAT positive units should be informed. If a person knows that they are HAV NAT positive, it is possible that they could take preventive measures to prevent transmission to others in close contacts, to their family members. Of course, this begs the question whether persons who are HAV NAT positive and without symptoms, whether they are, in fact, infectious. This is a little bit controversial and Steve Feinstone will go into that later today. Donors could possibly benefit from a timely administration of immune globulin. I should also say that this is not an established practice and it is not a recommendation, but a patient with an HAV NAT positive test result could go and talk to his or her physician about it.

Another reason that we believe that donors with HAV NAT positive units should be informed is that their close contacts could also possibly be given preventive immune globulin. There are a number of technical problems with this but, basically, I think it is correct to say that

at the FDA at the moment we believe that people who are HAV NAT positive should be informed of the result. Steve Feinstone wanted me to mention to everyone that HAV (hepatitis A) is a reportable disease in most states.

Unpooled units donated in the last three months should be retrieved, and donors should be deferred for three months. The basis for this was that the incubation period for HAV, from exposure to symptoms, varies from about two weeks and the longest that has been reported is eight weeks, with the majority of cases three to six weeks incubation period.

Recipient tracing in the case of transfusible components is not necessary because of the extremely few HAV transmissions by transfusion that have been reported in the world literature. Individual donations, therefore, also need not be HAV NAT screened.

So, that is all I have to say at the moment, and there will be other speakers going into greater details about how we regulate certain types of kits and also more detail about hepatitis A infection. Thank you.

DR. HOLLINGER: Thank you, Robin. I forgot to mention that for this section we have a guest, Dr. Raymond Koff, from the University of Massachusetts. Ray, just raise your hand so we can see you. Ray will be offering any expert comments as an expert in hepatitis A. So, we are

delighted that you are here, Ray. Thank you. Yes, Toby?

DR. SIMON: Can I ask a question of Dr. Biswas? I know this is a matter under discussion but at the present time anyone who has had hepatitis after the age of eleven is permanently deferred. Are you suggesting through this that either that would be changed to three months or that there would be a distinction between those who had a case of hepatitis versus those who had an HAV NAT?

DR. BISWAS: Currently, the way we are interpreting that is that somebody who has a history of a clinical, symptomatic hepatitis after the age of eleven is deferred. You know, for certain test results we have said that just a positive test result, for example, ALT or just an anti-core with no symptoms, in those cases the donor need not be deferred. So, I would think that if one just had an HAV NAT positive test result without any symptoms at all, you know, I think that that would be then for a three-month deferral.

DR. HOLLINGER: Yes, Jay?

DR. EPSTEIN: I think the problem, Toby, is that it would conflict with the current recommendation and that we might want a center to request a 641-20 exemption. As you are aware, the whole issue of dealing with history of hepatitis has been under discussion with the advisory committee and we hope to bring it to the fore with a rule-

making initiative on donor suitability.

We recognize that we really have not harmonized all our thinking. One of the options that we did discussion with the advisory committee -- which the committee actually did not favor, much to my surprise -- was that if you had a well-documented hepatitis with no known chronic risk implications you need not have a permanent deferral. You might still want a temporary deferral because of acute illness but that there wasn't a need for permanent deferral. The committee's feeling was that was probably too complicated, and that the data to support such an exception would be difficult to acquire, and that you would never actually be sure in the majority of cases so it wasn't going to be useful.

Basically, what you are pointing out is that if we are not concerned about chronic disease in the donor why are we deferring the donor? At this point in time, it is just not a well-resolved issue. So, I think the bottom line is that one might be captured and we might seek exemption requests but we would almost certainly honor requests based on well-described data.

DR. HOLLINGER: I think we will move on to the next section, which is on the regulatory options for HAV nucleic acid testing, and Sheryl Kochman will discuss this.

[Slide]

MS. KOCHMAN: One of the logical next questions that you would ask yourself after determining whether or not we are going to test for HAV NAT is how would we regulate those test kits? How would FDA expect those test kits to be handled?

The routine regulatory options for test kits used in testing blood for transfusion include the biologics license application. This was formerly a product license application and an establishment license application but we have recently harmonized with the Center for Drugs and we now have one application. In most cases this is preceded by the submission of an investigational new drug application or an IND.

Another approach that has been taken is the pre-market approval approach. This is the case where the device is a novel device. There is no predicate and it comes in as a Class III device and is reviewed according to pre-market approval regulations.

Probably what would be considered the least burdensome form of review would be the pre-market notification or 510(k) submission. In this case you have a new device that can be considered substantially equivalent, or SE, to a predicate device. A predicate device basically is a device that has been legally on the market.

[Slide]

Robin focused on what we have done with NAT tests in the recent past, but I thought it would be good to give a historical approach to how FDA has regulated a number of tests that are currently done on the blood supply. You will notice that the tests are sort of up here in the order that they were implemented in the blood community.

So, the very first that was done was a syphilis test. It is a required test at this time. It involves donor notification, deferral and/or lookback. Unfortunately, this one is the outlier. It has been regulated by the 510(k) mechanism, probably largely because it was the very first kit and the regulatory mechanisms weren't as well defined at that time.

You will see that the next tests that came along were tests for HBV. They were required. They involved notification, deferral and/or lookback, and we have handled those previously as PLA and now I am going to refer to them all as BLA.

The same thing goes then for any other test that has been required or recommended by FDA where we have recommended notification, deferral or lookback. We have generally had those come in as BLAs.

When we get down to ALT, you note that this test is not a required test. It is a test that is done

voluntarily by the blood organizations. Some of them have notification, deferral and lookback procedures; some of them don't. This kit is handled through the 510(k) mechanism.

Also, similar to ALT tests are the CMV tests where the testing is done voluntarily. It may not even be done on all units. It may be done on selected units. There is generally no notification, deferral or lookback. The unit is simply not used for a particular intended recipient. That, again, is handled as a 510(k).

The most recent addition to the list is the Parvo B19 test kits. As Robin mentioned in his talk, they are not required. There is no donor notification, different or lookback, and they are an in-process control.

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As an in-process control, these Parvo B19 test kits -- normally the plasma fractionator develops and manufactures the test kit in-house. They then supplement their biologics license application for their fractionated product to include an additional in-process test. FDA reviews that BLA supplement for the scientific soundness of the in-process control, and then has the opportunity to review the test and the results during post-approval inspections to ensure that the test has continued validity.

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I also wanted to compare and contrast standards

that are applied under the various mechanisms. Under the BLA mechanism we have a dual set of standards. Both the biologic standards and the medical device standards apply. The biologics standards include standards for safety, purity, potency, sterility, identity and lot release. The medical device standards include compliance with the quality system regulations, or they are also known as the current good manufacturing practices. There is a substantial number of labeling requirements under the medical device standards and there is a requirement for registration and product listing.

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If you look at the standards that are applied for a PMA, we have only one set of standards that apply here, and that is the medical device standards but more of them apply than applied to the BLA. We have performance standards, sometimes voluntary and sometimes not voluntary. We have to sorry about safety, effectiveness, quality system regulations, the labeling requirements and registration and listing.

[Slide]

The standards that are applied under the 510(k), if it is a Class I it is just general controls and safety, effectiveness and the rest. If it is a Class II we add in the special controls. So, the Class II 510(k) would be more

stringent than a Class I.

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So, what does this mean in terms of the regulatory burden both for FDA and for a manufacturer of the test kit? With a BLA there would be extensive clinical trials. As I mentioned before, those clinical trials would have to be performed under an IND. There would be a pre-approval inspection by Center for Biologics staff. There would be post-approval inspections by the team Biologics staff, and the kits would be subject to routine lot-by-lot lot release.

For a PMA you can have pretty much the same level of clinical trial testing performed. There would also be a pre-approval inspection, but those inspections would be done by the field. Post-approval inspections would also be done, and they would also be done by the field. But we have no mechanism built in for lot release for PMA products, although sometimes if we feel the need for it we can request it.

Finally, the 510(k) mechanism -- there can be limited clinical trial data. There are no pre-approval inspections for 510(k)s and post-approval inspections are, at this point of time, only done on a for-cause basis. The limitations on resources are such that the field has pretty much said they will expend their resources on Class III devices, which would be the PMA devices, and those other

devices for which there is a need to go out and inspect. So, they would be for cause and, again, there is no lot release for 510(k) products.

[Slide]

So, where does HAV testing right now fall? The current HAV tests that are available have been regulated by CDRH. Their current indication for use is detection of antibodies to HAV in human serum or plasma. They are regulated as Class III devices, which means that general and specific controls are insufficient to assure the safety and effectiveness of the device. So, they are reviewed under the PMA mechanism. That was the middle one on the previous slide.

[Slide]

For the purposes of how CBER might choose to regulate HAV NAT tests, if for some reason we thought we could review them by other than a PMA mechanism, we do have the opportunity to utilize Section 207 of FDAMA 1997. This is known as the evaluation of automatic Class III designation or also known as do novo classification.

[Slide]

In this case the kit manufacturer would submit a complete 510(k) for an HAV NAT test, and their specific intended use would have to be different for it to qualify for the de novo. We would recommend that the intent

indication for use be something along the lines of testing plasma pools for the presence of HAV DNA. After receipt of the 510(k), CDER would review it and determine is there a predicate; are there deficiencies in the submission; is the device considered low risk; and if there is no predicate, could it qualify for de novo classification?

[Slide]

Under the current system there would not be a predicate for a device that is intended for use in testing of plasma pools for the presence of HAV DNA. So, CBER would have to prepare an NSE letter, which means not substantially equivalent. We would list any deficiencies that we may have found in the review of the submission. We would state that there is no predicate, and we would also state that the device might qualify for the de novo classification. After the firm receives that letter, they have 30 days to submit a request to FDA for a Class II designation under the de novo classification mechanism.

[Slide]

FDA then reviews that request, and a response to that request must be made within 60 days. The things that are reviewed at that time are the previous review of the NSE 510(k); whether or not there were deficiencies; whether or not they can be addressed. They base it on the review of the request for classification. If the firm has requested

Class II, does the FDA feel that it fits appropriately into Class II, and there is a risk evaluation made.

[Slide]

If, for some reason, the FDA determines that the new test kit has to be classified as a Class III, then there would be a submission of a PMA or a PDP required. If, on the other hand, FDA agreed that the test could be classified as Class I or Class II on the basis of the fact that a 510(k) has already been submitted and reviewed, assuming it is acceptable, it can be deemed to be cleared. It can go to market immediately, and it then serves as the predicate for future submissions of similar kinds of test kits.

[Slide]

Lastly, in all of these cases the kind of data that will be needed would have to cover accuracy, specificity, sensitivity, precision and stability. The data requirements could be different though based on the kind of submission that would come in. They would be most burdensome for a BLA and the least burdensome for a 510(k). In any case, the applicant would be advised to seek guidance from CBER to know just how much testing needed to be done. That is it.

DR. HOLLINGER: Is this clear to the committee, how this works? Are you saying that the FDA prefers this to be a 510(k) because it requires less extensive evaluation?

MS. KOCH: I don't think we have made that decision, that we prefer it that way, but if we follow current thinking it would make sense to review it as a 510(k). So, there was a little bit of a focus on 510(k) but it is not a done deal.

DR. HOLLINGER: And what would be the predicate device for that decision?

MS. KOCH: In this case, that is why I was explaining the de novo classification. There is no predicate for this device. So, we have to utilize the new mechanism available to us under FDAMA, the de novo classification. So, normally when there is no predicate the device is automatically classified as Class III and automatically has to come in as a PMA, but just to present the fact that there is an option if the committee were to recommend, because of the level of importance of the test, that we could go with a lower regulatory mechanism, the 510(k) mechanism is available to us. It is just not a straightforward one.

DR. HOLLINGER: Thank you. Jay?

DR. EPSTEIN: I think that Dr. Koch answered the question, but basically what we are saying is that should the committee recommend, and should we concur, that there is not a need for routine donor screening, if you concur that, nonetheless, when that is done on a minipool you should

identify the positive unit and the infected donor and inform the donor, that is then medical testing.

Well, medical testing for hepatitis A has precedence in the agency. It is reviewed as a Class III PMA in CDRH. So, we wouldn't see a real difference between a NAT test versus an antibody test versus an antigen test. It should be treated as a medical diagnostic. So, what we are trying to explain is that if we get that recommendation from the committee and concur, we wanted the committee to understand what was at stake with oversight of that test as a medical diagnostic, and what we are saying is that the current system would require that it be a Class III PMA but that there is a legal mechanism under the FDA Modernization Act for it to be, if you will, down-classified to a 510(k), which would then make the oversight more consistent with the way we deal with other non-required tests which are, nonetheless, sometimes reported as medical information to the donor, and that would include CMV, syphilis and ALT.

So, what we are saying is if you go that route and concur that this need not be a routine donor screen, because it should still be viewed as a medical diagnostic, we are suggesting that there is a route for harmonizing it with the other tests that are viewed similarly. Is that helpful, Blaine?

DR. HOLLINGER: Yes. Dr. Koerper?

DR. KOERPER: Could you please just briefly refresh my memory as to the difference between Class I, Class II and Class III?

MS. KOCH: A Class I device is considered a low risk device such that general controls, which would be registration, listing and adherence to GMPs, are sufficient to ensure the safety and effectiveness of the device. A Class II device has a little bit higher risk, and it has been deemed insufficient to have just general controls. We think that there are special controls in addition to general controls that may be necessary. A Class III device is considered the highest risk device, and general controls and special controls alone are inadequate or insufficient to ensure the safety and effectiveness of the device so we require the clinical trials and a pre-approval application, and there are usually some sort of performance standards that are developed along with that application.

DR. HOLLINGER: Yes, Dr. Chamberland?

DR. CHAMBERLAND: Perhaps the presentations later on will help address this point but I wanted a clarification. Can we assume that the manufacturer who has approached FDA with his application for HAV NAT testing is really only providing the agency with data that addresses the sensitivity, the specificity, the accuracy of the test itself and has not provided or is intending to provide the

agency with data about the donor notification? We are all in the middle of this giant IND trial, if you will, for HIV, HCV NAT testing that includes not just how good the test works but this whole notification process etc. So, are there any data that are going to come now or at a later date?

MS. KOCH: I think some of the future speakers are going to address that a little more.

DR. CHAMBERLAND: Okay, because to me that would be a big consideration as to how frequently donor notification might happen and how timely that might occur because all of that will impact on whether or not the potential preventive measures for secondary transmission could be practical or effective.

DR. BISWAS: Mary, what we got was basically like the B19 NAT.

DR. CHAMBERLAND: Okay.

DR. HOLLINGER: And the agency will probably have a standard for HAV for sensitivity that can be utilized in these tests, because that will be critical.

DR. BISWAS: That is certainly something that we will do. You know, we haven't got there yet but that is something we will do.

DR. HOLLINGER: Just in case this goes into the record down the line, on your slide 11 for the de novo

classification you had testing of plasma pools for presence of HAV DNA and it should be HAV RNA.

MS. KOCH: Oh, I am sorry.

DR. HOLLINGER: If there are no further questions, we will go on to the next speaker, and this is a review of history of hepatitis A transmitted by transfusion. Dr. Farshid?

Review of History of Hepatitis A Transmitted by Transfusion

DR. FARSHID: Thank you.

[Slide]

Hepatitis A virus, as we have heard already, is a non-enveloped RNA virus, and it is almost always transmitted by the fecal-oral route through person to person contact or ingestion of contaminated food or water. However, rare cases of transmission by blood and blood products have been reported, as we will see in the next few slides. Hepatitis A virus causes only acute infections. In certain rare cases there is some prolonged and relapsing infection which Dr. Feinstone will probably discuss those with you.

[Slide]

As mentioned earlier, the blood-borne transmission of hepatitis A is very rare. This is based on the absence of documented cases of hepatitis A in studies of post-transfusion hepatitis. These are studies which were performed in the '70s and '80s to assess post-transfusion

hepatitis due to non-A/non-B. In those studies, which were large studies, no cases of hepatitis A were detected. Also, there were studies in the '70s and '80s which showed a lack of any differences between serological prevalence in rate of hepatitis A in a transfused and non-transfused population.

[Slide]

What are the causes of rare transmission by blood transfusion? There are a number of factors involved. There is a short viremic period and absence of n HAV carrier state or persistent infection, and also low concentration of HAV in the blood and overall low incidence of HAV infection. Also, we need to consider that almost 50 percent of the population is already immune to HAV.

[Slide]

As mentioned earlier, there are cases in the literature which indicate transmission by blood by either packed cells of fresh-frozen plasma. This is not all that are reported. I think there are probably three excellent reports which I did not include here. But overall as we see, the number is not large. The striking feature that we see here is that large number of the newborn or neonates and also the large number of the secondary infections.

The report in 1983 by Dr. Hollinger and his colleagues is particularly important because it represents the first clear demonstration that hepatitis A virus from a

donor sample can produce post-transfusion hepatitis A. This is the case, right here, where a 10-year old child developed acute hepatitis A, as indicated by jaundice and also by IgM anti-HIV and the infection was traced back to a donor who donated and also developed acute hepatitis 7 days after donation, and died of hepatic failure. HIV antigen was detected in the plasma from the original samples and also in the liver of the donor. There were also chimp studies where the chimpanzees were transfused with the plasma from the original sample and they developed hepatitis A and seroconverted 3 weeks after infusion.

The other interesting case which underscored the importance of secondary infections, by Noble, were packed cells were given to a number of neonates and 11 of them developed acute hepatitis A. Also, the studies showed that the first case that actually came to attention was when one of the nurses developed acute hepatitis A. Further investigation showed that 16 percent of nursery personnel had hepatitis A as the result of this one particular case, and 4 percent of the physicians who were in contact with the patient also developed hepatitis A, and 25 percent of the family members. That 25 percent rate of secondary infection among family members has also been reported by others.

[Slide]

This table shows transmission into clotting

factor. There has not been any report of transmission by clotting factor until the late '80s where outbreaks were reported from Europe, in Italy, Germany and Ireland, and other places like South Africa and later, in 1994, in the U.S.A. and also the latest one from Germany.

Because time is short, I will not go through these one by one, but overall the common feature among all of them is that all the patients received highly purified solvent-detergent treated clotting factor concentrate. The earlier reports from Italy and Germany and Ireland relied primarily on epidemiological evidence to indicate transmission. All the product was manufactured by one single manufacturer in the corresponding countries. There were no other risk factors for hepatitis A among patients, and the patients were geographically dispersed. There was also a correlation between the quantity of Factor VIII concentrate received by the patient and the HAV infections. There was very little sequence analysis in the early cases, but in the most recent ones, the ones from South Africa, the U.S.A. and Germany, in addition to epidemiological studies that I mentioned there were also some sequence analyses. Viral sequence analysis was done from samples from the patient, from the product and also from the plasma source, and the sequence identity was determined in these three samples.

[Slide]

Basically, I just want to say that the sequence analysis was done in different regions of the HAV genome including the VP1 and VP2 and, in addition, in the VP1 and 2A region which are variable regions of the genome. It is important that the sequencing be done in different parts.

In all those studies, it was shown that there were identical strains in the patient product and the source plasma. Also, there were some laboratory studies, done by Stanley Lemon, which basically looked for the fate of HAV during the manufacturing process. This is the process which uses ion chromatography and solvent detergent treatment. He has shown that neutralization reduced the viral load by two logs and as a result of the cryoprecipitation almost 99 percent of the virus will remain in the supernate and only one percent will go to the cryoprecipitate. The supernate will be used to develop Factor IX concentrate and the cryoprecipitate will be for Factor VIII. Solvent-detergent treatment basically showed no reduction. However, it is important to mention that he also found that solvent-detergent did not interfere with the neutralization, as has been suggested by some investigators. In fact, it may even enhance the neutralization to a certain degree, probably by stripping the virus of some of the host lipids. Subsequent steps in the manufacturing process had little or no effect on overall viral reduction. The conclusion from his study

is that the margin of safety provided by this manufacturing process is not sufficient to prevent HAV infection if one or two HAV-contaminated units get into the plasma pool.

[Slide]

Then the question is what is the cause of these outbreaks? Overall, it can be summarized as simultaneous changes in the purification process, change in viral inactivation techniques, and change in epidemiology of HAV. The purification process to provide low purity and intermediate purity product contain sufficient amounts of HAV to confer immunity to the recipient. However, in the highly purified product by high purification you actually remove the antibody so there is no more passive protection. As we saw in the viral inactivation technology, the solvent-detergent had no effect on viral reduction. As far as epidemiology, there seems to be a shift toward the older population and the donor age group also. Overall, the prevalence of HAV is declining which indicates that there is less antibody in the plasma pool. Since the donor age is more vulnerable, it is more likely that they will get infected, and if they are a donor they can pass on the infection.

[Slide]

What will be the implication? This also will most likely be covered by Dr. Feinstone, but just to mention that

HAV is a mild infection, however, in those who already have preexisting chronic liver disease it may exacerbate the problem and in certain cases cause death. It has been reported that 95 percent of U.S. hemophilia patients between the age of 20 to 40 are already infected with HCV, and 8 percent are chronically infected with hepatitis B.

[Slide]

Then the question is what should be done about it. There are a number of suggestions. There is vaccination against HAV in anti-HAV negative hemophilia. The experts agree that using vaccination is cheap, inexpensive and very effective in preventing infection. Also, terminal heat treatment for Factor VIII has been suggested. I should mention that although HAV is relatively heat stable, heating may reduce effectiveness of Factor VIII and may cause denaturation and also produce inhibitor perhaps as a result of formation of new antigen. So, it is more complicated than simple heating. Also, the use of recombinant Factor VIII without use of plasma derived product has been suggested. I should mention that in some of the recombinant factor they use albumin as a stabilizer and that theoretically will produce risk for HAV. Therefore, it is suggested that vaccination should be done in this group of recipients as well.

[Slide]

Also, screening of plasma pools for HAV has been suggested, and that is what we are discussing here. I tried to come out with a rough and crude estimate, and 0.67 is the fraction of the population that is not infected with HAV, and 9 is the prevalence of HAV. This is the notification rate for HAV by CDC, 9 per 100,000 per year. If we estimate the average window period to be 3 weeks in a year, the rate will be 0.35 per year. So, it will be 3-4 units per million per year. I must mention that the numbers that are there may change, especially the one that says 9 per 100,000 per year. It is fluctuating, and I think I got this from 1994 estimates by CDC.

Finally, development and implementation of viral inactivation are steps that are effective in removal of non-enveloped viruses, and there are a number of methods which are currently being investigated. Thank you.

DR. HOLLINGER: Thank you, Dr. Farshid. Any questions? Yes, please, Dr. Koerper?

DR. KOERPER: I would just like to comment on your slide about improving product safety for HAV for hemophilia patients. First of all, the Medical and Scientific Advisory Committee of the National Hemophilia Foundation has strongly recommended that all hemophilia patients be vaccinated for hepatitis A, and that is currently being implemented and the effectiveness of the vaccine is being tested in a nationwide

study.

Secondly, while in the early '80s, when heat treating Factor VIII and IX was first proposed, there were concerns about the possibility that Factor VIII and Factor IX would lose some of their potency and that neoantigens would be exposed, resulting in increased inhibitor formation. Those concerns have been negated. In other words, the Factor VIII and IX are still completely active and we are not seeing an increase in inhibitor formation due to the heat treatment process. So, that was universally recognized as a first approach toward eliminating viruses in factor concentrates. It has been supplemented by such things as solvent-detergent and column chromatography, but heat treating is an important adjunct to eliminate some of the viruses that are not eliminated by solvent-detergent, and most manufacturers include that in their processing of product that does come from plasma.

Thirdly, with regards to the recombinant factor products, while most of the Factor VIII products do contain albumin, to my knowledge, there has been no transmission of hepatitis A from albumin --

DR. FARSHID: Yes, I mentioned that actually there has not been any report of transmission of hepatitis A by any of the fractionated product except for Factor VIII and Factor IX, which was from the U.S.

DR. KOERPER: Right, by not from albumin --

DR. FARSHID: Not from albumin.

DR. KOERPER: So, the feeling is that the use of albumin as an excipient in Factor VIII is probably okay, although the manufacturers are moving away from that. So, I feel that we have taken many steps to help eliminate this problem in our hemophilia patients.

DR. HOLLINGER: Yes, Dr. Chamberland?

DR. CHAMBERLAND: Could you please review one more time -- I didn't quite get it all -- your estimate of the number of donations per year that might be captured in that formula? You might want to put it back up.

[Slide]

DR. FARSHID: The 67 percent of the population basically are not positive for anti-HAV. So, these are all anti-HAV negative. They have never been exposed to hepatitis A. This is the notification rate as determined by the CDC per 100,000 per year. I think that was given from 1994 or '92. Maybe Dr. Feinstone will clear that estimate up. It is important to determine that not all cases of HAV are reported to CDC, and they estimate that probably the actual number will be 4-5 times what we see here. The average incubation period for hepatitis A is estimated to be 3 weeks. As I mentioned, this is a very crude estimation and hopefully the other speakers will give us a more

accurate estimate, but I put it here basically to stimulate more discussion, and that what we are dealing with is a very rare event.

DR. HOLLINGER: Yes, Mr. Rice?

MR. RICE: I just have a question. I know that HAV vaccinations have been recommended for persons with hemophilia, but I was wondering if there was any difference in that recommendation for persons -- and this would be for Marion probably -- who have HIV chronic infection and exacerbated HAV status as to whether or not they are also recommended also to get the HAV vaccination basically because this risk of the lower purity products from recombinant bearing some risk of transmitting HAV is becoming to be more of a possibility in recent guidelines on reimbursement from DOJ. It has actually forced some people on Medicaid to have to now not take recombinant product and have to go to some lower-level purity product which conceivably, if that person has HIV infection and is not vaccinated against HAV, that puts that person at risk. That is the real world coming in, basically now forcing people back from the highest technology for other considerations.

DR. FARSHID: If I may defer that question to Dr. Steve Feinstone, he will talk about the pathology of the virus and he is more qualified to answer that question.

DR. HOLLINGER: Yes, Kenrad?

DR. NELSON: I think the 9 per 100,000 estimate has to be taken with a huge grain of salt. You don't get 33 percent prevalence of antibody with 9 per 100,000 attack rate. It is much higher than that because most infections are asymptomatic, and asymptomatic infections may easily transmit.

DR. FARSHID: That is true.

DR. NELSON: I realize it was an estimate --

DR. FARSHID: Actually, as I mentioned, the number is probably five times what we saw here, but the CDC estimate is that the rate of infection is between 80,000 to 120,000 per year for HAV infection, and that will not come out to 9 per 100,000; it would be much higher. But, I thought I would put a number where I have some documentation for that and, as I mentioned, it is much higher. But even if we say five times what is there, still the rate would be very low.

DR. HOLLINGER: Yes, Dr. Mitchell?

DR. MITCHELL: I wasn't clear about the relative risk of HAV between blood components -- whole blood versus fresh-frozen plasma versus Factor VIII and Factor IX.

DR. FARSHID: Certainly, there is no data to show what is the rate. I mean, the risk is so small and probably approaching zero. If you look at transmission by blood from 1981 until today, I think the total report is probably 13 or

14 cases that have been reported. In case of the factor concentrates, from late 1980 until today there were about 116 reported transmissions, with some of them maybe even questionable by factor. So, the incidence is very small, extremely small.

DR. MITCHELL: I am still not clear. Are you saying that it is higher in the factor concentrates than in other products?

DR. FARSHID: Your question is, is it higher in Factor VIII compared to other fractions in a product? There is no report of transmission -- is that the question?

DR. MITCHELL: No, that is not the question. The question is compared to whole blood does Factor VIII, Factor IX, those types of components, do they have a higher rate of transmission of HAV?

DR. FARSHID: Actually, I don't know based on what I see and the number of outbreaks, most likely there would be more in Factor VIII concentrate because you start from the pooled source. If you compare the number of years and the number of infections, you have a much higher level of infection through clotting factor than you have through blood transfusion. Through blood transfusion mostly occurs in neonates, and there have not been that many.

DR. HOLLINGER: Thank you. Our next speaker is Dr. Stephen Feinstone, who is going to talk on the

epidemiology, clinical implications, prophylaxis of hepatitis A virus. You are going to do that in a short time. How can you do that, Steve?

DR. FEINSTONE: Well, actually I wasn't planning on taking a short time!

DR. HOLLINGER: Oh, good! I don't think you should.

[Laughter]

Hepatitis A Virus:
Epidemiology/Clinical/Implications/Prophylaxis

DR. FEINSTONE: Actually, there is almost no reason for me to be doing this with Dr. Hollinger and Dr. Koff here who are world experts in this problem, but I will try to just go through this very quickly because there is a lot to cover.

[Slide]

So, as you see, hepatitis A is one of the five well-recognized hepatitis viruses and it is classified as a picorna virus, which are a group of viruses that have single-stranded RNA genomes.

[Slide]

This is a list of picorna viruses. It includes the enteroviruses, the rhinoviruses, cardeo viruses and apthoviruses of animals. Hepatitis A is not classified as an enterovirus; due to some of its unique features, it is in

its own genus.

[Slide]

This is the virus itself. It has a small non-enveloped di-icosa hedral structure of about 17-28 nm in diameter. Morphologically, it is virtually indistinguishable from any of the other viruses that you saw in that list of picorna viruses. But the important aspect from this is that it is non-enveloped and, therefore, it is not sensitive to lipid solvents.

[Slide]

I just want to make one point from this slide on acid stability and heat stability. This virus is relatively heat stable, even relative to many of the other picorna viruses, and heating the virus to 60 degrees for one hour would not be expected to eliminate total infectivity. So, the processes that have been used to inactivate, say, HIV, HCV and HBV have not been validated to inactivate hepatitis A virus completely.

[Slide]

This is hepatitis A in cell culture. The point I want to make here is that the virus grows in the cytoplasm. I don't know if you can see from this immunofluorescence study but the fluorescence appears as cytoplasmic granules.

[Slide]

We think what these granules represent are small

vesicles inside the cell that contain the virus, here stained by peroxidase in a study done by Yoko Shimizo. We never actually see the virus free in the cytoplasm of the cell. We only see it inside these vesicles.

[Slide]

I must tell you this is only my conjecture, there is no real hard data for this but the virus replicates by the same general mechanism of the other picorna viruses. It enters the cell. The RNA genome functions both as a message molecule and a template for new RNA virus production, and it goes through a series of steps and virus maturation but inside these vesicles. I think what may be happening is that these vesicles themselves are extruded from the cell and typically into the bile where the action of the bile salt and detergents break down the vesicle and release free virus particles.

[Slide]

However, in this picture, by Lucy Asher, in the serum of a primate with hepatitis A we see virus contained still within a vesicle. So, this is free virus in the serum.

[Slide]

This picture, by Yoko Shimizo, is of virus contained within a vesicle in a stool sample. So, the virus may be contained, at least at times, within these vesicle

structures.

[Slide]

Now, the epidemiology of this of virus -- and first I want to thank Miriam Alter, from the CDC, for sending me some updates on these epidemiology slides -- this virus has a worldwide distribution but parts of the world, obviously, have much higher rates of infection than other parts. Generally tropical countries but also some northern countries, such as Greenland, have very high rates of hepatitis A prevalence. Then there are intermediate countries such as Asia, most of the former Soviet Union and southern Europe, and then the low prevalence areas such as the United States, western Europe and Australia.

[Slide]

So, what has been seen worldwide are different disease rates but also different types of disease. Where the endemicity is very high, the infections, as most enteric viruses, are in early childhood. Transmission is primarily person to person and we rarely see outbreaks amongst the indigenous populations in those situations. Then, if you go to areas where there are moderate rates of infection, the age of typical infection usually increases and we see actually more disease because the disease in young children is usually in a parent. Then, you go to low and very low areas of the world and there, again, the age of infection

usually increases to young adults. In the very low rates there is virtually no transmission within those countries and most of the infections we see are imported or in travelers. The disease burden in these countries is not very great because of the low rates.

[Slide]

So, this again sort of depicts this. This is the high prevalence areas. This is the time of acquisition of antibody. As you see, it is very, very early in life. In one study I did in Kenya, we had 100 percent seropositivity by age two. Then, in the very, very low rates you see virtually no disease occurring in young people. Then, in the older cohorts of people, and these probably represent childhood infections that occurred at a time when the epidemiologic situation was different. Then you see these countries in the middle where there is probably a changing epidemiologic pattern, where this curve begins to sag.

[Slide]

In this slide I just wanted to show sort of the public health impact of hepatitis A in these different countries. In the developing world where the infections occur mostly in children and where the infections are frequently in a parent, you see there is really not that much recognized public health impact. But as the age of infection increases, the average time of acquiring hepatitis

A increases and the overt disease rate increases, you see a more pronounced public health impact. Then, of course, in the very low risk countries, again, it disappears because there are so few cases.

[Slide]

This is simply some actual data to show that type of situation. This is data from Chili in which they look at the rates of typhoid fever and the rates of hepatitis, and this was mostly hepatitis A, over many years. As you see, as the epidemiologic situation improved the rates of typhoid fever decreased but the apparent rate of hepatitis A increased because the age of infection was increasing and the rate of overt clinical disease increased.

[Slide]

In the United States, hepatitis A is estimated to account for 55 percent of acute hepatitis cases in this country -- as has just mentioned, probably around 100,000 cases a year although it is grossly under-reported.

[Slide]

This slide shows the risk factors. As you can see, the largest groups of patients have no known risk factor. However, the most important way that this virus spreads is really person to person contact. But other important means of spread are international travel, travel to endemic areas. Daycare centers have become recognized as

an important nidus where infections occur. Men who have sex with men are known to transmit the disease when the virus is prevalent in those communities. Injection and drug use has also been associated with hepatitis A. This may be a life style relationship more than actual parenteral transmission of the virus but that is not completely known. I think you should notice from that that transfusions are not an important means of transmission.

[Slide]

These are the reported case rates in the United States over the years. As you can see, the incidence of disease tends to occur in waves over time and in recent times, as you can see, we have had declining rates of hepatitis A although it is still, as I mentioned before, an important disease in this country with probably about 100,000 cases per year.

[Slide]

Incubation period -- I think this is an important topic for this discussion. These are analyses of experimental infections in primates, done in Bob Purcell's laboratory. This shows the incubation period, the time to the first ALT elevation after an intravenous inoculation of hepatitis A virus in varying doses. What you can see is that the incubation period is generally dose related. The higher the dose, the shorter the incubation period. We can

see incubation periods a short as 1 week in marmosets given more than 108 infectious doses of virus, but stretching out to 7 weeks or even a little more with very low doses.

[Slide]

If you go back to some of the old data when there were human volunteer studies going on -- this is from some of the studies conducted by Saul Krugman at the Willowbrook State School. As you can see again, with greater doses of the virus, in this case a stool extract, administered to volunteers the incubation periods ranged up to 70 days, I believe, 71 days. These incubation periods are relatively long but I think one thing we have to remember is that the tests that we had in those days were much less sensitive. He was looking at things such as thymol turbidity or bilirubin levels and most likely the ALT levels would reflect a somewhat shorter incubation period. But I think you can see that incubation periods can certainly range to greater than 6 to 8 weeks.

[Slide]

This is a cartoon of a typical case of hepatitis A, exposure being at time zero. You see ALT elevations occurring after the incubation period which averages about 4 weeks. About the same time that ALTs come up, one sees the first appearance of serum antibody which, if you analyze it, actually is a combination of IgG and IgM. IgM levels

elevate very briskly in hepatitis A, both specific hepatitis A antibody as well as IgM in general levels go up.

So, about the time of symptoms one generally sees serum antibody, especially IgM antibody, which is the basis for the diagnostic tests for acute hepatitis A in which on a single serum sample a patient reports with symptoms suspicious of hepatitis A. A positive for hepatitis A, specific IgM, is generally considered diagnostic. There are no approved nucleic acid tests for diagnosis of hepatitis A at this time. Serum antibody is long-lasting; we think for a lifetime. We think immunity is lifelong.

[Slide]

Now, this is some studies that we did in experimentally inoculated chimpanzees. They are very similar to some studies reported by Stan Lemon. We looked at the response in these animals to intravenous inoculation with hepatitis A virus. Again, you see ALT levels. It is a little hard for me to read this slide, but in this case IgM levels are here and this line is neutralizing antibody. As you can see, neutralizing antibody comes up very early with the earliest antibody. When we separated this serum into IgM and IgG components, we found that the IgM itself was capable of neutralizing hepatitis A virus in vitro.

[Slide]

Now, some recent data by Bowers and colleagues at

the CDC, using a highly sensitive reverse transcriptase PCR assay, nested PCR assay, have looked at the time of viremia. In this case, you can see that they were able to detect HAV RNA in the serum for very long periods of time after acute infection, up to 400 days.

[Slide]

This is one of the cases that they studied. Again, you see long-term RNA delectability. This is ALT levels and detection of serum antibody. So, even in the face of serum antibody they are able to detect the HAV RNA in the serum. What form this is in we don't really know. I won't to go back to those pictures I showed you of the virus contained in the vesicles but I think it is possible -- there is no data to support this but I am just saying that it is possible that some of this virus may exist protected from serum antibody because it is still within these vesicles that have been extruded from the hepatocytes.

[Slide]

Again going back to some earlier data from Saul Krugman's studies on actual infectivity of clinical samples during the course of hepatitis A infection, and these are from experimentally infected volunteers and then transmitted to new volunteers, as you can see, stools taken during the incubation period -- this is the incubation period, up to 40 days; this was the time of disease; and this is after the

appearance of symptoms. So, prior to the incubation period stools and serum were found to be infectious for hepatitis A. After the incubation period the serum was found to be infectious for the first 3 days after the appearance of symptoms, but after that was not infectious.

So, exactly what does this mean, the long-term viremia or at least HAV RNA positivity in the serum? I think we really don't know. We can't really say that these people are infectious at this point in time in these studies. I should say that there have been other human volunteer studies with similar results which say that the serum is not infectious for long periods of time after the appearance of symptoms. Stools also seem to rapidly lose their infectivity, both from experimental studies and also epidemiologic studies, and seem to show that transmission doesn't occur for periods very long after the appearance of serum antibody which coincides with the appearance of symptoms.

[Slide]

This is just some real data from Ian Gust, in Australia, in which they looked for virus by a much less sensitive technique, electron microscopy, following the patient's arrival at hospital, which usually coincides with the appearance of dark urine. As you can see, they were able to detect virus in the stools for a period of almost

two weeks in a very few patients after the appearance of symptoms, but most patients had lost the virus by that time. Again, it is not clear that these patients are actually infectious or liable to transmit the disease commonly at this period of their disease.

[Slide]

This is some other data from CDC showing what bodily fluids contain virus. The stools, of course, we know are where most of the virus is shed; serum at a lower level. Virus has been detected in the saliva. Those are the main places. We don't really know if the virus in the saliva is being excreted there or if this is low-level blood contamination.

[Slide]

Now, control of hepatitis A -- the best way to control hepatitis A on the large scale is to improve living conditions, primarily sanitation. Providing clean water supply, separated from sewage disposal, is probably the most important thing that we can do. So, this is really a disease that can best be controlled by sanitary engineers.

Beyond that, the classic way that this virus has been controlled is by passive immunoprophylaxis with immune globulin. Immune globulin has never been effective in really reducing the rates of hepatitis A in any endemic areas. It is effective in controlling the spread among

contacts of cases, and intensive campaigns can be used in small community outbreaks of hepatitis A. But now we have the advent of active prophylaxis with hepatitis A vaccine.

[Slide]

So, the principles of this vaccine -- it is a killed vaccine, very much analogous to the original killed polio vaccine. The virus is grown in cell culture. This is the only one of the hepatitis viruses that grows reliably into reasonable titer in cell culture. So, the virus is grown in cell culture and the adaptation to cell culture has generally had the additional effect of attenuating the virus for infection in man, which is kind of an extra safety factor. The virus is then purified and inactivated by formalin, much like the killed polio vaccine. In distinction from the killed polio vaccine, this vaccine, with alum, has been shown to be highly immunogenic in man, such that in reality a single dose is generally sufficient to provide at least short-term protection.

Studies are underway to determine whether or not this can provide long-term protection as well. The current recommendations are for anyone who may have long-term exposure to hepatitis A to get a single dose of vaccine and a booster dose at about 12 months, in which cases people got very high doses of antibody and should be protected most likely for life.

[Slide]

Here are two licensed products in this country, the SmithKline product and the Merck product. There is very little difference between them. They were made originally with two different strains of virus, but one of the features of this virus is that there seems to be universal serologic cross-reactivity. There is only one serotype of hepatitis A that we know about. So, both of these vaccines are highly effective and both have been shown over the past few years to be very, very safe.

These were the original efficacy trials performed by these two companies. There was a large-scale trial performed by the Army in Thailand in which there were nearly 40,000 people who participated with a very high efficacy rate. The study done in Monroe County, New York, by Merck was really one of the most classic vaccine trials I think ever published, in which there was a very high endemic rate of hepatitis A in a Hasidic religious community in New York State. They went in and started vaccinating, and within three weeks after initiating vaccination the cases just disappeared from the vaccinated group whereas they continued in the non-vaccinated group. Very quickly they broke their code and started vaccinating everyone. So, this was really a beautiful demonstration of the effectiveness of this vaccine.

[Slide]

So, these are the recommendations for the use of the vaccine. I think one of the most important uses now is to sort of interdict these community-wide outbreaks of hepatitis that can really smolder for years and cause tremendous disruption in communities. Then, beyond that, the vaccine is presently recommended for people who are at increased risk of infection. There is a long list of these people but that group now includes anyone who is receiving blood products on a routine basis. I certainly feel that this should be a very strong recommendation who receives clotting factors or any other blood product.

That concludes my presentation. I think one thing I did forget to mention was the occurrence of the recurrent disease. About 10 percent of patients who get acute hepatitis A end up having a recurrence of symptoms and usually ALT elevations. This can happen with two or even three episodes over the course of as long as a year or a little longer. However, all of these patients eventually recover. Hepatitis A is only an acute disease. There is no chronic stage, although fulminant hepatitis can be associated with hepatitis A. I believe in the Shanghai epidemic in which there were about 300,000 reported cases there were 47 deaths. So, it is not a completely innocuous disease, and it certainly makes people sick for extended

periods of time. I will be glad to take any questions.

DR. HOLLINGER: Thanks, Steve. Questions for Dr. Feinstone? Yes, Col. Fitzpatrick?

COL. FITZPATRICK: In individuals who have been vaccinated is there a high enough level to be detected by NAT DNA during a period of time after the vaccination?

DR. FEINSTONE: Well, first, this is an RNA virus. The vaccine is administered intramuscularly. I don't know if anyone has actually done that. I don't think anyone has actually done that. You can clearly detect it in the original vaccine but, don't forget, this is an inactivated vaccine and the thoroughness of inactivation is very carefully monitored. They go through extensive long-term sub-cultures of this virus to prove that it has been inactivated. Not only that, but both the virus that is in the SmithKline product and the Merck product are virtually non-infectious for humans.

COL. FITZPATRICK: Right. No, I realize that, but are we going to pick up donors who have been vaccinated for a period of time.

DR. FEINSTONE: I don't know of anybody who has done that.

DR. HOLLINGER: Yes, Dr. Ohene-Frempong?

DR. OHENE-FREMPONG: Just a question about any long-term consequences of hepatitis A in the endemic areas

as far as liver disease.

DR. FEINSTONE: Hepatitis A is not associated with chronic liver disease of any form. In patients who already have chronic liver disease, based on either chronic viral hepatitis B or C or any other form of chronic liver disease, should all definitely be vaccinated. That is one of the current recommendations because an acute hepatitis A episode on top of chronic liver disease can be fatal.

DR. HOLLINGER: Yes, Dr. Chamberland?

DR. CHAMBERLAND: Just a point of clarification, I believe according the ACIP recommendations that were published in the MMWR last fall, they were very specific in recommending that the vaccine be given to individuals with, quote, clotting factor disorders. So, it wasn't a global --

DR. FEINSTONE: Well, that is the ACIP recommendation. The labels for both products indicate anyone receiving blood products routinely.

DR. CHAMBERLAND: Does the FDA have reason to believe that other blood products, like IVIG etc., are at risk for this?

DR. FEINSTONE: No. In fact, I am of the belief that the episodes that occurred with clotting factors were more of an aberration. We didn't see them before; we haven't seen them since. I think that they are very unusual. My personal feeling is that the nucleic acid

testing probably should not be done but this whole problem should be handled by vaccination, and that these people should be vaccinated, not only to prevent them from getting hepatitis A from any blood product, but also because they frequently are chronically infected with other hepatitis viruses and it is important that they be protected against hepatitis A.

DR. MACIK: You mentioned as far as treatment that heat treatment doesn't kill hepatitis A. You mentioned that was one hour at 60 degrees. Do you have any information about pasteurization or high temperature at a longer time?

DR. FEINSTONE: Yes, I should have brought a slide on that. Hepatitis A can be killed by heat. It is partially inactivated by 60 degrees for one hour. It is generally inactivated by 60 degrees for 10 hours, which I think is within some of the heat inactivation procedures. Certainly, 80 degrees kills the virus quite reliably. But my point was that none of the heat inactivation procedures that have been proposed to eliminate HIV, HBV, HCV have actually been validate to inactivated hepatitis A virus. I think if you do killing curves, you would see that hepatitis A would be killed more slowly than those other viruses.

DR. MCCURDY: I think the data you presented on persistence of RNA in these vesicles over a long period of

time is just very interesting. Would it be possible in any sort of system that if somehow antibody was removed that this RNA could become infectious? I am thinking of any sort of processing of blood product that might render the persistent RNA to be infectious.

DR. FEINSTONE: One of the interesting things is that if you look at that study that I showed from Saul Krugman in which at day 3, after the appearance of symptoms, there was infectivity in the serum. That serum almost undoubtedly contained antibody at that time. As I showed from my slide, that early antibody should neutralize the virus.

In another study, published by Lou Barker in 1977, in which he looked at a family outbreak of hepatitis A and transmitted acute-phase sera to marmoset monkeys -- tamarins we call them now -- they showed that those samples that transmitted hepatitis A infection to tamarins did contain pretty good levels of serum antibody. Now, it is possible that that virus is protected by these vesicles. But it is possible that the solvent-detergent treatment breaks down those vesicles and actually makes it more infectious because by that time maybe much of the antibody has been eliminated or the solvent-detergent itself prevents the neutralization by serum antibody. We really don't know. This is all conjecture; we don't know the answers to any of these

questions. But we do know that acute-phase serum with antibody can be infectious if inoculated parenterally. We also know that that antibody in an in vitro assay, in a cell culture assay, can neutralize hepatitis A virus.

DR. HOLLINGER: Thanks, Steve. We are going to move on to the last speaker. This will be on HAV transmission by Factor VIII concentrates, Dr. Michael Chudy, from the Paul Erhlich Institute, Germany.

HAV Transmission by Factor VIII Concentrates

DR. CHUDY: Ladies and gentlemen, I would first like to thank the FDA for inviting me to this meeting to present our data for the HAV transmission by Factor VIII concentrates.

[Slide]

This table summarizes all episodes of HAV transmission by solvent-detergent treated Factor VIII concentrates. In most of these episodes it was not possible to reconstitute the chain of infection from plasma pool to product to patients. You see here that in this incriminated lot from the Italian episode and the Ireland episodes animal studies were performed but they were not successful. This large episode in Germany happened in 1997.

[Slide]

This is the prehistory. Let me focus your attention to the right part of this slide. Production pools

from several manufacturers were tested by NAT for HAV. That is a screening procedure. You see that manufacturer C has a pasteurization step for inactivation and there were 2 out of 132 pools positive for HAV but no transmissions were reported from final products manufactured from these positive starting materials.

You see here that we have tested from manufacturer D the solvent-detergent inactivation procedure. From 43 tested pools, none were active by NAT but from one starting material there were 6 HAV transmissions by Factor VIII.

[Slide]

This is a genome of HAV. For a screening procedure we use the conserved region of the terminus VP3; and for sequencing we use the junction of VP1-2A.

[Slide]

I now come to the last episode of transmission in Germany. It was in 1997, and seven hemophilia patients had an infection of HAV, and six of them developed acute hepatitis A. All of them were recipients of Factor VIII from a batch from the manufacturer I showed earlier. The plasma pools were screened by NAT and were negative in our lab and also in the lab of the manufacturer. But in retrospective studies we see that pool A was positive in 7 out of 11 runs. The incriminated lot was positive in 6 out of 17 runs. You see that the virus is in the limiting

dilution. Not every run will give us a positive result in the NAT. So, we can calculate the viral load by the percent distribution, and we get a viral load of the plasma pool of 600 genome equivalents/ml and of the incriminated lot of 300 genome equivalents/ml.

[Slide]

This summarizes 9 patients, all of them anti-HAV negative who received the same incriminated lot. The first 6 developed acute hepatitis A. I should mention that patient 6 received a bolus infection of only 4000 units of Factor VIII. I should also mention that the bleeding date for our retrospective studies is done at a time point very, very late, nearly 40 days after onset of the symptoms.

[Slide]

Here are the results of our molecular approaches in the two regions. You can see there is 100 percent homology between pool A, the incriminated lot and all the patients and for the VP1-2A junction and also for the VP3 region. I should have mention that we have used PCR control in this matter to exclude wild contamination. You see that there is only homology in this region of nearly 90 percent and 94 percent in this region.

[Slide]

For animal studies, usually chimpanzees or tamarins are susceptible animals for an HAV infection. This

is a tamarin, a New World monkey, and we use it for our animal studies. Animal transmission studies performed in the context of earlier transmission episodes were not successful because larger amounts of Factor VIII preparation had to be administered. Nevertheless, the manufacturing question initiated an animal study again.

[Slide]

This slide shows us the study design. We used three tamarins. They were caged individually but they had acoustic contact with each other, and the Factor VIII product was carefully concentrated and each animal received an equivalent of approximately 28,000 units of Factor VIII of the implicated lot. That corresponds approximately to 104 HAV particles. The animals were observed up to 132 days post-infection. The following parameters were investigated, from the feces the HAV antigen and HAV RNA, and from the sera the liver enzymes, ALT and also all serological markers and HAV RNA.

[Slide]

Unfortunately the first tamarin died after 30 days post-infection, but no signs of HAV infection were observed. These are the results of animal two. You can see classical HAV infection with seroconversion. With the first marker we could detect HAV in the serum and later also in the feces. The ALT was detected nearly four weeks after PI, and after

seven weeks seroconversion could be detected.

[Slide]

The second animal -- there was only in feces samples HAV RNA detected and later antigen, and only a slightly elevated ALT but no seroconversion could be observed.

[Slide]

To come then to the summary, we have sequenced all samples from the animals and we can now summarize all samples from the chain of infection and from the tamarins, all have 100 percent homology in the sequences.

[Slide]

Summarizing data from the animal studies, it was for the first time that infectious HAV in a clotting factor concentrate, by experimental infection, could be detected. There was complete identity of the HAV sequences from the animals and the chain of infection.

[Slide]

To summarize all the data, from the molecular approaches and from the animal studies -- there was 100 percent homology of all HAV sequences in two different HAV regions, and there was a singular sequence of a unique HAV strain. So, we can calculate the titer if we assume there is one positive donor in the plasma pool, and we have calculated the titer of this donor and it was approximately

106 particles/ml. That was the titer of the donor of the contaminated plasma pool.

DR. HOLLINGER: Let me just ask you a question. I wasn't quite clear on the first part. You said the plasma pool, the screening by an HAV TPCR was negative --

DR. CHUDY: Yes.

DR. HOLLINGER: -- and then the other pools were positive. Can you clarify that for me?

DR. CHUDY: Yes, it is from the statistical point of view. If I perform a screening and I do one run, and for prospective studies you have several runs with survivals in the limiting dilution. So, it is a statistical problem to detect one particle in one assay. But you have a chance to detect it if you repeat and repeat these runs and that happened in this case.

DR. HOLLINGER: So, a Poisson distribution --

DR. CHUDY: Yes.

DR. HOLLINGER: -- the screening was negative but when you went back and retested it several times --

DR. CHUDY: Maybe I can have the next slide. I documented some titers in the window period and some possible recommendations for pool testing.

[Slide]

We have a window titer from our donor of 106 particles/ml and we have a detection limit of an assay of

nearly 1000 copies/ml. Compared to HCV it is not so sensitive, but maybe it can be explained by not destroying by lysis because it a virus without envelope. For a pool size, I would propose a minipool of not more than 100 because then we come in conflict with the titer in the window period.

[Slide]

That is the view of the manufacturer. I have to show that but it is not my view.

[Slide]

I especially have to thank Christina Stahl-Hennig for her excellent handling of the tamarins. Thank you for your attention.

DR. HOLLINGER: Thank you, Dr. Chudy. Any questions for Dr. Chudy?

DR. MACIK: I just wanted to go back to the one point that you made when you were looking at the different neutralization techniques. In one it was a pasteurization process where you had 2 out of 100-and some odd --

DR. CHUDY: Yes.

DR. MACIK: -- but they did not transmit disease.

DR. CHUDY: Yes. That is maybe the same question as earlier. Maybe pasteurization of nearly 10 hours at 68 degrees may be more effective than solvent-detergent. If you look in the literature, there are no reports of Factor

VIII and Factor IX products inactivated by pasteurization.

DR. HOLLINGER: We have been going for a good long time now so I think we are going to take a 20-minute break. It is 11:20 now. So, we will reconvene at 11:40 and we will have the open public hearing and then we will discuss the questions. Thank you.

[Brief recess]

DR. HOLLINGER: We have two groups that have asked to speak to the question on plasma pool screening by nucleic acid tests for hepatitis A virus. The first one is Dr. Louis Katz, from the American Association of Blood Banks and Chairman of the Transfusion and Transmitted Diseases Committee for that group.

Public Open Hearing

American Association of Blood Banks

DR. KATZ: Those of you who picked up the series of statements that AABB will make over the two-day meeting, I will read this boiler-plate paragraph once, and Dr. Hollinger told me that I wouldn't be allowed to read it a second time.

The American Association of Blood Banks (AABB) is the professional society for over 9,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,200 institutional members, including community and Red Cross blood collection centers, hospital-based blood

banks, and transfusion services as they collect, process, distribute, and transfuse blood and blood components and hematopoietic stem cells. Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety and availability of the nation's blood supply.

The AABB appreciates this opportunity to provide comment to the BPAC. The AABB supports the continued performance of HAV NAT on plasma pools for further manufacture as an in-process control, rather than as donor screening.

We arrive at this position from consideration of the rarity of transfusion-associated HAV infection from single donor blood components, the generally benign course of the illness, and the lack of medical rationale for donor notification. if required or performed as donor screening, with a requirement for tracing donors and components and counseling positive donors, the logistics and cost of HAV NAT would be multiplied. Furthermore, those donors notified, based on the current time lines for screening and reporting of NAT results on recovered plasma, would have recovered from their infection and their contacts would be outside any reasonable window for preventive therapy.

We applaud the effort of the plasma industry in the implementation of this testing designed to minimize the input of virus in large plasma pools to which hundreds of recipients are exposed. Its value is especially obvious for those products for which viral inactivation techniques are not robust for non-enveloped pathogens. Thank you.

DR. HOLLINGER: Thank you, Louis. The next person who asked to speak is Dr. Susan Stramer, from the American Red Cross. Dr. Stramer?

American Red Cross

DR. STRAMER: Thank you. The American Red Cross thanks the FDA for allowing us time to address the Blood Products Advisory Committee. My name is Sue Stramer, and I am the Executive Scientific Officer, National Testing and Reference Laboratories, of the American Red Cross.

The American Red Cross is composed of 36 blood collection regions that collect approximately one-half of the whole blood in the United States. Products from Red Cross collections are manufactured into transfusable components, platelets, red cells and fresh-frozen plasma. Additionally, the majority of the plasma that is recovered from the collected units is used for pooling and further manufacture into virally inactivated, therapeutic products.

The American Red Cross supports the continuing efforts to increase the safety of whole blood components and

plasma derivatives and, therefore, supports the performance of nucleic acid testing as an in-process control for the detection of hepatitis A virus. We believe, however, that this testing should be managed in a fashion that does not involve donor notification of the management of individual donations. HAV is a very infrequent contaminant of voluntary donations, estimated at much less than one per million. The infection is acute and self-limited due to the production of neutralizing antibodies, and there is no carrier state. Thus, there would be no benefit in notifying donors several weeks after donation, and infection among recipients of single donor products does not appear to be a matter of current concern. During the short window period that HAV is present in biological prior to clinical disease, that is, less than 7-10 days in most individuals, the concentration of HAV in blood is relatively low. Infectious virus is believed to be rapidly cleared by the appearance of antibody at the time of clinical symptoms. In addition, immunity to the agent increases with age and there is the possibility that other transfused units or the transfused product itself may, in fact, contain anti-HAV. Also, as has been mentioned this morning, HAV vaccine is recommended for recipients of clotting factor concentrates.

The American Red Cross' proposed current strategy for the management of HAV in the context of manufactured

plasma products is designed to assure the absence of detectable HAV RNA in the final products. HAV PCR will be performed on pools of plasma prior to fractionation. In the event of a positive result, the manufacturing pool would not be used and would be destroyed. Red Cross has performed a qualification run to determine the logistics and feasibility of this strategy. A pilot study involved the equivalent of 540,000 donations that were pooled into 45 manufacturing pools of 3200 L. Each pool was tested for HAV RNA by PCR at National Genetics Institute. All pools tested negative for HAV RNA. We believe that this strategy for HAV screening for recovered plasma from volunteer whole blood donors is the most reasonable approach at this time. Thank you.

DR. HOLLINGER: Thank you, Susan. Yes, Dr. Finlayson?

DR. FINLAYSON: John Finlayson, FDA. Is the procedure that you described the one that you would plan to continue to use, that is testing 3200 L pools?

DR. STRAMER: Yes, that is the stage at which the first pooling occurs, and that is the smallest pool size that we can get retrieval for a sample.

DR. FINLAYSON: You didn't mention what level of detection NGI anticipated getting, but if I did my arithmetic correctly, this represents units of an average size of 266.66 ml being diluted to 3200 L.

DR. STRAMER: Correct.

DR. FINLAYSON: So, that is approximately a 12,000-fold dilution. My question is, depending on your level of detection, you said in your statement that the level is low in infected individuals, do you ever expect to ever find any positives?

DR. STRAMER: The sensitivity of the NGI test, coupled with the dilution factor -- you are right, we are looking at 3.2 X 106 to 3.2 X 107 as the detection limit per milliliter of starting material. So, the technique is not very sensitive, but in the event that there would be a very high titer unit this would be the procedure to catch that unit.

DR. FINLAYSON: I guess my question is, is it worth doing?

DR. STRAMER: That is certainly a question. Currently we are doing it. One could argue is it worth doing it at the frequency we see HAV in the donors. But because the issue has come up and we do manufacture a product, the question has been asked how we should proceed and so this is one feasible way to proceed at this point.

DR. FINLAYSON: Well, I wasn't asking the question in the sense that I was implying that one shouldn't do it. It is just that I had an uncle who used to recite over and over to me "if it's worth doing, it's worth doing well" and

I think we will leave it at that.

DR. STRAMER: Okay.

DR. HOLLINGER: Thank you, John. Is there anyone else who would like to comment from the public at this time? Yes, Dr. Miriam Alter, from the CDC.

DR. ALTER: I guess the major issue that I would like to address is the benefit to the donor should notification take place. It would seem to me that most of that discussion has focused around the opportunity to prevent secondary transmission to the donor's contacts. And, I would like to make sure that we have a realistic picture of what that would mean after the donation took place. We assume that the majority of these donors are in the window period. We can make an assumption that they are in the early phase of their acute infection, let's even say the first two weeks of their infection. Presumably fecal shedding of virus, which is the phase of infection during which transmission to contacts occurs which is an issue separate from transmission through transfusion or through a blood product -- that is, prevention, the administration of immune globulin would have to be given to the contact within two weeks of their exposure, that is, within two weeks of the time during which the donor was shedding virus.

Even with rapid turn-around of testing results, is it realistic to expect that the donor can be notified and

that the donor will get evaluated, and the contacts will then be evaluated within, let's say, a four-week period of time, such that the administration of Ig could even hope to prevent infection or ameliorate disease in these individuals? Unless it could take place at a maximum, actually, of that period of time, it would not benefit the contacts of that donor. So, I think we need to take that into account when discussing notification because the blood collection group is going to have to write a letter of phrase the information. They are going to have to explain to the donor what this means. So, we need to be very sure we understand what it means to that donor and what that donor is supposed to do about. Thank you.

DR. HOLLINGER: Any other comments from the public? Yes, please, and state your name.

MR. HEALY: My name is Chris Healy, and I am Director of Government Affairs for ABRA. We are the trade association for the source plasma collection industry. I appreciate the opportunity to address this issue before you.

We believe that there may be a substantial "right to know" interest in donors being notified about positive HAV test results. However, we don't think that the public health reasons support donor notification. As Dr. Alter just described, we think that by the time NAT results are reported back to these collection centers and they are given

an opportunity to notify the donors, they are already probably fully symptomatic and would have encountered any secondary exposures, and that would have already occurred. So, the public health doesn't, we don't believe, support the donor notification while there might be "right to know" interest in donors being notified.

Further, we don't believe that donor deferral and lookback are warranted based on HAV by NAT. As I think probably most of the people on the committee know, temporary deferral really means permanent deferral for most donors. Once you turn them down, they are typically gone for ever. They are going to be symptomatic and sick, and are unlikely to donate, and should they come in after the symptoms clear up and donate still infectious units, that would again be picked up by the testing and could be eliminated.

Given the short window period by NAT if we can assume it is about two weeks, there would be virtually no donations to perform a lookback on and if there are any, it would simply be a single unit or two given the frequency of plasma donations and that could be managed in-house very easily. So, we don't believe that lookback and donor deferral are appropriate either. Thanks.

DR. HOLLINGER: Thank you. Jeanne, I didn't mean to cut you off. Did you have a question for one of the people? Yes, please.

DR. LINDEN: I have a question for Dr. Stramer. In light of Dr. Alter's comments about the time frame for intervention, could you please explain to us the logistics and time frame of the pooling and testing that you do?

DR. STRAMER: The stage of pooling that I presented, the 3200 L stage, that is within a manufacturing pool and at that time point those pools would not be broken down, or they are not able to be broken down into the individual donations. If we were doing this on a minipool basis, then it potentially would be feasible, and the time frame of that, as we do for HIV or HCV NAT, would be donor notification within several weeks of collection. But that is still too late, as Miriam has discussed, as far as preventing secondary transmission and having any benefit to the donors themselves.

DR. LINDEN: How long is it before the pooling and the testing occurs though?

DR. STRAMER: For the pool that I described?

DR. LINDEN: Yes.

DR. STRAMER: It is at least 30 days.

DR. HOLLINGER: I was going to ask Toby, but if you are up here maybe you could do it -- and, Toby, you can jump in here too --

DR. SIMON: I can do it for the plasma industry and then we can add for the blood banks. We wanted just to

put this in a time frame for the committee to kind of understand the logistics of how we operate. As Dr. Chamberland said early on, this will be key in terms of the notification. But if several companies were to be doing this testing, each would have a different protocol. I tried to do an informal survey to find out what they are at present with nucleic acid testing and so I will describe several different protocols.

The earliest that any of the collectors are learning of a positive nucleic acid test result is in the 7-14-day range. There are one of two companies that are doing this testing in such a way that they are currently providing a positive test result in 7-14 days.

There are several other company protocols where the material is shipped after it is negative for serologic testing. Then, from the warehouse the samples are taken, based on the crates or boxes, and then pool testing is done and then, of course, you have to test back to the individual unit. The soonest, under those kinds of protocols, that you would be notified would be about four weeks.

Now, the material from ABC goes to Switzerland and is fractionated there and then sent back as final product, and we are looking at a minimum of four, probably as long as eight weeks before any notification could occur under those circumstances. I gather that with your current plan at the

Red Cross it would be in the four to eight weeks range also.

DR. STRAMER: At a minimum, thirty days.

DR. SIMON: That of course is the time until the center gets a result back. Then they have to, of course, attempt to locate the donor either by mail or by phone and get the donor in for counseling. So, I think time frame-wise it is going to be uncommon, unusual to notify and counsel a donor before two weeks have elapsed since the positive test result, and more commonly it is going to be four weeks or longer.

DR. HOLLINGER: Thank you, Toby.

DR. STRAMER: I think in any environment looking at less than a two-week period of notification post collection is truly unrealistic. Even as we work with HIV and HCV and we have a yield sample and we aggressively try to contact the donor, especially for the purposes of follow-up, we are always looking at a period of at least two weeks.

DR. HOLLINGER: Yes, Dr. McCurdy?

DR. MCCURDY: I think this time frame discussion is quite pertinent, but there is one question I would like to raise in a slightly different area. That is, I think the assumption is being made that these are window period donations, and I think they much more likely are going to be inapparent infections, that is, infections that never have clinical symptoms that are recognized. I think there are

probably 3-5 inapparent infections for every one who actually gets jaundice and gets disease that is recognized. So, I think the frequency we may not know. I think the duration of time is perhaps more pertinent in the self-limited aspects of the disease usually.

DR. HOLLINGER: But, Paul, most of the studies that have looked at clinical disease in adults, as distinct from children, show that virtually 85-90 -- I mean, these are large studies where they have looked at seroconversions so probably in adults 85-90 percent of patients, if not more, develop clinical symptoms as compared to children where maybe it is only going to be 15 percent or less. So, I would think that if a person had hepatitis A, clearly the vast majority would present with clinical disease some time after they donated the blood, so within a short time.

DR. MCCURDY: I think I was basing it, at least in part, in the increased proportion of seropositivity in the population as they got older, which would imply, if they didn't have a history of hepatitis, that they either forgot or didn't have clinical disease. But I think you are probably right, it is mostly in children.

DR. HOLLINGER: Yes, Dr. Schmidt?

DR. SCHMIDT: We did a study some years ago of blood donors who, of course, denied any history of hepatitis and, as you went up on an age frame when you got up to age

70, 70 percent of them had their antibody and, of course, it increased over time. So, it is what you are saying. I don't think one out of every five people who are infected have clinical symptoms. It must be a lot, lot less than that.

DR. LATER: Miriam Alter, CDC. Actually, I would sort of like to address that. I agree that there is this asymptomatic component, although we do think that adults are much more likely to be symptoms certainly than children. However, going to the other extreme, even without symptoms one could presume for the purposes of preventing secondary transmission that the maximum period of viral shedding in the stool was going to take place in the two weeks or so after the period of viremia, if one wanted to try and make some kind of estimate. So, even without the symptoms people are still shedding virus in their stool. That is the whole problem with our outbreaks of hepatitis A. We have all this fecal shedding of virus and a lot of people who aren't symptomatic, particularly children.

Anyway, the point is that presumably you could prophylax for contact and prevent infection based on themselves fact that the donor was found to RNA positive and, therefore, at some in the next few weeks that donor was going to be shedding virus. Therefore, you go ahead and give Ig to the contacts because presumably they have been

exposed. However, regardless of whether the donor becomes symptoms or not, the time frame, as just stated in the previous discussions, would probably be outside that which would benefit the contacts regardless.

DR. HOLLINGER: Yes, Col. Fitzpatrick?

COL. FITZPATRICK: Dr. Feinstone presented data on individuals who had high levels of circulation antibody and low levels of RNA. Is there anything to tell us whether those individuals are still infective or not?

DR. HOLLINGER: Doubtful, but I will let Steve answer that.

DR. FEINSTONE: As I said, there really is no data on the infectivity of those individuals, to my knowledge unless somebody has tested them recently. But the old data -- and there is nothing wrong with old data, just because it is not PCR-based. I mean, these were carefully done studies by some terrific investigators. Those studies say that the serum and the feces are not infectious very long after the appearance of clinical symptoms. I think that is still very reliable data.

DR. HOLLINGER: Yes, Dr. Simon?

DR. SIMON: I just want to clarify, maybe while Dr. Feinstone is still there, as I understand it, we would not be detecting window cases. Window cases would be the period before if the NAT is positive, I believe. So, the

cases we would be detecting would be from the time of viremia, the first NAT positivity. So, it is from the time of our first detection until approximately two weeks thereafter that would be useful in terms of interdicting spread. Am I correct?

DR. FEINSTONE: I am not clear why you would not be detecting window cases.

DR. SIMON: I think we used the definition of window before a positive test result --

DR. FEINSTONE: Okay, antibody appears at about the time of clinical symptoms. The major period of viremia and the major period of stool shedding is prior to the appearance of antibody and clinical symptoms.

DR. SIMON: So, we are calling that the window period?

DR. FEINSTONE: That would be the classic window period.

DR. SIMON: So, it is from the first appearance of an NAT positive test until symptoms begin --

DR. FEINSTONE: Yes, and that is the period when people are infectious. That is when they are dangerous to their contacts.

DR. SIMON: And that period is approximately two weeks.

DR. FEINSTONE: it is quite variable I believe,

but it is on the order or two weeks.

DR. EPSTEIN: Steve, could I press the point a little bit? I thought I heard you say that these recurrences occur in about 10 percent of patients, and it was not clear whether the recurrences were the same thing also being observed with chronic, persistent detection of RNA. The question is in the earlier studies that looked at infectivity of plasma and stool, what were the numbers? And, were the numbers sufficient to capture the relatively infrequent cases that might have the relapses or chronic viremia? In other words, isn't there a statistical problem here? If you had a small number of volunteer studies and if only 10 percent or less might have actually had this chronic course, one simply could have missed them in the studies. So, I am not sure that the early studies are dispositive, although I don't think that in any way imputes the quality of those studies. It is a statistical problem.

DR. FEINSTONE: I understand what you are saying but, again, there is no epidemiologic evidence that these patients who have recurrent symptoms are infectious for their contacts. I don't believe there have been any secondary cases reported from those groups. Is that right?

DR. ALTER: One, in a premature infant.

DR. FEINSTONE: One.

DR. ALTER: There has been one instance of

transmission due to fecal-oral exposure from an index case with prolonged viremias, and it involved a premature infant who had an extended hospitalization in an intensive care nursery, whose source of infection was actually a transfusion. Four months or so after the original infection that infant transmitted to nurse. It is the only instance and we believe that it is unique to that particular situation and the immune competence of the premature infant.

DR. HOLLINGER: Dr. Koff?

DR. KOFF: Yes, just to follow up on that, Dr. Epstein, I think the evidence is if you look at fecal-oral transmission virtually all of the secondary cases occur within one incubation period. So, even though there may be some kind of RNA that still is present in stool and maybe some kind of denatured RNA -- I don't know -- that in some instances is still present in blood, really evidence of infectivity, other than this one instance, just isn't there, and that has been true now for about 30 years of looking at secondary cases. Most of the secondary cases that occur that were shown, in fact, occurred in the neonatal intensive care unit. Household cases have just been exceedingly unusual.

DR. HOLLINGER: Thanks, Ray. Is there anyone else who has not spoken and wants to speak from the public right now? If not, what I would like to do at this point is to

have Robin Biswas present the questions that are going to be focused on here for the committee so we can sort of focus on what we are really here for, and then discuss around those parameters. So, Robin, let's start with the first two questions, 1a and 1b.

Open Committee Discussion

FDA Perspective and Questions

[Slide]

DR. BISWAS: Questions for the committee, 1a. Should the Food and Drug Administration recommend that, if a plasma pool or minipool is found to be HAV NAT positive, the individual HAV NAT positive donor should be identified and notified of the test result?

1b. If so, should the FDA recommend that the implicated donor be deferred from donating for three months?

[Slide]

2. Should the FDA recommend that unpooled units from donors, that were donated within the three months prior to the HAV NAT positive collection, be quarantined?

3. Should the FDA recommend that recipients of transfused components from donors that were donated within three months prior to the donor's HAV NAT positive collection be traced and notified?

Committee Discussion and Recommendations

DR. HOLLINGER: Let's go back to the first

question, 1a, which is concerned with notification of the positive donor, identified and notified, and deal with this issue right here. So, I would like to sort of focus the questions on this particular question. Any comments? Yes, Dr. Linden?

DR. LINDEN: Well, I have a question for Dr. Epstein. Following up on what you said before in terms of understanding the implications of this, if somebody is identified and notified, that means that they would then have a history of hepatitis? Maybe I misunderstood what you said earlier.

DR. EPSTEIN: As Dr. Biswas stated, we currently interpret the regulation on history of viral hepatitis only to encompass clinical hepatitis, which means identified signs and symptoms and/or clinical diagnosis. The sticky wicket here is that if you create a report of a positive NAT test and then the donor is 80 percent likely also to then become recognized symptomatic, it would be captured as having had a history of clinical hepatitis. So, then they would be captured by the current by the lifetime deferral policy, and there would be a 20 percent subset that might not because they never had colleague symptoms but the majority would. Since we don't currently have a policy whereby a well-established diagnosis of hepatitis for a hepatitis with no chronic implication can be exempt from the

lifetime deferral, there would have to be sought a case by case exemption. So, that is what I was trying to explain. But, I also stated that that entire policy is being reexamined.

DR. HOLLINGER: Jay, while you are still there, I want to clarify for the committee that NAT testing for HAV is currently being done by the plasma industry. Is that correct? We are not dealing with that issue here, are we?

DR. EPSTEIN: No.

DR. HOLLINGER: The issue here is not whether it should be done but what should be done about the results, and so on? Is that correct?

DR. EPSTEIN: No, it is not correct. There are some fractionators that have voluntarily introduced NAT and at different levels of their process. We have one request for modifying the license specifically to include that procedure. Other companies have suggested that they may become interested. So, we don't currently have an industry practice.

DR. HOLLINGER: But there are no questions here -- unless I am just missing them -- that specifically say should the plasma industry test -- whatever, many pools or pools or a certain size for HAV by nucleic acid testing. Am I correct in saying that? I don't see the questions here. They are dealing with the assumption that it is being tested

and then what should be done with the results.

DR. EPSTEIN: Well, I think we are responding to the fact that we have an application which requests approval as an in-process procedure as part of a license. So, that is what we are trying to deal with.

Perhaps we should have also simply asked the committee should all donations be screened for HAV, but the agency wasn't expecting that that would be our interest and concern. I mean, if you want to raise that question initially and have the committee vote, I think that is fine but we were reacting to a specific request to do this as an in-house, in-process procedure and, therefore, how should the FDA view this? Should we require that the scope be extended? But we were really not envisioning moving that to a requirement to screen all donations. But that is certainly a logical and pertinent question if you want the committee to look at it.

DR. HOLLINGER: Well, I would just like to ask the committee. I mean, I would think that the first question should be should plasma pool screening be performed by nucleic acid tests for hepatitis A virus, or should we not deal with that? I would like to hear what the committee would like to do about this. Yes, Dr. Simon?

DR. SIMON: Well, just from the industry point of view, I am sure industry would prefer to be able to deal

with this on a voluntary basis. My take on the presentations we have heard is that there is not an overwhelming or highly compelling case in terms of recipient safety for the FDA to mandate this, but one or more companies may wish to do this as a further enhancement of safety. So, my preference would be that we not extend the discussion and that we stick to the questions FDA has given us, which is how should they handle the situation when a company wishes to introduce hepatitis A virus nucleic acid testing.

DR. HOLLINGER: Col. Fitzpatrick?

COL. FITZPATRICK: Based on what we heard from the Paul Ehrlich Institute and the comments after, I question the utility of saying you have a safe process when the odds are you are doing a test that is going to detect nothing. So, I think we should address that question.

DR. HOLLINGER: Which question?

COL. FITZPATRICK: Whether or not testing for HAV by NAT should be done.

DR. HOLLINGER: I think John's comments were that with pools of 3200 L and even a concentration of virus that is 105 -- most are 104 or less, you know, you would have to have something that is going to detect 10 genomic equivalents/ml at best to even pick up one, and that would be without looking at the Poisson distribution. I mean,

unless you do it multiple times that would be very difficult. I think it is a good comment. Yes, Dr. Schmidt?

DR. SCHMIDT: I don't think the FDA can stop the companies from doing it if they want to do it. It just brings up the question and becomes part of their SOP and how you handle it from there. Right?

DR. HOLLINGER: Yes. Dr. Mitchell?

DR. MITCHELL: I think it is a valid question because I think it needs to be clear that presumably we are not recommending that this be done, and that there is sort of a discussion about the usefulness of HAV testing.

DR. HOLLINGER: Yes, Dr. Ohene-Frempong?

DR. OHENE-FREMPONG: If the recommendation is made that those who receive plasma products that are likely to transmit HAV, they must be vaccinated against something that we presume exists. If we are vaccinating or recommending vaccination but we will not survey the products that they receive, it would seem to me that we are trying not to find out whether the problem exists at all. Maybe at some point vaccination will no longer necessary.

DR. MACIK: I think part of the answer to that though is that the vaccination is for HAV that they might contact in the community, not necessarily what they are getting from their concentrate. So, if they already have hepatitis C from their blood product and you want to protect

them with the hepatitis A vaccine so if they get hepatitis A from a restaurant they are okay, and I don't know if the idea to vaccinate them wasn't totally driven on the fact that we are trying to protect them from their concentrates on that one.

DR. HOLLINGER: Yes, Dr. Boyle?

DR. BOYLE: I don't think we have heard enough about what people are doing. It sounds like there is a variety of things out there. Some are not doing minipooling; some may be proposing minipooling; and I don't think we really have enough information to speak to the broader issue of whether or not people should be doing the HAV testing and how it should be done, but I think there is enough information to speak to the questions in front of us. And, I think depending on how we vote on 1a, that might determine whether people are doing HAV testing in the future.

DR. HOLLINGER: I think that is fair enough. Let's look at it this way then, assuming that there might be testing or there might not be, it doesn't matter, the fact is that if there is testing then the issue would be should the individual positive donor be identified and notified of the test result? That is what the question is. So, if there were testing, should you notify the donor? That is one of the big issues. So, let's deal with that question

and we will put it up for a vote if there are no comments. Yes, Dr. Boyle?

DR. BOYLE: The question I wanted to ask earlier, Dr. Epstein, is if you are notifying donors of test results, does that not require a higher level of approval than if you were doing something that did not involve what would effectively be a diagnostic test?

DR. EPSTEIN: Yes, that was the point of Miss Kochman's presentation. If we recommend and implicitly require donor notification, then we are not just looking at a process control procedure, we are looking at a medical diagnostic test. What we are saying to you in effect is we would like to hold that to the same standard as other medical diagnostic tests, which is at the very least a 510(k). Whereas, if it doesn't become part of donor notification, then it can be a process control. We still are concerned with it being validated and we still would be concerned with its performance characteristic including the setting of some standards for minimum sensitivity, but we would not require that it be validated as a medical diagnostic.

DR. HOLLINGER: In comment though, I would think, again, why do we notify people? We notify them because of some implication about their health -- chronicity, more serious liver disease and so on, for example, or we notify

them to prevent transmission or other things going on. So, the big issue here is in a disease that does not cause chronicity, and by the time you get the data, from what was just described here, you are looking at weeks down the line before you would probably be able to do anything beneficial. Then, it looks to me like it is not very appropriate to notify somebody at that point and I think that is the difference with this and the others, at least in my opinion. Other comments? Yes, Dr. Mitchell?

DR. MITCHELL: I agree with what you said but I also believe that there is a "right to know" and for people to be notified about things that are found. To me, it is sort of different and that is why I think we should address the first question, which is whether it should be done. Now, if we are saying that it shouldn't be done, then I can justify saying that people shouldn't be informed of the results if it is positive. That is why, you know, to me it is important to ask that first question. Otherwise, it sounds like you are getting some information about an individual's health and you are sort of withholding that information.

DR. HOLLINGER: I guess the issue would be what information is that about their health. I guess that is the issue. Right now, for B19 apparently the donor is not being notified but you would feel that they should be also, I

presume from what you said.

DR. MITCHELL: I think, again, there is a difference between recommended testing and not recommended testing. You know, if it is not recommended that the test be done, then I think that the burden of notification is different.

DR. HOLLINGER: Dr. Nelson?

DR. NELSON: Not being a blood banker, I am not too sure but if you had a positive pool for hepatitis A and the donor did not need to be notified or there was no recommendation for notification, would you still test down to the individual unit or only that pool? In other words, depending on this recommendation, would the process be different with regard to what the blood bank or the plasma industry did?

DR. SIMON: The answer, I think unfortunately, is going to vary between companies but I believe if you do not require notification, then it would be the choice of the company as to whether it would be preferable at some point to simply dispose of the pool and not use it in further manufacture to decrease potential infectivity but not attempt to determine the particular donor, or whether they would go ahead to minipools and do the donor. So, if you vote no on this and if the FDA follows that advice and the companies are allowed to use it as an in-process control,

then it would be the company's choice, as I understand it. If anyone in the room feels I am in error -- but it would be their choice, based on product cost issues and so forth, whether they would identify the unit or simply eliminate a small pool. It sounds like the Red Cross has already made that decision and that they were not planning to identify and they were just going to eliminate those pools. If you require notification then, obviously, the company would be obligated to go down to the individual donor.

DR. NELSON: You know, there is always a concern about false positives but when we were talking about looking at pools for hepatitis C or other agents, there were always instances where pools were positive but you couldn't identify the positive unit. What that represented is unclear but if the pool would still have to be quarantined or destroyed, then we may not be as concerned about the false positives or about testing individual units.

DR. HOLLINGER: Dr. Chamberland?

DR. CHAMBERLAND: Just a couple of comments. It occurred to me when Dr. Mitchell was making his comments vis-a-vis the right to know, and Chris Healy has said this earlier, given the demographics of the donor population, meaning that most of them are adults that will go on to develop symptomatic disease, most of them are going to know in a short matter of time that they actually have acquired

hepatitis A infection.

Just in follow-up to Toby Simon's comment, I was curious since our only precedent for in-process control that I am aware of is the parvo B19, have any of the manufacturers made the decision to go down to individual donor notification, that you are aware of?

DR. SIMON: I am not aware -- I think some are doing that in the validation phase of the test but I believe it was the intention not to do it going forward.

DR. HOLLINGER: Yes, Mr. Rice?

MR. RICE: I just had a question. If a company can either choose to do the test or not do the test, I am just wondering are they going to be using that information in any sort of representations to consumers who use that product? If that is the case, I am wondering, one company to the next, if we do HAV NAT testing, well, if you are a consumer and you are choosing which product you will consume, I wonder how that communication is going to be made and what will that really mean for a difference in one product to the next, or are we trying to figure out whether that is something we are even concerned about? I am just saying if a company is doing the test, are they going to say to the potential consumer of their product that they are doing the test? What will that really mean if we don't have some sort of guidelines? Otherwise, maybe we shouldn't do

anything about it. Let them do it internally but if they are going to reveal this as being something else they do, I am just trying to picture how that can have an effect on a person's choice of consuming the product.

DR. KOERPER: Certainly, the companies are doing this so that they can have an added edge when they are marketing their product. But I don't believe that this committee should be in the position of somehow saying that companies shouldn't do the testing. I think that is the company's right, to decide whether that will add, even if it is a marketing edge as opposed to anything else. I don't think we can tell companies they can't do this testing.

With regards to the right to know, I was sitting here trying to think, well, why do they need to know this? As people have already said, it is not like this particular infection causes a chronic disease like HIV or hepatitis C. It is not like, therefore, there is a need to intervene with treatment. Also, unlike HIV and hepatitis C, it is not like there is a potential for ongoing transmission. So, the only reason why someone would want to know that is because, therefore, they are already immune and they don't need to get vaccinated. You know, I just can't see that as a valid reason for requiring that identification of individual donors who are positive should be a requirement of these companies. I think if they want to test the pool, that is

fine but I don't think we should require them to find the individual donor and notify the donor. I just don't think there is any overwhelming health reasons why the donor needs to be notified.

DR. HOLLINGER: And let's not forget, I suspect that 50 percent of patients that I see, and I think Ray would probably agree with this, you know, never knew that they had hepatitis A in the first place. So, they have had hepatitis A in the past. They have gotten over it and they have never known it. It is an asymptomatic disease and so that has not made a difference in their life. Yes?

DR. MCCURDY: It seems to me that the most critical issue here is the notification of the donor to prevent secondary transmission. I think the logistics we have heard of so far would suggest that this would be difficult, if not impossible, unless you changed how things are being done. Even if you were to test the donations immediately after you obtained them, as is being done in many pools for hepatitis C and HIV at the present time, it still would be not easy to get to the donor within the two-week window, which I think we have been told is necessary. So, to me, that is the critical issue there.

There is one other comment and a question. If we are discarding pools that are positive either, as John Finlayson said, we are loading the dice so that we never

find a positive or we have a pretty adequate plasma supply and can afford to toss 3200 L pools at random. I suspect it is not going to happen very often, but that seems to be a little bit of a disconnect.

Blaine, I have a question that is largely directed at you because I am quite sure that you are as close to this as anybody in the room. In the studies that were done looking at non-A/non-B hepatitis before hepatitis C was found, I presume that the recipients at least were tested for antibody development to hepatitis A so that you could, indeed, say that whatever they got was not hepatitis A in the non-A part?

DR. HOLLINGER: You know, we have said this on many occasions, that this was the case, but, very frankly, I am not sure if all of them were tested for anti-HAV. I know the patients who seemed to get clinically ill were tested for hepatitis A. In terms of the whole population, I don't think they were tested.

DR. MCCURDY: About TDV, where there were serial ALTs done in follow-up --

DR. HOLLINGER: No, those were tested but outside of those, yes.

DR. MCCURDY: And I presume Harvey Alter has been testing all of his as well. So, within the limits of the numbers of those several studies --

DR. HOLLINGER: But, remember, in the case of TDV, even though it was a large number, it was only 1500 patients. So, that is not a large number.

DR. MCCURDY: Yes.

DR. HOLLINGER: Yes, Col. Fitzpatrick?

COL. FITZPATRICK: I don't disagree with any of the implications to the donor about the need to know, and the need to know and the right to know are not the same thing. The ABB Standards Committee struggled with "right to know" over a number of issues, and the new standards that are going to come out will state that any abnormal test result is to be communicated to the donor when feasible. Now, by testing a 3200 L vat and making it very difficult to get down to the donor, the plasma industry can probably justify not notifying the donor.

But I don't want to see the committee being perceived as endorsing a procedure that provides little practical additional safety to the product by answering this question. And there could be confusion on that issue. If we say you don't need to notify the donor, fine. Whether you test or not because there is very little implication to improving the donor's health or reducing the risk to their associates, fine. But is someone going to construe that as we are endorsing testing of pools as some perception of an improved safety in product? That is a concern I have.

DR. HOLLINGER: Yes, Dr. Alter, you had a comment on one of the questions that was asked?

DR. ALTER: Actually, there are two issues. One is that although the sample size of the prospective studies of transfusion recipients that identified patients with non-A/non-B hepatitis were not sufficient, I suppose given the frequency of acute HAV infection in the donor population to detect an infection, we do know that all of those cases that were identified and labeled as non-A/non-B hepatitis did not have anti-HAV and did not develop serologic markers for acute HBV. So we do know that -- symptomatic and asymptomatic.

The second issue is one to do with the sensitivity of the testing method for detecting HAV. The outbreaks that occurred in persons who received clotting factor concentrates were related to pools -- were related to what we call hot lots. These pools had extremely high titers of virus. There was an infected donor who was highly viremic at the time they donated. In all of the episodes that I am aware of in which this was looked at, there was a lot of virus there. So, presumably it would be detected by these methods, whereas low levels of virus -- I am not aware -- in pools have been implicated in transmission. So, that is just a piece of information.

DR. HOLLINGER: Dr. Tabor?

DR. TABOR: In answer to Dr. McCurdy's question, I just want to say something similar to what Dr. Alter said. All of the basic studies of non-A/non-B post transfusion hepatitis included anti-HAV testing. Even though the assays were not commercially available when many of those studies were done, they were available at research labs and there was a standard of the art at the time. You called it non-A/non-B hepatitis if you had anti-HAV testing done.

DR. HOLLINGER: Yes, Dr. Mitchell?

DR. MITCHELL: The point that I had with the "right to know" -- I agree with all the things that have been said about that -- is, in fact about the interpretation of the public. I think that most people who don't know would assume that the risk for hepatitis A is just as bad as the risk for hepatitis C and hepatitis B. So, again, I think that there is a need to just be on the record to say that it is not the same, and for us to say that it is not recommended -- you know, not that we are prohibiting any company from doing it, but not recommended and, therefore, we don't need to have the full "right to know" because it is not the same risk as hepatitis B and hepatitis C.

DR. HOLLINGER: I guess I am somewhat concerned, I mean, the fact is if these pool sizes are such that you never detect anything that is positive, then there are not going to be any donors to notify anyway.

DR. SIMON: I think that was Dr. Alter's point --

DR. HOLLINGER: Yes.

DR. SIMON: -- that it takes such a high titer donor to spread it -- am I interpreting it correctly?

DR. ALTER: Yes.

DR. SIMON: Okay, that was her point, that because it is such a high titer to cause these very sporadic outbreaks, it is a way, in fact, to detect the case that it might occur.

DR. HOLLINGER: I don't think we have any data to support that.

DR. SIMON: Well, I have to depend on Dr. Alter.

DR. HOLLINGER: I mean, it is a hypothesis but I am not sure that the data is there. Yes?

DR. ALTER: It is sort of looking at the opposite side of the coin. The only episodes of transmission or outbreaks -- actually, there have been outbreaks in Europe. There has been an outbreak here, and then there has been a cluster, a small number of cases associated with a particular product. In all of those episodes the implicated lots had very high levels of virus, or the pools from which the lots were made.

You are right, we don't have the opposite information. So, one could say that we don't know that but still we do know that what we have observed has been related

to very high-titer pools.

DR. HOLLINGER: Dr. Boyle?

DR. BOYLE: Thanks. I would just like to put my two cents in here. I think I agree with many of you that what we have been hearing about the advantages of the hepatitis A tests -- they appear to be marginal; they don't appear to be dramatic and they are only going to be good if they are done properly. How they are done properly is something the FDA should be addressing in terms of its requirements for the specificity and so on, and would be done through the licensing process. I think the key question here is that from the standpoint of the question if we do the tests do we have to notify the donor? Number one, I don't think we have heard any information that the donor really benefits from a clinical standpoint in terms of being informed or that we avoid spread, and it is very clear that if we inform the donor then the test has to be put at a higher level and increase the logistics for those people doing it. So, to a certain extent, it discourages the process.

So, from what I am hearing here, I would say that I don't want to discourage the process but leave it to the FDA to specify what is necessary to make sure that the process is done properly.

DR. HOLLINGER: John, I just want to come back

because you had mentioned before about the study that we had done sometime ago, just to give you sort of a feeling because this is a simple case, but it happened to be a donor who was a sanitation engineer who donated a unit of blood. Two days after the blood was donated it was given to a recipient, a ten-year old girl -- only a single unit -- who came down with hepatitis A. Four days later, after he donated, they had a birthday party for this individual with all his family there. Seven days after he donated he developed icteric hepatitis. Now, with that alone, if we are on top of things all members of the family should have been given gamma globulin or something should have been done at that point because it wasn't until 21 days after he donated that he was hospitalized. That is 14 days after he became icteric. And, it wasn't until about three or four weeks after that birthday party or after he became icteric that his daughter developed icteric hepatitis, and then two of her children subsequently developed hepatitis about a week or so later.

So, the point is that as he got ill he would have been notified, without having any of this in place about donor notification in that time period. And, if it is taking two weeks to four weeks, and probably you would be fortunate if you could do it in two weeks, then I think it is probably not going to be appropriate to notify a donor.

DR. YU: This is Mei-Ying Yu, from FDA. I just want to add some information. I wish Biotech's representatives were here but they are not here. However, they did reveal the things that I am going to say in a recent public meeting. So, it is in the public forum. I just want to tell that they indicated that -- this is about ST-treated plasma -- of 520 lots they assayed, they found 3 lots positive. But, as you know, each can be about 2500 units of plasma so the pool size would be a lot less than what Susan Stramer indicated. It is not 3200 L; it is probably one-tenth or a little smaller because each is approximately 2500 units of plasma.

Anyway, what they said is that, you know, if they calculate -- so they found three lots positive. And, just assuming one donation per pool, per lot, then they found about one out of maybe half a million will be positive among all the donations. And, the plasma level for that donor -- it has to be higher than 104 copies/ml in order to be detected. Okay? That is one piece of information.

Another piece of information is heat-treated plasma. In the Phase IV studies they have used quite a few lots and they found no seroconversion. This is for HAV. I am not quite sure whether these three lots were involved or not. Okay?

DR. HOLLINGER: Thank you very much. Yes, Dr.

Nelson?

DR. NELSON: To get back to the question, it appears to me that given the question and the current status that if the committee feels that individual donors need to be notified, it may in fact inhibit HAV testing unless HAV testing is also recommended and required. I think that there have been outbreaks of hepatitis A related to pools, pooled products, and it may be that it is worthwhile to detect occasionally with a high viral load because all of these pools also have antibody similar to the B19. So, I would think that not requiring testing of individual units and, therefore, a lot more expense etc. would perhaps promote or open the road to perhaps increased safety by allowing testing of pools that otherwise might not occur.

DR. HOLLINGER: All right, if there is something unique about the process, which is probably even more correct because, I mean, if you believe that vaccination which produces antibody protects you against the disease, if you believe that giving gamma globulin, which is a very small quantity of antibody, protects you against getting the disease, then the antibody in the plasma ought to protect you from getting it. So, something happens after the plasma is pooled in the process of preparing clotting factor concentrates, I think, that resulted in these small outbreaks in these circumstances.

I think we will call for the question here -- yes, Dr. Chudy?

DR. CHUDY: Maybe a comment to your view. I see also a difference between solvent-detergent treated plasma and solvent-detergent treated plasma products. I have not heard of outbreaks of solvent-detergent plasma because maybe there are enough antibodies. We have measured antibodies, or tried to measure antibodies in Factor VIII and we could not measure any antibodies because the pool has enough and maybe during the high purification drifted, and in the concentrates there are no antibodies.

DR. HOLLINGER: I am going to read the question once again and then I am going to call for a vote from the committee. The question that we have up there is should the Food and Drug Administration recommend that, if a plasma pool or minipool is found to be HAV NAT positive, the individual HAV NAT positive donor should be identified and notified of the test result?

On that question, all of those that agree with that statement and vote yes, raise your hand.

[No response]

All those opposed?

[Show of hands]

Abstaining?

[Show of hands]

The consumer representative? Mrs. Knowles?

MS. KNOWLES: No.

DR. HOLLINGER: And the industry representative? Dr. Simon?

DR. SIMON: No.

DR. SMALLWOOD: The results of voting for question number 1a, there were no "yes" votes; 9 "no" votes; 3 abstentions. The consumer representative, "no" vote. The industry representative, "no" vote.

DR. HOLLINGER: Thank you. I guess based on that vote, 1b. would no be appropriate then. I mean, there is nothing to vote on that one. Then, what about number 2?

DR. SIMON: The same problem, Blaine.

DR. HOLLINGER: Yes, exactly. And, number 3., should the FDA recommend that recipients --

DR. SIMON: It may be the same issue.

DR. HOLLINGER: The same issue. Any comments? We kind of wiped that one out, didn't we? Any comments? I think the issue here, and the FDA will have to deal with this, the question is if you are going to do testing and it is going to be required, then what quantity -- oh, there is a correction here.

DR. SMALLWOOD: There is a correction in the voting. There are 13 eligible members here to vote and according to my original count there were 10 "no" votes and

3 abstentions -- 10 "no" votes and 3 abstentions.

DR. HOLLINGER: Thank you. So, as indicated, I think the issue then is whether there should be NAT testing by HAV and, if there is, then I think the issues are going to be about what size pools, sensitivity of the assays, and so on down the line.

Anybody have any other comments before we break for lunch? If not, it is one o'clock right now. I think we will break until two o'clock and be back here to start this afternoon, and the session is fairly heavy this afternoon so there will be a lot of information imparted today.

[Whereupon, at 1:00 p.m. the Committee recessed, to reconvene at 2:00 p.m.]

AFTERNOON SESSION

DR. HOLLINGER: Why don't we just start with the open public hearing? Someone said that they have slides that they could present. Yes, if you would? Could you state your name and affiliation?

Open Public Hearing

Guardian Scientific, Inc.

DR. CHOWDHURY: My name is Afzal Chowdhury. I am from Guardian Scientific, Columbia, Maryland.

[Slide]

I am going to talk about our HIV-1 Quix M and O and HIV-2 blood test. The test is for the rapid detection of antibodies to HIV-1 and HIV-2.

[Slide]

This is less than six minutes. The rapid test involves a number of reagents. The first procedure is that this is the device where all the reaction is going to happen, and the first step is adding buffer and the second step is where the plasma sample can be added. Then you wash it through the same buffer again and then take the filter off which separates the whole blood, then wash it again using coidal gold conjugate. Then finally it is resolved in five to six minutes.

[Slide]

This is the procedural control line here and I am

explaining to you the principle of the procedure. The six o'clock position will indicate the HIV-1 including group M and O if it is reactive. This is at the three o'clock position for the HIV-2 if it is reactive. In principle, this product is peptide based. It will detect any antibodies against the immunodominant region of GP41 and for HIV-2 it will be the GP36 region.

[Slide]

The interpretation of the result is that if this part is lighted, then you call it HIV M or O, and if this part is lighted, then it is HIV-2. This would be negative but it has to have a control line.

[Slide]

Since this product is peptide based, the peptide was designed in-house at Guardian Scientific. We tested this peptide in rapid membrane based format as well as the ELISA format to find out if the peptides are specifically reactive with the specification of the samples. We tested HIV group M and O samples, like 92 samples. Then we tested HIV-2 samples, and then some selected negative samples. A total of 219 samples were tested in this study. At the end we found that the peptides were specifically reactive and we could move forward with our in-house preclinical studies using the peptides in the rapid test format.

[Slide]

So, we took the peptides designed into our rapid format and then we used samples from different countries including the U.S. and all over the world to cover all the subtypes of HIV-1 and HIV-2 to see if we covered the whole thing.

[Slide]

Included in the samples of HIV-1 group M, all different possible available subtypes of HIV-1 group O and from all different variants that were available, HIV-2 from the BBI panel and other sources from the Ivory Coast, and then HIV negative samples including different disease conditions.

[Slide]

The samples included in our in-house study with this peptide-based test is that we used 10 finger stick, 50 whole blood, 380 plasma, over 1000 serum and a total of 58 samples were tested in-house.

[Slide]

The results appear to be that HIV-1 group M and O, total samples is 723 and total HIV O positive samples tested were 39. HIV-2 samples, we tested 169 and both peptides is a negative sample of 627. So, a total of 1558 samples were tested.

[Slide]

Our in-house studies all indicated that the Quix

HIV-1 M and O rapid test correctly identified all the HIV positive and negative samples. We did not find any false positive or false negative in our study. However, we had 28 unlinked samples from only one source, Uganda, that were unresolved because they were not linked from Uganda. And, we did Western Blot but all were indeterminate. So, we excluded them.

[Slide]

Based on the fact that we were quite satisfied with the in-house study, we gave our product for external evaluation to the Institute of Human Virology and Dr. Niel Constantine did the study. In his study, he included HIV-1 group M, 75 positive samples for a total of 270 samples. And, he included HIV-1 group O, 20 samples and HIV-2, 160 samples from the Ivory Coast and he used non-U.S. origin HIV positive 98 samples from different countries. He concluded his study as no false positive and no false negative, however, he also had some discordants that could not be resolved.

[Slide]

So far I have talked about this product, which is Quix peptide-based product. As some of you may know, we had a product which was recombinant-based, which we called the first generation product of Quix 1-2-0. The product was submitted for FDA approval and the clinical was completed,

and the study was done with close 10,000 samples.

The result of the study was that it was 100 percent sensitive and there was 99.8 percent specificity. So, since this is our second generation product that is peptide based, in our study we always compare our product with our first generation product to make sure that this is as good or better than our first generation product. The only place we had this equivalence study done outside was at the Walter Reed Army Institute. They did the study using 1679 samples. They used both first generation and second generation. As far as the result is concerned, there was concordance. Both products showed equivalence. They had a number of discordants but the discordants also in concordance as far as these two products are concerned -- side by side.

So, at this point we are moving forward with this new generation peptide-based product. We had a pre-IND meeting with FDA. So, we are hoping to submit the IDE and move forward with that product. Thank you.

DR. HOLLINGER: Thank you, Dr. Chowdhury. We may come back and ask some questions in a minute. I think we will go ahead now and start with the regular presentations so we can move through because I think in those regular presentations there will be some background with the different types of tests that are being used and so on out

there with the rapid tests. So, to start off is Dr. Poffenberger, who will give us a background and introduction.

Development of Rapid HIV Tests

Background and Introduction

DR. POFFENBERGER: While we are wrestling with technology, I want to thank Dr. Chowdhury for leaping into the fray and filling in on the spot. Thank you very much. What he presented was an example of a rapid test that his company is developing. What I am going to do today is to essentially give you an introduction to these tests and how FDA is handling them.

[Slide]

So, welcome to our session which has already started. You will be reviewing a lot of information this afternoon so my presentation is aimed at providing an introduction and frame of reference for the rest of the talks.

[Slide]

The rapid HIV tests under development are not intended for blood screening. They are intended as an aid in diagnosis for use in various healthcare settings. These sites include public health settings, outreach clinics, hospitals and other clinical settings.

[Slide]

What is a rapid HIV test? You had a real quick introduction to one kind. What the class of rapid HIV tests is, are tests which provide results within 20 minutes, and many tests can be done in less than 10 minutes. This test is provided as a complete kit with all reagents included. No specialized equipment is needed for the tests. In fact, some of the tests do not require refrigeration. A rapid HIV test is an immunoassay that detects antibodies to HIV. The result is based on visual detection of an HIV antibody spot or line.

[Slide]

Although there are four formats for rapid tests available worldwide, two formats are the primary focus in development of tests for the U.S. market. These formats are flow-through membrane immunoconcentration and lateral flow immunochromatographic strips.

[Slide]

The committee has a sample of the licensed flow-through membrane immunoconcentration test cassette on the table in front of them. This type of test includes a cassette that houses a permeable membrane. HIV antigens are bound to the membrane in specific spots. The specimen for these tests is typically serum or plasma, although some tests have a pre-filter to allow their use with whole blood specimens. A sample is added to the well of the cassette

and flows through the membrane to an absorbent pad. After sample addition, multiple steps are performed to wash away non-specific interactions and to detect HIV antibody. Development of a spot or line indicates the presence of HIV antibodies in the sample. The flow-through immuno-concentration tests are typically considered to be of moderate complexity by CLIA guidelines.

[Slide]

This is a photo of the licensed Murex SUDS cassette indicating a positive sample result. The SUDS test is a test of moderate complexity. The center blue spot indicates the presence of antibodies to HIV.

[Slide]

The other type of rapid HIV test under development is the lateral flow immunochromatographic strip test. These tests consist of a nitrocellulose strip, with absorbent pads attached, that has HIV antigens applied as a line. In these tests the sample is applied at one end of the strip where it mixes with signal reagents and then migrates, by wicking action, along the strip. These are very simple one or two-step tests. Again, the development of a visible line indicates the presence of HIV antibody. The tests include a control line to indicate that the sample has migrated far enough. These are typically considered to be low complexity tests. Everyone on the committee and in the audience will

get a little more information about these types of tests in a later talk.

[Slide]

In addition to the tests under development, FDA has licensed two tests for use in the United States. The first to be licensed was the Cambridge Biotech Recombigen HIV-1 latex agglutination test. The second test licensed was the Murex single-use diagnostic system, HIV-1 test, known as the SUDS test which you saw in an earlier slide. I need to mention that Murex is now a part of Abbott.

These tests were licensed with the limited claim for blood screening in facilities where EIA plate tests are impractical. The Recombigen test has been withdrawn, leaving the SUDS test as the only rapid HIV test on the market in the U.S.A. today.

[Slide]

In contrast to the test on the market, the rapid HIV tests under development that we are discussing today are not seeking a claim for blood screening. As diagnostic in vitro devices for the detection of antibodies to HIV, these tests are considered to be Class III devices. The regulations pertaining to rapid HIV tests intended for diagnostic use are different from those pertaining to licensed blood screening tests. These regulations are found in the sub parts of the 21 CFR 800 series. Manufacturers of

rapid HIV tests follow the path of investigational device exemption (otherwise known as IDE) and pre-market approval (known as PMA) submissions to get to market.

Although IDE approval is only required for some studies of rapid HIV tests, depending on trial design, FDA encourages manufacturers to submit IDEs to obtain guidance on their clinical trial design and to assure that the trial will lead to product approval. The inter-center agreement places responsibility for these tests at the Center for Biologics and review is conducted in the Office of Blood Research and Review. That is why the committee is hearing about these tests today.

[Slide]

Several studies have demonstrated that there is a public health need for having more rapid tests available. In particular, there is a need to provide a test result during a single visit to individuals seeking testing and to individuals presenting for care in clinics, hospitals and emergency rooms. The current practice for providing results is to use an ELISA assay to screen samples and to supplement a Western Blot test to confirm ELISA positive samples. This algorithm takes up to two weeks to provide results. Individuals do not get results unless they return for a second visit. CDC has estimated that up to 8000 positive individuals per year do not return for their results.

Letting these individuals know they are positive should prevent them from causing secondary infections. You will hear more about this from Dr. Robert Janssen.

[Slide]

Having HIV test results available quickly should help in making treatment decisions for individuals with percutaneous exposures to blood from patients with previously unknown HIV status. Dr. Nancy Wade, one of this afternoon's speakers, has shown that treatment intervention for neonates begun within 48 hours of birth can reduce perinatal transmission of HIV by as much as 50 percent. Treatment begun during birth might improve this benefit. Dr. Wade will discuss the New York State Health Department's experiences with testing and perinatal transmission.

[Slide]

Meeting the public health needs I have described presents some challenges to rapid test characteristics. Rapid HIV tests must be able to provide results quickly. They should be easy to perform and to read. They should be safe and effective and should provide meaningful results in the intended use populations.

[Slide]

FDA has been taking action to facilitate approval of rapid HIV tests. These actions include maintaining an ongoing dialogue with sponsors. This dialogue includes

holding pre-IDE, pre-PMA and other meetings and participating in conference calls. FDA has also been working with sponsors to enable access to rapid tests through treatment IDEs and expanded access routes. In March, 1999 FDA postponed the requirement for inclusion of group O antigens in rapid HIV tests.

[Slide]

FDA has also reduced the sample size requested for clinical specificity studies in low risk populations. The sample size requested for rapid HIV tests is 6000 as compared to the sample size of 10,000 that is a requirement for donor screening assays. Today, FDA is seeking to clarify approval standards for sensitivity and specificity of rapid tests. FDA is also proposing specific labeling for use of these tests.

[Slide]

FDA recognizes that the public health needs for rapid HIV tests are different than those for blood screening tests. Because these needs are different, the standard for approval of rapid tests is different. FDA is seeking to clarify its approach for approving rapid HIV tests according to a separate standard from blood screening tests.

[Slide]

These approval standards are based on data which will be discussed in presentations by Drs. Zahwa and

Janssen. Published studies in developing countries have shown that rapid tests can be reliable and that sensitivity and specificity vary among populations and among tests. Data from U.S. populations is much more limited. FDA has been working with CDC to determine state-of-the-art performance of rapid tests in U.S. sites.

[Slide]

The approval standards for rapid HIV tests will assure that each test achieves state-of-the-art clinical performance levels for sensitivity and specificity. This current state-of-the-art performance level in U.S. populations for serum or plasma specimens is 98 percent sensitivity and 98 percent specificity.

[Slide]

FDA is proposing a two-part sensitivity standard for rapid HIV tests. Each test should demonstrate 100 percent sensitivity, correctly identifying 11 of 11 positive samples on the FDA HIV-1 panel. Each test should have a lower bound for the 95 percent confidence interval for sensitivity studies of at least 98 percent. This lower bound is based on confirmed positive samples from two study populations, from known positive individuals with a total sample size of 1000 and from positive individuals identified in testing of high risk populations with a total sample size of 500. The number of positive individuals in this last

study depends on the prevalence of HIV infection in the high risk population.

[Slide]

FDA is proposing a specificity standard based on clinical studies, to total 6000 studies from low risk populations. The lower bound for the 95 percent confidence interval must be at least 98 percent.

[Slide]

How will these rapid tests be used after they are approved? These tests will be used in non-donor settings. They will provide a preliminary result for HIV serostatus during an initial visit.

[Slide]

This means that when a sample has a negative rapid test result no further testing of the sample is performed. The individual is counseled that they are negative for antibodies for HIV.

[Slide]

When a sample has a positive rapid test result the sample will be sent for confirmatory testing. The individual will be counseled that their preliminary result is positive and they will be advised to return for a second visit to get the results of the confirmatory test.

[Slide]

Approval of additional rapid tests will also offer

the option in the U.S. to use a multiple rapid test algorithm during a single visit.

[Slide]

The multiple HIV antibody test algorithm is a combination of screening tests for HIV antibodies. This combination was initially a mix of ELISA and rapid test. It was developed to be used instead of the EIA and Western Blot algorithm in developing countries, where the instrumentation, complexity and cost of the EIA-Western Blot algorithm were prohibitive. In 1997, the World Health Organization revised their recommendations for using this algorithm in three different strategies. There is substantial field data for performance of different multiple rapid test algorithms from developing countries. Much of this data has been collected under the auspices of the CDC.

[Slide]

The multiple rapid test algorithm can be designed toward improving accuracy of the test result. The factors that influence accuracy of the algorithm result are the sensitivity and specificity of the test chosen for the algorithm, the order for performing tests, that is, whether they are done sequentially or simultaneously. Another major factor is the decision rule for determining the algorithm result.

Two of the possible rules are listed here. In the

first case, sensitivity is optimized by letting any single individual test positive result yield a positive algorithm result. In the second case, specificity is optimized by requiring that all individual test results must be positive to yield a positive algorithm result.

[Slide]

This table provides an example for results expected from using a two-rapid test algorithm. In this case, I am showing the worst case expectations for two tests that have the minimum sensitivity and specificity according to the proposed standards. So, for this chart, test A and test B are both at 98 percent sensitivity and 98 percent specificity. If they are combined into a two-test algorithm, using rule one, which is shown along the first row, both individual test results must be positive in order for the algorithm result to be positive. The worst case assumption that the individual test error is not overlapping yields a 96 percent sensitivity and 98 percent specificity for rule one.

If rule two is applied to the two-test algorithm, sensitivity is optimized by having a single positive test result yield a positive algorithm result. In rule two, sensitivity is 98 percent and specificity is 96 percent.

I want to emphasize that this is the worst case scenario. Under typical circumstances a testing site would

combine tests with better sensitivity and specificity, and with varying sensitivity and specificity, in an algorithm designed to improve the accuracy of testing.

[Slide]

Data from developing countries shows that multiple rapid test algorithms can improve the accuracy of the HIV antibody test result. The sensitivity and specificity achieved in multiple rapid test algorithms approach and can exceed that of the EIA and Western Blot algorithm. Downing et al. reported achieving 100 percent sensitivity and specificity for certain populations.

[Slide]

In the United States studies are ongoing under t he direction of the CDC. Algorithms may be recommended by the CDC and/or the Public Health Service. The combined data from field and current studies indicate that using a multiple rapid test algorithm to improve the accuracy of HIV antibody test results may be appropriate in certain settings.

[Slide]

FDA is proposing to allow use of multiple rapid test algorithms in conjunction with approval of individual rapid tests. Review of submissions, approval and labeling will be done separately for each test. Manufacturers must provide data to show that each test meets the approval

standards. Manufacturers must also provide evidence of consistent manufacturing and test reproducibility.

[Slide]

The labeling will follow current practice to read, "for use as an aid in diagnosis ..."

[Slide]

The labeling may indicate that "this test may be used as part of a multiple test algorithm to improve the accuracy of testing in settings where the use of an approved supplemental test for HIV antibodies is impractical of unfeasible prior to patient counseling."

[Slide]

This completes my introduction. This session will continue with data presentations and discussions from other public health and private points of view. You will hear more about the need for rapid HIV tests and the performance of these tests. You will hear data from multiple rapid test algorithm studies, and you will be more familiar with some of the different tests in development.

[Slide]

Through the rest of the presentations I would like to ask the committee to keep in mind the questions that will be posed later this afternoon, namely, does the committee agree with the FDA standards for approval of a rapid test for use in the diagnostic setting? And, does the committee

agree with the FDA proposal for labeling rapid tests, that is, to allow use of multiple test algorithms for each approved test? Thank you.

DR. HOLLINGER: Thank you. The next presentation is by Dr. Robert Janssen.

Presentation by Robert S. Janssen, M.D., Div. of HIV/AIDS

DR. JANSSEN: I am happy to have the opportunity to address BPAC on what we feel is an extremely important issue, that of rapid HIV testing. Before I begin my formal presentation, I want to take a moment to talk about a "Los Angeles Times" article yesterday that was reprinted in "The Washington Post," in which it quoted a CDC employee. I want to be very clear that the quote in the paper does not reflect CDC's position, that although CDC strongly supports the need for rapid testing, we respect the critical role that FDA must play in assuring all new HIV tests meet standards of accuracy and consistency of manufacturing. It is not in the best interest of CDC, nor in the best interest of the FDA, or the federal government, or the people in this country to have tests available and on the market that cannot provide consistent, high quality performance in a variety of settings. We have worked closely with our colleagues at the FDA for a long time. They share our passion for ending the epidemic and getting these tests to the market as soon as possible, and this close work has

brought us here today to make a case for the importance of rapid tests for your consideration.

It is unfortunate that the articles in the paper yesterday painted a different picture. Please know that we made sure all media following up with us on this article understand CDC's position, and we have also apologized to our FDA colleagues. We offer similar apologies to this advisory committee, and hope that CDC and FDA can continue to move forward together on this and many other important issues.

[Slide]

I am excited to have this opportunity to talk because I think, to some extent, this is an unusual situation. When I talk about or think about a test, I think sort of about the standard uses of tests, and I think this committee particularly looks at blood screening, a very sort of regimented testing scenario. And, what I am going to talk about is actually way beyond that. Where we would like to go with rapid testing is to the streets, and that is a very different place from where people have been thinking about testing, and I am going to give you why we think that.

[Slide]

Simple rapid tests, as Kim pointed out -- I won't belabor the point -- are really critical tests. The test that is on the market now is not a simple test. It is a

rapid test and it does qualify as that. It doesn't enable us to get out of the laboratory easily and that is what we need to be able to do. Tests need to have minimal equipment requirements, and need to have also the opportunity for immediate test results. Kim touched on a single test result -- and I will mention the algorithms later as well -- as the direction in which we eventually want to go. We want multi-rapid test algorithms so that you can tell somebody when they come to see you, whether it be in a mobile van or in an emergency room -- within a half hour you can give that person a confirmed HIV diagnosis. They wouldn't have to wait for two weeks.

[Slide]

The context of all this for us is in the very important HIV prevention initiative that we have just launched, that we call "The Serostatus Approach to Fighting the HIV Epidemic." We have targeted our prevention programs on a lot of different factors -- risk factors, geographical factors and a number of other factors. Now what we want to do is expand our prevention focus by using serostatus.

[Slide]

What is SAFE? SAFE is a new CDC prevention initiative that is designed to complement our existing prevention activities. It is based on the knowledge that services and interventions for high risk negative

individuals may not address the needs of HIV-infected individuals, and it is specifically intended to more directly target the prevention needs of HIV-infected individuals and their partners. HIV prevention money is put out through the community planning process throughout the country. Only 30 percent of HIV community planning groups in this country identify HIV-infected individuals as priority populations for HIV prevention activities.

[Slide]

Why do we need it now? Our estimates of HIV incidence have been stable at about 40,000 since 1992. In addition, because of treatment advances, more people are living better and longer lives and, thus, the potential for more HIV transmission. Finally, treatment advances have also contributed to complacency and increased risk behavior in communities at highest risk, particularly this has been noted by outbreaks of syphilis among gay and bisexual men in a number of cities across the country. It started out on the West Coast; it is now seen across the country -- men in their 30s, where 50 to 75 percent of these individuals are HIV infected.

[Slide]

If you are going to take a serostatus approach to fighting epidemic, then serostatus obviously is important. Well, what do we know about serostatus? We estimate that

800,000 to 900,000 people currently live in the United States with HIV infection; that about 625,000 know that they are HIV-infects; and then we estimate that 175,000 to 275,000 don't know they are infected. That is a critical number and that is why rapid tests become important.

How do we reach those people? We believe that the majority of new infections are occurring from people who don't know their HIV serostatus. Only one study has addressed this at all. It is the OPTION study, in San Francisco, where they have linked 17 people, source recipient pairs and 11 of those 17 infections were caused by people who did not know they were infected. This was in San Francisco. This was last year, in an area where testing is very high.

[Slide]

There are advantages, both personal and public health advantages to knowing the serostatus for HIV-infected individuals. The first is a personal benefit -- people are living longer and better lives. HIV treatments to date now have improved life expectancy by at least 5 years from the untreated natural history.

But there are also public health benefits. This slide demonstrates one of the public health benefits. This will be published tomorrow in the MMWR. Basically what it says is that people who find out they are infected don't

want to infect other people, and they reduce their risk-taking behavior. This is a study of men who have sex with men and women, and what they did in the 12 months after they were in their serostatus, and 60 percent used condoms more often, 49 percent had sex less often, 36 had not had any sex, and 10 percent had sex only with other HIV-positive persons.

We also have data from several other studies. Some of them have been submitted; some of them are in preparation, none of them have actually been published yet, that substantiate this as well and over time -- not true for everyone. There are definitely HIV-infected people who do not reduce their risk behavior and who we definitely want to try to get into prevention services.

The third reason that people who are infected should know their serostatus is a potential public health benefit, and that is where HAART reduces HIV transmission. There is a lot of indirect data that suggest that people with undetectable viral load due to HAART may actually be less infectious. It is not clear to this point. It is just a potential benefit.

[Slide]

So, what is SAFE then? SAFE has five action steps. The first one, which is where rapid tests comes in, is to increase the number of HIV-infected individuals who

know their status as early after infection as possible. The second then is, once you identify these people, you need to link them into healthcare and prevention services. Once they are there, you need to increase the number of infected people who are receiving appropriate care and treatment services. You need to support them in adhering to their prescribed antiretroviral medications and support the adoption and maintenance of HIV risk reduction behavior.

[Slide]

I want to focus on action step one for this talk, and that is to increase the number of infected people -- how we think we want to approach this is in two ways: encourage people to seek testing but the second is to provide testing; make testing more available, and we see that that is where the critical role of HIV rapid testing comes in, and it is getting into alternative settings, settings that can be reached by community-based organizations.

We are putting out about eight million dollars this year to community-based organizations, asking them to form partnerships with health departments to provide innovative testing strategies for people in their communities. We hope that rapid tests will be available for these community-based organizations because we really believe that that is the technology that will enable us to reach some very hard to reach populations. We have also

been thinking about where you can find HIV-infected people who don't know their serostatus, and another place is hospital emergency rooms.

[Slide]

This is a slide that gives the seroprevalence in several hospital emergency rooms across the country, ranging from 6.4 percent in the ER at Johns Hopkins, 5.4 percent at Bronx Lebanon in the South Bronx, down to 2.3 percent at Grady Hospital in Atlanta, and Cook County in Chicago, and we also have done a study. So, there is high prevalence in these ERs. But we have also done a study called the Sentinel Hospital Study, which finished in 1996, and in 1996, in 14 high prevalence hospitals across the country half of the HIV-infected people, going through those emergency rooms, did not know they were infected.

So, we think an important place to do routine voluntary testing is in hospital emergency rooms. There is no way you can do that and wait two weeks to get a test result. Rapid tests offer that opportunity.

[Slide]

Finally, the other point I wanted to mention also is where rapid tests could be very valuable, where can you find HIV-infected people? There are a number of injecting drug users who traffic through our correctional facilities and increasing, again, routine voluntary testing in

correctional facilities may be another way to help people learn their status.

[Slide]

Now, there are additional public heath needs for rapid tests, which I will just barely mention because Kim mentioned it and Nancy Wade will be talking about perinatal but the first is high rates of non-returned for test results. The second is need for immediate information or referral in two settings that Kim mentioned so I won't talk about them.

[Slide]

We did several studies in the mid-1990s, looking at rapid tests. There is a problem in publicly funded counseling testing sites where people don't come back for their test results. About 28 percent of HIV-infected people don't return for their test results. Overall it is about 50 percent.

This is based on data -- Bill Kassler did a study in which he was able to provide rapid testing in a single test. So, someone got a preliminary result if they were positive or if they were negative they got the result. It increased the proportion of people who knew their status dramatically, including HIV-infected people. Just giving them a preliminary result, they came back two weeks later to get their confirmed result.

When you apply those data to our overall counseling testing system, which pays for about two million tests in this country a year, you see an increase here if you added rapid testing, an increase of 8000 to 9000 or almost 10,000 people learning they were HIV-infected who would not have learned it otherwise -- I am sorry, up to 700,000 who were HIV negative who would have learned their test results. So, we feel it is very important in a routine testing facility -- rapid tests can give us a tremendous impact.

I just want to say once again that people in the HIV prevention community are looking at rapid tests as having the potential for transforming HIV testing, and I think there is a real opportunity for that. Thanks.

DR. HOLLINGER: Any particular questions for Dr. Janssen at this time? If not, the next presentation is by Dr. Zahwa.

Presentation by Lt. Zahwa, DOD

LT. ZAHWA: First and foremost, I would like to thank the organizing committee for inviting me to present on the topic of HIV rapid diagnostics.

[Slide]

My name is 1st Lt. Zahwa. I am from Walter Reed Army Institute of Research. We belong to the Medical Research and Material Command. The reason I am here today

is to describe to you why we are doing this rapid testing and to describe our experience with rapid testing. We have worked very closely with the CDC and the FDA and many of the collaborators our there in industry regarding this issue.

[Slide]

The objective of being here today is to explain why we are doing rapid testing; describe how we are doing rapid testing; present the testing platform very briefly and summarize the test results. And, it is up to the organizing committee as to how they want to open up the questions and answers, or whatever, after my session or later on.

[Slide]

As we say in the military, we use the acronym BLUF, which is "bottom line up front," why are we doing rapid testing? We are doing rapid testing because our deployment rate has quadrupled over the past ten years. We are deploying to more places; we are deploying more troops to places that we have never been to before. Our number of peace-keeping missions has also increased dramatically, the peace-keeping missions where our soldiers interact directly with the endogenous population, and in these peace-keeping missions we are not in a war scenario but we are also exposed to the population under hostile conditions sometimes and our soldiers are exposed in these conditions. Last, but not least, which might be a concern for this committee here,

is that when we deploy to an area overseas each one of us wearing this green suit is considered "a walking blood bag," meaning if we run out of supply and we have to use blood or come up with more blood, then the soldiers are our next choice here. We are screened on a routine basis for HIV. We are screened every two years for HIV. We are screened within six months of deployment for HIV. So, we are considered a low prevalence, pretty much safe population, however, when we are deployed for periods of 90 days and more we are exposed to the population out there and we have seen soldiers who have contracted HIV when they are overseas.

[Slide]

With a disease that is spreading like brushfire, you can see that the newly infected HIV during 1998 is 5.6 million. The point I am trying to bring with these slides is how the disease is spreading worldwide, and we are going to these places. If you look at Africa, where we are deploying people now for peace-keeping missions, or to Europe where we are also deploying people for peace-keeping missions, we are being exposed to individuals who are infected with HIV. We are doing that on a daily basis.

[Slide]

I must first apologize for the quality of the slides. Being from a sister agency to the FDA, I did not

expect the high quality and the high technology. I was shocked to see 35 mm slides, audiovisuals and cameras.

[Laughter]

Over the past decade or over the past five years, the vision of the Army of how we fight has changed. We are no longer an army that is controlled by the terrain or limited by the knowledge that we know today to go into war. We are an army that is expanding the battlefield, and controlling the battlefield with satellite feeds and PVAs held by soldiers that feed information back to the line to make decisions.

What I am trying to say here is we are no longer fighting a way in Kosovo and staying there and not knowing what is there. We are expanding the whole theater of operation. It is a European theater now that we are deploying soldiers to, and these soldiers move from one area to the other.

[Slide]

This is the most important slide -- I am just kidding! This is the combat service support comparison. This shows why we are involved in rapid diagnostics. In the past, the way we used to fight wars, the medical hospitals, the main medical units used to be in the rear of the battlefield where we could supply them with generators, air conditions -- it used to be the best job in the field to be

a medical service corps officer. Now when we are deploying we are moving these things to the forefront of the battlefield where we have individual teams, surgical teams, etc., etc. taking care of our wounded soldiers, and we are being exposed to populations so we need to know, in exposure prophylaxis situations, whether we need to administer that or not.

[Slide]

How are we getting samples? How do we do this? As I mentioned earlier, we are screened in two-year cycles so we have access to over 25 million samples right here, down the street from us. These samples were previously screened with EIAs and Western Blots, FDA approved, and/or non-FDA approved nucleic acid testing. The samples are frozen at minus 80 degrees, and the samples were collected from active duty National Guard or Reserve individuals. Every sample we collect, we keep. We do not throw anything away. That is the mentality of the federal government -- "we might need it one day so we might as well keep it."

[Slide]

As was mentioned earlier today, the acceptability criteria -- this is not by any means the FDA's or the CDC's acceptability criteria; this is what we set for ourselves to be acceptable. What we set to be acceptable is a 100 percent sensitivity platform and a 99 percent or better

specific platform that is easy to use by the soldiers. We want a positive predictive value of 100 percent. We want a test efficiency that is close to 100 percent.

As you will see later on in the slides, these criteria that we set up were near impossible to achieve. We set the bar to be way too high, but we figured out a way how to fix that -- not by fudging data but there are other ways of doing it.

[Slide]

The way we evaluate platforms is we design panels. We looked at our freezer. These are all frozen samples. This is not the intended use of these tests, therefore, the sensitivity and specificity speaks only to the trials that we performed. There are other trials that are being done by the CDC that are prospective trials that are for the intended use of this test. However, the collaboration between us and the CDC allowed us to do this, and for them to have a better idea instead of deploying a platform prospectively when the sensitivity and specificity is not acceptable.

First of all, we designed a panel of 100 samples. If we are approached by company X that says they have a platform and this platform works like a miracle and it is 100 percent sensitivity and 100 specific, we will be glad to evaluate that. We will obtain 175 devices. We will

evaluate it on this panel that has 25 reactives and 75 non-reactives. We will repeat all of our reactives in duplicates under all platforms that we will discuss today.

Again, I apologize for the poor quality. There are two colors on this slide, a red color and a green color. The red color is a "no-go" and the green color is a "moving forward." At the end of this evaluation we will look at our sensitivity and specificity and ease of use.

If we decide that a product is worth our time and is promising, we will move over to 1000 panels where we have 250 and 750. Again, we will look at the product, if it is sensitive and specific, and meets some other criteria that we insert here in the 1000 panel, such as HIV-1 subtype E, subtype O we will move over to an 11,000 panel. The 11,000 panel is 10,000 non-reactives, 1000 reactives. At this point, our generals made a commitment not to deploy a test that is not FDA approved, and we stand behind our generals on that, we will not deploy a test that is not FDA approved.

So, when we get to this point and we obtain the sensitivity and specificity, if the product is not good or is not performing well in our hands we will discourage use. We will discourage all our medical facilities from using this product and we will hold discussions with the FDA and the CDC. If the product is good, meaning that it has the acceptable sensitivity and specificity, we will only

recommend the use of this product after the FDA approves it. Again, my boss, who is Lt. Col. Nelson Michaels and some of you might know him, is talking about a 100,000 panel, that we might expand these studies to 100,000 samples to test the sensitivity and specificity before we deploy it.

[Slide]

As was mentioned earlier, the two platforms are well-known, the flow-through device and the lateral flow. As was mentioned earlier also, the control line in the lateral flow devices is crucial here. It tells us whether the sample has been added and if the test is completed. Some of the newer flow-through devices have a control dot on them that will also show the same thing.

[Slide]

I will move through these slides pretty fast. These slides are not meant to be detailed. They are just to show you what platforms are out there and by no means are these all the platforms out there. These are the ones that we evaluated. This is SUDS, Murex and Abbott now. This is the only FDA approved product on the market today for HIV testing. Again, SUDS works on the serum and plasma. It takes 30 mcl and, as was mentioned earlier, it is a moderate complexity test.

[Slide]

Another product by Abbott -- Abbott is a well-

known company, as you might well know. They make Determine, which is made in Japan and brought over here. Determine is another good product. It has serum, plasma and whole blood. It takes 50 mcl. I want to take a few minutes to describe these tests because it is crucial to understand how simple they are and how detrimental the results can be if they are not read correctly and if they are not within acceptable criteria.

You apply 5 mcl of serum or plasma down here. The test migrates on its own. There is a control line all the way out here, as you see in the tannish or red color. That indicates the completion of the test. The test bar is down here. A positive test will be something like this, where you read a bar, and a negative test will be nothing at all.

Abbott's test, the Determine, needs a reagent to be added for the whole blood, and the whole blood has to be measured to be 50 mcl before it is added to the strip.

[Slide]

The next test that we are very interested in is the Hemastrip, made by Saliva Diagnostics Systems. I believe they used to be out of Washington State and now they are in New York. Again, this works on serum, plasma or whole blood. It takes 3 mcl, and the start to finish time of these tests, as was mentioned earlier, is less than 20 minutes. This is a fairly simple test to perform in the lab

that can be done with a finger prick. You can collect the sample, perform the test, see the result and, hopefully, provide a physician with the results when it is FDA approved for counseling.

[Slide]

This test is UniGold, by Trinity Biotech. They are in Jamestown, New York but the test is manufactured in Ireland. Again, it works in serum, plasma or whole blood, 50 mcl. As you can see, it is a similar principle but this one is in a casket. You apply the sample here and you add buffer to it and it migrates through. This is a good picture where it shows the control line and the test line, the control line in a negative sample.

[Slide]

Epitope is another good product that we evaluated briefly before and we are looking at now in a full magnitude. I will explain that later. Epitope is a test that works on saliva. Our colleague, Bernie Branson from the CDC, showed at previous meetings how simple it is and how well it works by actually taking one out of is pocket, performing the test, setting it on the table in front of him and by the end of the talk the test result was available. This is a test that has a pad on the front of it, right here, which you stick in the patient's mouth and collect the saliva. You stick it in the buffer and it migrates through

-- the same principle; it just works much faster.

[Slide]

Multispot is a test that differentiates between HIV-1 and 2, and it can be performed with 40 mcl of serum or plasma. This is another platform that we are looking at in full scale now.

[Slide]

The Cambridge Biotech, which is now Trinity Biotech -- this is the Capillus platform latex agglutination that was mentioned earlier.

[Slide]

Quix by Universal Health Watch, serum, plasma or whole blood, 50 mcl. They added a control line, which you can see here, and two dots for HIV-1 and HIV-2, one of the few tests out there on the market that can distinguish between HIV-1 and HIV-2.

[Slide]

When I first took over this job about three years ago, this was the first test we evaluated, latex agglutination based on particle size that will make it or not through this filtration membrane. I am not sure if the company is still around today to provide us with a test but you will see the results later.

[Slide]

Last but not least, HIV 1/2, and this is not to be

confused with the Maryland test HIV 1/2. This is an HIV 1/2 test that is made out of New Jersey. I was in a meeting down in San Antonio a couple of years ago, and some guy approached me with a very promising test. We obtained 175 devices, performed the test and you will see that the results were very discouraging, and that is why we developed panels in the manner that we did -- 100, 1000, then 11,000.

[Slide]

This is where the rubber hits the road. This is our experience. This is what we have done and this is what we are here to show you today. So, I will spend a few minutes talking about this slide. These test platforms are in no order whatsoever, and the testing is not done simultaneously at the same time, meaning that when tested the Hemastrip or UniGold we did not test Hemastrip and UniGold at the same time. These 10,000 samples are not tested at the same time with Hemastrip and UniGold, and may not be the same 10,000 samples but you will see a discrepancy table that follows this one that shows comparison between platforms, which does not attest to the sensitivity of the product.

Let's read, for example, Hemastrip across the first line. We have tested 10,290 samples. We have tested 511 reactives. We had 1 false negative. We have tested 9779 non-reactives; 1 false positive which yielded a

sensitivity of 99.8 and a specificity of 99.9.

One point I would like to mention on this table, when you look at UniGold, this is one of the few tests that had 100 percent sensitivity. I want you to bear in mind the number of positives that we evaluated. We have looked at the magnitude of 500, 700 or 300 for some of the tests and you will see the sensitivity a little bit less than 100 but we have only looked at 122 with the UniGold. This is one of the platforms that we are looking at now with their new peptide generation.

This is HIV 1/2 that I told you about. You will see why we developed panels that way. Look at the specificity, 65 percent. We were going to tell 30-some percent of our population that they are HIV positive when they need not be notified, and this is why platforms like that are being evaluated now.

Bear in mind that HIV 1/2 Abbott ELISA is 100 percent sensitivity and 99 or 94 percent specific. So, when you look at these things, put them in perspective with what the ELISA can offer you.

[Slide]

This is a discrepancy table. I have printouts of these slides for anyone who is interested. The discrepancy table shows the samples that were discrepant on one platform, how they performed against other platforms, and

how they performed on EIA, Western Blot and we also did RNA PCR on these samples. Pick any sample that you want, for example one that was missed by Abbott, if you look at any that was missed by Determine you will see that it was picked by Epitope, for example, but the RNA was positive and the Western Blot was positive.

The reason I am putting this table up here is not to show why one company missed a product, but this is the point that I will drive to later, that two platforms are as good as an EIA and a Western Blot and this is what we want to show. There are not two good tests that we feel are promising that miss the same sample.

[Slide]

This is too much data to digest in one slide; this is just to give you an idea that the data exists. So, what is next? We are doing simultaneous testing. We learned from our first experience is that one of the biggest points against our trial, the first trial, is that we did not do the tests at the same time. So, with this new trial that we are doing now we are doing testing at the same time. We will pull the samples out of the freezer; thaw them out one time; do all five or four platforms that we are evaluating; put them back in the freezer -- we are done. We are not going to bring them out again and test another platform until we are done with that panel.

I prepared these slides yesterday, and we have completed testing on the 100 panel on Epitope, Multispot, the second generation UniGold and MedMira. We are going to move forward with some of these products. Again, they have to meet our sensitivity and specificity criteria in order for us to move forward.

What I did not add in this slide is a product that is made by -- I forgot the name! It is made in Canada. It is HIV 1/2. It is the one that I mentioned earlier that should not be confused with HIV 1/2 that we had on the screen. We are going to add that to the panel and, hopefully, the next time we meet or the next time you hear from me you will see results on that.

[Slide]

What do we want? Why are we here? Where do we see ourselves going? What we want, we want one card. In the military we like to make life simple. When we are out there in the field and we have to pack a million things to take with us that we may never use out there, we want one thing that we may use -- a card, one simple card that is as big as this thing right here, that can tell us some STD diseases that we may encounter out there in the field -- HIV, hepatitis or any endemic disease that we may encounter in that theater of operation that we are deploying to. These cards can be modified to fit the theater of operation

that we are deploying to.

This is where the idea started; this is how we started. Col. Hess, the Division Director of Blood Research at Walter Reed, approached us with a similar idea. He said we need something out there to be able to see if our soldiers are infected or not. This is just a prototype that we developed. We thought this would provide Col. Hess and many others with an idea of what our soldiers have out there in the field.

We could not pursue this because there are too many things to evaluate at one time. Since our division is funded for HIV research and HIV diagnostics only, we concentrated on HIV virus. We figured if a company can develop a platform that works on HIV, they can develop a platform that will work on any other communicable disease that we see.

[Slide]

The conclusion -- it is a pretty strong conclusion that we drew after we evaluated the first 10,000. We feel that there is not a single test out there that can give us the sensitivity and specificity that we want. However, combining two tests will give the sensitivity and specificity that we want.

We also realize that evaluating rapid diagnostic tests is an ongoing process. This is not a process that

will end when we finish this trial. We will replenish the panel. We will get another 12,000 and we will evaluate new product.

Since the CDC had opened the doors with their first MMWR publication that screening should be done with rapid testing, and FDA has been very cooperative in looking at these things and working with the companies in evaluating these products. Many companies have jumped on the wagon. Many of them are sold and approved overseas for this use but now they are bringing them here, to the United States, for PMAs or IDEs.

[Slide]

Last but not least, as you can tell this work is huge and tremendous, and it cannot be done with one or two individuals. This is work that is done in strong collaboration and guidance from Lt. Col. Nelson Michaels who, regrettably, cannot be with us today. You should all hate him for this, he is in Cape Hatteras, in North Carolina, on the beach as we sit here --

[Laughter]

-- Miss Jennifer Malia, the laboratory supervisor, who is with us here today, Scott Feese, who is the newest addition to our laboratory, Syad Zyad, who is also a newest addition to our laboratory. If you wonder how we handle all this data and how we put it in the computer, it is by Mr.

Dennis Lucas. He is our admin. person.

With that, I would like to ask the committee whether you would like to open it up for questions and answers now or wait until all the presentations are done?

DR. HOLLINGER: Are there any questions? Yes, Dr. Mitchell?

DR. MITCHELL: Yes, you said that you retested a number of the samples that were positive with different types of tests. Did you do repeat testing using the same test and, if you did, then did you get the same result or different results?

LT. ZAHWA: That is a good question. The sensitivity and specificity results when we say a specific test missed one or two samples, this is after repeat testing. We will test initially. We will do repeat testing and we will draw a conclusion. Two out of three positives will make that test positive. The repeat two negatives will make that test negative. Therefore, yes, we included that in sensitivity and specificity. We looked at repeat testing. We did that in duplicates.

Any other questions? What I want you all to remember is that the work we do is for those of us who are out there in the field, being exposed to HIV and other diseases, that we are safe here back home. Thank you.

DR. HOLLINGER: Thank you. The next presentation

is by Nancy Wade. Dr. Wade?

Presentation by Nancy A. Wade., M.D., NYS Dpt. of Health

DR. WADE: Good afternoon. I want to thank the committee for inviting me to participate in this session.

[Slide]

I am going to share with you some information from New York State Department of Health on the prevention of perinatal HIV transmission, expedited HIV testing for pregnant women in the labor, delivery and in the neonatal setting.

[Slide]

I think you have to understand a little bit of the chronology of what has been happening in New York State to understand where we are today. In November, 1987, a survey of childbearing women began, and that was basically blinded testing of all newborns.

In May, 1996 to January, 1997 by regulation, sites were required to offer prenatal counseling with recommended testing, and this was in all regulated settings so it really excluded some of the private practices but it was a standard of care at those sites. Consented newborn testing began in May, 1996. What happened was, when this started to be offered, about 90 percent or more of the women who were actually offered the test results opted for the test result to be returned to them.

In February, '97 a new law came into effect. This was that comprehensive newborn HIV testing program whereby all newborn testing now was reported back to a designated physician at the hospital who then, in turn, passed themselves information on to a pediatrician who gave the result to the mother and the family.

Then, in August, 1999 there was a new regulation and this basically said that if a woman came to labor and delivery and she did not have an HIV result from the current pregnancy and she wasn't known to be HIV positive, she had to be offered HIV testing in the labor and delivery suite. If she declined testing, then her newborn, as an extension of newborn testing, was tested immediately after birth and that testing could be with counseling but it was without consent.

[Slide]

The universal prenatal HIV counseling and testing program -- if you look at data from 1998, there were about 250,000 women who delivered in New York State and 54 percent of them were tested during the current pregnancy. This is at a time when regulation required counseling and voluntary testing in all sites. Of the 16 percent tested prior to pregnancy, some of those women would be infected; some of those women may have become infected and not known their accurate status. About 24 percent had no prior testing

history and about 5 percent had an unknown testing history.

[Slide]

The problem was that about 45 percent of women had no documented HIV test from their current pregnancy, and that translated to about 520 HIV-positive women who may not have known their HIV status and that represented a serious missed opportunity for prophylaxis to prevent HIV transmission.

[Slide]

I think most of you are familiar when perinatal HIV transmission occurs. About a third is thought to occur in the antepartum period. Two-thirds is thought to occur in the intrapartum period, and breastfeeding adds probably 14-16 percent to transmission.

[Slide]

Then, during 1998 and 1999 there were a number of publications that came out that looked at abbreviated regimens. The standard regimen for an HIV-infected pregnant woman resulted in the 076 regimen where women were given ZDV in the second and third trimester, intravenous infusion during labor and then the newborn was given 6 weeks of zidovudine.

The abbreviated regimens in Thailand -- ZDV was administered at from 36 weeks on and during labor. Transmission was 9.4 percent in the group receiving ZDV

versus 18.9 percent in the placebo group.

The UNAIDS PETRA study looked at ZDV and 3TC intrapartum and for 1 week postpartum for the mother and the baby. Transmission again, 10.8 percent in the group receiving antiretrovirals, 17.2 percent in the placebo group.

HIVNET 012 came out in the last year where women received either ZDV or Nevirapine intrapartum and then for the newborn. This was a very, very short course regimen. The transmission rate was 13 percent in the Nevirapine group and 25 percent in the ZDV group. I believe that was at 14 weeks and, remember, this was a breastfeeding population.

Then, our data from New York State -- this was observational data and it looked at ZDV intrapartum and in the newborn period or in the newborn period alone, and the transmission rate was 10 percent when it was initiated in the intrapartum period, 9 percent when it was initiated in the newborn period, and 26 percent when no antiretroviral was administered.

[Slide]

I think if you look at reasons for having no HIV test result at the time of labor and delivery, one would be no prenatal care, and among the HIV-infected pregnant women probably in the vicinity of 15-20 percent have either no or inadequate prenatal care. Prenatal care without HIV

counseling, and that again was most commonly occurring in the private offices. The women may have been counseled and opted not to be tested, or the test result may not have been transferred to the delivery medical record, and that has sometimes been an issue just based on confidentiality of transferring records.

[Slide]

The current program, however, in New York State, again, continues to require prenatal HIV counseling and testing is recommended. It is consented testing.

Then there continues to be routine screening of all infants under the newborn screening program, and this is part of the metabolic screening that goes on in the hell-stick blood spot.

Then the test results from the newborn screening program are available in one to two weeks and, again, that is too late to actually initiate any prophylaxis.

We can demonstrate strong linkages to care once an infant is identified. Better than 99 percent of the infants are in care by our marker of a first diagnostic PCR test that comes to the state.

Then expedited HIV testing is required intrapartum with consent or of the newborn without consent if the HIV test result is not available from the current pregnancy.

[Slide]

I think if you look at the rationale for expedited testing -- and I think we call this expedited testing because we had one rapid test so in some instances facilities were opting to use a STAT ELISA, or whatever. It promotes access to intrapartum and newborn ZDV prophylaxis. If the mother is unable or declines prenatal or intrapartum ZDV the newborn may still benefit from prophylaxis, and it promotes early identification of infected infants, allowing the initiation of combination therapy as early as possible.

[Slide]

The regulation in New York State, again, applies only when the mother's status is unknown at delivery, and it requires that birth facilities -- hospitals, provide immediate HIV testing of the mother with consent during labor and of the newborn immediately after birth if the mother has not been tested.

[Slide]

It requires that the results be available as soon as possible, and the outside limit of this was 48 hours, although they are advised to get the testing done again and initiate treatment as soon as possible. It is really fairly similar to the hepatitis B surface antigen testing requirement for New York.

This new regulation allows reporting of preliminary HIV test results when requested by a physician,

where in the past an ELISA which was positive couldn't be reported until the Western Blot was completed. A positive SUDS or a positive ELISA alone done in duplicate could be reported and acted on while you were waiting for the confirmatory test result.

[Slide]

Again, the facility responsibilities I think I have pretty well covered already.

[Slide]

If you do have a positive preliminary HIV test result with our current rapid test, I think you have to discuss the likelihood of a true positive based on the risk factors of the mother, as well as the seroprevalence in the facility that you are in; offer initiation of zidovudine prophylaxis; advise against breastfeeding pending the confirmatory test result.

[Slide]

Then, on discharge from the hospital, it is important to be sure that the confirmatory test result is either back, arrange a follow-up clinic visit and advise the mother when the confirmatory test result will be back if it is not back before discharge. Ideally, it is returned before the woman is discharged, and we have encouraged people to even delay a discharge if necessary in those instances. The infants are sent home with zidovudine;

appropriate referrals for care; and then the woman is also referred for additional services and needs that may occur as the result of the testing.

[Slide]

If you look at the projected utilization of expedited HIV testing in New York State and, again, with about 250,000 births per year statewide seroprevalence is about 0.4 percent. We have about 1000 HIV-positive women giving birth each year for the last several years. In the last several months, since expedited testing began, the number of women who are tested during pregnancy has gone up dramatically so that now about 90 percent of all pregnant women are tested during pregnancy or are known positive. For HIV-positive women that number is somewhat lower and it is around 80-82 percent who are actually tested during the current pregnancy or know their status. That leads to about 25,000 pregnant women who are eligible for expedited testing, and approximately 120-200 of these women will be HIV positive each year.

[Slide]

We do continue with the universal newborn screening program. In a way, it is kind of a check on the system to be absolutely sure that somebody hasn't been incorrectly diagnosed. So, all infants are still tested for HIV. In the postpartum period, all women will be counseled

about the universal HIV testing in the newborn screening program so that they can expect to see that test result return.

[Slide]

If you look at the predictive value positive of our currently available tests, SUDS and EIA, SUDS performs less well than some of the standard EIAs and, again, it really is largely dependent on the seroprevalence of the hospitals. I think if you look in some of the rural areas of the state, the predictive value is down in the 18 percent range, whereas in some of the high seroprevalence areas the predictive value of a positive test is up in the 90-some percent range and EIA is, again, better. Hospitals have been advised to choose an algorithm. We have given them a suggested algorithm, either SUDS or EIA. If the test is positive they repeat it in duplicate. If that is positive they are advised to ideally use an alternate test method. So, again, ideally if you had a positive SUDS you would follow it by a STAT ELISA and in a few hours have a confirmed test.

[Slide]

In the testing program from 10/99, over this six-month period, among HIV-positive women there were 484 births; 59 percent were tested during pregnancy; 29 percent tested prior to pregnancy; and 13 percent, or 61, required

expedited testing. Of those, 45, or 75 percent of them, had expedited testing done and there were 16 missed opportunities, or about a quarter.

The data on actual expedited testing among the negative women is not as clear. We require that any positive expedited test result be reported to the state so that we are able to track what happens and try to get a handle on false positives.

[Slide]

Then, if you look at preliminary positive test results, to date we have had 58 positive expedited screening test results come in. Eight of those were from previously known positive women, and if a woman doesn't have documentation of the test then sometimes the hospital would go ahead and do a rapid test also, and 38 of those, or 66 percent, were confirmed positives; 18 of them were EIAs and 20 were SUDS. There were 17 false positives, 3 among the EIA and 14 among the SUDS. Then, there is a number that is pending and one was an indeterminate Western Blot. These data are really still quite preliminary as we are continuing to pull them in.

[Slide]

On this slide I really just wanted to point out the change in the testing during the current pregnancy. This is all women in New York State, and back in '97 it was

around 50 percent, by August of '99, when the expedited program started, it was around 70-75 percent and it is now up around 90 percent. For HIV-positive women the level is about 80-85 percent of women being tested during the current pregnancy.

[Slide]

I think the conclusions are that antiretroviral therapy during labor or soon after birth presents about a 50 percent decline in mother to child HIV transmission. It is certainly not as good as the full regimen but it is a good option.

About 10-15 percent of HIV-infected pregnant women are diagnosed at labor only with the use of rapid tests. In fact, that number may be closer to 20 percent.

In New York State alone approximately 50 HIV infections in infants each year can be prevented by expedited testing and timely antiretroviral therapy. The use of more than one rapid test would prevent the unnecessary treatment of 30-40 percent of the infants whose initial rapid test is false positive and, obviously, the anguish that goes along with that. I think, finally, additional approved rapid tests are really urgently needed.

I don't know if the committee wants me to take questions.

DR. HOLLINGER: Any questions for Dr. Wade right

now? Yes, Dr. Nelson:

DR. NELSON: Are there any circumstances in which a woman had a history of being tested but was tested again at the time of delivery?

DR. WADE: We have documentation of at least a couple of women who have seroconverted during their pregnancy. They were negative early in pregnancy, that didn't have a rapid test, but the baby was picked up subsequently on newborn screening. We recommend if it is a high risk situation that people consider testing later. It is not part of regulation but I am aware of at least two instances of that happening.

DR. HOLLINGER: Yes, Jeanne?

DR. LINDEN: Since you were talking about using the second test to avoid unnecessary treatment, presumably you are using the formula of both tests would have to be positive to be considered positive. That is, you are sacrificing sensitivity for the sake of specificity.

DR. WADE: Currently, we are not requiring that they do two tests. If they have simply a SUDS available at their facility, then that is what they are working from so their chances of a false positive are much higher. If we had available other rapid tests, then we would move forward with that. Any positive test, obviously, is tested by ELISA and Western Blot but there is a lag before that gets done.

Not everybody is able to do them in a few hours. It is more commonly a day or two before that is completed.

DR. HOLLINGER: Thank you, Dr. Wade. I think, Dr. Janssen, you have another presentation?

Presentation by Robert S. Janssen, M.D.

DR. JANSSEN: Yes, thank you. When you have the opportunity to give two talks you can remember something you didn't give in your first talk and add it to the second one.

[Slide]

I wanted to start by just mentioning that one of the very important reasons for rapid tests that we see is that we have recently begun an HIV prevention strategic planning process. One of the goals of that process is within five years to increase the proportion of HIV-infected people who know their serostatus to 95 percent from the current estimated 70 percent.

Nancy Wade stayed on the perinatal -- a very important use of these tests. Nationally, in 1998, less than 250 babies were infected perinatally by their mothers. The majority of that transmission occurred from mothers who did not receive antenatal care. So, being able to use rapid tests at the time of delivery I think will be crucial, based on the data that presented from the short course AZT data and from the New York State data as well and the Nevirapine data.

[Slide]

What I want to talk about now is some of the challenges to public health. I think you have seen this slide before so I won't dwell on it. The point clearly is that when you have one test, as prevalence goes down your predictive value positive also goes down and your false-positive rate goes up.

This is an example of what happens in that situation. These are data from New York, as Nancy Wade presented. Twenty-four percent had children who would have been diagnosed only at birth. They had not had any antenatal care. There was no diagnosis prior to birth. At Charity Hospital, in New Orleans, 20 percent. The difference here is the prevalence, 0.3 percent in New York; over 3 percent in New Orleans. This is the real-world example of that table before, where 40 percent of the HIV tests in New York were false positives based on the single SUDS test and only 17 percent in Charity, and it is purely based on prevalence. Predictive value, 60 percent in New York; 83 percent at Charity and very similar to that predicted based on the performance of the assay.

[Slide]

So, we can do better and there is a need for several rapid tests. There is only one currently licensed, as you know, and the use of two could increase sensitivity

and specificity and predictive value to nearly 100 percent.

[Slide]

In fact, these tests are being used in other countries. This is a study that Harrison Stetler, from CDC, published in Honduras. I believe there are other co-authors in the audience, actually. Basically, this was using a combination of tests, a variety of rapid tests, and basically what you can see in both low prevalence and high prevalence settings is very good or excellent predictive positive and predictive negative values.

[Slide]

This is another example of use internationally of these tests. Again, we can't do this here yet but we look forward to it. This is an example of an agglutination test, the Capillus test, which has some trouble with specificity, but this has been used in Uganda in 1997 on 35,000 people. Now, there were over 7800 HIV positives who then got tested with Serocard. Those that were HIV negative on Serocard -- there was a tie breaker with Multispot. What is interesting is that 862 out of those 7800 initially HIV positive on Capillus test turned out to be false positive. But these tests are being used successfully in international settings.

[Slide]

So, to turn to CDC's efforts about the availability of rapid tests and what we have been trying to

do to make rapid tests available in this country, we have been trying to encourage manufacturers to commercialize rapid tests. We are conducting clinical trials to establish test performance in settings of intended care, and I will show you some of those data in a minute. Data also that we would anticipate would be provided for PMA applications to speed FDA approval. Finally, I will show some data in which we are evaluating the use of specific combinations of rapid tests to increase predictive value.

[Slide]

Our clinical trials that are necessary for prospective tests were really focusing on our intended uses, that is, the public health intended uses of rapid tests, those particularly that we would be funding and these are in both high and low prevalence settings. The low prevalence setting has been talked about already, and that is the antenatal care setting. But high prevalence settings abound in the work that we do, particularly STD clinics and outreach.

In addition, these settings are key to us. I said CDC but the military -- we don't do those. You have heard about those and then also the combination test algorithms.

[Slide]

You have seen these pictures so I will go through these quickly. Fortunately, Hassan has shown a bunch of

pictures that I have so I can just go through them quickly. This is SUDS.

[Slide]

The idea behind this is that SUDS, although a rapid test, is not a simple test. It requires multiple reagents --

[Slide]

-- centrifugation, several reagent steps --

[Slide]

-- and also a blue color that apparently can be somewhat difficult to read.

[Slide]

The selection criteria for the tests that we have involved in our studies are listed here, the first being availability of clinical performance data from the manufacturers and preclinical data. Then, what we wanted to look specifically at was user-friendly performance characteristics, those that are easy to use, with clear interpretations, minimal technical requirements, and are suitable for use in field settings, particularly on whole, blood finger-stick specimens or on oral secretions.

[Slide]

You have seen these. This is the Determine test.

[Slide]

Determine tests can be done multiply, and are

suitable for multiple tests being run at one time.

[Slide]

You have seen these. This is Hemastrip, which is a finger-stick blood specimen.

[Slide]

And, the results can be read in about 15 minutes.

[Slide]

You have seen similar pictures to most of these.

[Slide]

That is UniGold.

[Slide]

Then, MedMira, which is done a little differently. It is a flow-through device.

[Slide]

The results can be read immediately.

[Slide]

There is a reader, for example, with this test which allows one to reduce subjective interpretation of the result.

[Slide]

And, an ability to store the results for the medical record.

[Slide]

The OraQuick test that you have seen --

[Slide]

-- in which the results can be available within 20 minutes.

[Slide]

The last one is Quix.

[Slide]

So, what did we do? We did some lab evaluation based on 400 stored samples. These are bank CDC repository specimens that were used, and then a clinical study, 900 persons with known HIV status who came in to establish performance using whole blood and finger-stick specimens. These were matched specimens. So, people gave both specimens at the same time. Then, there was the larger clinical study of 6000 persons with unknown HIV status to determine sensitivity, specificity and predictive value of combination tests.

[Slide]

So, the test results are here. This is the first group, sensitivity and specificity on serum. These are the repository specimens. You can see all the tests performed, both in terms of sensitivity and specificity, very well, as good as or better than those tests that are currently licensed.

[Slide]

These tests weren't available when we did the first test. So, this group is done with a second set of

repository specimens but, again, this is serum-based on frozen specimens.

[Slide]

The next two slides will show the comparison of the performance on plasma and on whole blood in a prospective study in Los Angeles, which has been performed in a series of clinics as well as a mobile van. In these, again, you can see excellent sensitivity and specificity for all the tests that we have been looking at.

[Slide]

This is the whole blood test. I think, again, you can see good performance on all of these, but perhaps the UniGold test here does not seem to perform as well as some of these other tests but, again, the numbers in these studies are small.

[Slide]

Also, we have done some evaluations of Multispot. Many of these are historical and were done overseas -- studies in the Bahamas and, again, if you look here under sensitivity and specificity, very consistently high with studies done in a variety of places -- the Bahamas and Trinidad and Honduras and, not quite an international location, Bronx Lebanon Hospital in the South Bronx.

[Slide]

Then, New York State has also done Multispot

evaluations and is using the Confirm HIV-2. Again, here you see the same thing with very high sensitivities and specificities, including in the expedited newborn testing and then in a prospective evaluation as well.

[Slide]

This shows basically a similar slide to what Hassan showed, which is extremely difficult to read, but it basically shows that these tests, when they pick up or miss something they tend to be different. So, a combination of these tests is likely to pick up something -- one test is likely to pick up a specimen that another one is not.

[Slide]

So, lessons from our international studies are, first, and most importantly I think, rapid tests have been used internationally at least for the last four to four and a half years in a number of studies that we have done, including clinical use and supporting clinical use in countries, particularly in Uganda most recently and Malawi. Both clients and staff prefer same day results. Quality counseling can be provided in these circumstances. Combination test algorithms yield accurate results, and same day results help clients to receive immediate referrals and services that they need.

[Slide]

Looking at our international experience, this are

the algorithms that we have been using internationally. These are sequential algorithms, done in four countries, South Africa and Malawi. On the next slide I will show you the other results. You see the sensitivity and specificity in the combination of the tests. This is each one by itself and then combined in the algorithm. What you are seeing is, again, excellent sensitivity and specificity. They weren't missing many and in some cases missed different ones.

[Slide]

The same thing with Botswana and Uganda, with very high sensitivities and specificities, again, in combination algorithms.

[Slide]

In summary, rapid tests are essential for early access to prevention care and support services. The currently approved rapid test doesn't really meet the needs that we have and I think I made that pretty clear before. We really need a test that we can move out of the laboratory if at all possible to be able to begin to achieve our goal of an increase in the proportion of people who know they are infected.

* Rapid testing with quality counseling is feasible. It can help staff provide immediate care and support. There are numerous accurate rapid tests that exist, many of them being used overseas today, and the need to approve simple

rapid tests really is urgent in our opinion.

[Slide]

Where do we go from here? We concur on the clinical trial requirements for HIV screening indication. The reduction in the size of clinical trials should speed clinical trials and should speed approval of tests.

We are encouraging the submission of PMA applications with available U.S. as well as foreign clinical trial data. We are supporting and are willing to support any necessary additional trials that are needed. Finally, we recommend also that consideration be given for post-approval requirements for other indications. In this country HIV-2 and group O are of interest, primarily academic interest. They are certainly not a public health interest. We have recently pretty much given up our HIV-2 surveillance. We haven't completely but we are doing much less of it because of the 675,000 people who are infected in this country, it seems there are about 100-150 who are infected with HIV-2. So, we would actually recommend that approval for these kinds of claims be done post-approval rather than a requirement for getting these tests on the market if they are going to delay getting these tests on the market. Thank you. Questions?

DR. HOLLINGER: Thank you. Yes, Dr. Katz?

DR. KATZ: I am just interested in your

sensitivity and specificity numbers. Those all look like point estimates to me and I am wondering if you have the numbers, or can give us a feeling for how they would fit into the FDA's intention to talk about a lower bound of a 95 percent confidence interval at 98 percent.

DR. JANSSEN: I want to acknowledge Bernie Branson who has really been the major push on rapid tests and has provided a massive amount of work, including all these data. Bernie, do you want to address that? Bernie is intimately familiar with these data.

DR. BRANSON: Those data were used to generate the FDA's state-of-the-art estimates so that those tests basically would all meet the recommended standards that the FDA has presented today.

DR. HOLLINGER: Yes, Dr. Nelson?

DR. NELSON: I know that one population has not been considered for rapid tests for discussion, and I think it is probably appropriate given that we are talking about the United States. But, I think worldwide blood donors are a very important group and only half or so of the blood donors in the world are even tested but of those that are tested, even with high quality tests in places like Thailand where there is a delay in the results -- the problem is that when we have tried to notify people of their results, the positives, we were able to notify about 70 percent because

there aren't phones; you have to try to find the people.

I think a rapid test in the setting of a blood bank where the prevalence in the donor population is fairly high is an important use because these are people mostly who are healthy, who come in often, populations with a large heterosexual epidemic. Knowing at least presumptively that somebody is positive when they are in the blood bank, where they can be counseled, is critical. Yet, you know, this wasn't mentioned here. I am not suggesting necessarily that the current algorithm in the U.S. donor population should be replaced or modified, but I think if we are thinking about the global AIDS epidemic, this is a very important population.

DR. HOLLINGER: Yes, Dr. Mitchell?

DR. MITCHELL: I have a question on the algorithm for the four countries. When you talked about the tests, were they repeated?

DR. JANSSEN: They were repeated.

DR. MITCHELL: Each was repeated, and then in combination they were also repeated?

DR. JANSSEN: Yes.

DR. MITCHELL: One time?

DR. JANSSEN: One time.

DR. HOLLINGER: Just a couple of questions, Dr. Janssen. Some have to do with the testing as it is looked

at, and I would like to get your feeling about this, but one of the reasons would be, as you said, first of all, to decide who would take advantage of these rapid tests here, in the United States. Presumably, people who don't have the funds to maybe go somewhere else, and there may be other reasons for it.

So, one of the questions is what is the social responsibility of the individuals who might come in and do this who may be given an answer that they are positive in terms of their preventing transmission to other people anyway? Are these the individuals in general who might come in and want to test, who can't afford it otherwise, who may then go out and ignore the very advice you are going to give them in terms of transmission? That is one question.

The other is that you mentioned that many people don't know they are even infected. I guess then the question is why would they come in anyway if they don't know they are infected, or are not sure that they might be infected? They probably would not come in anyway to get tested.

Then, the third thing is, if it is for treatment, many patients are not able to afford the HAART treatment and so on, and there are not funds in the public sector to even treat these people, or perhaps provide them certainly with HAART treatment at least in the indigent population. So,

could you sort of take a stab at those?

DR. JANSSEN: First of all, I assume you are talking about what is currently licensed with the single provisional test result.

DR. HOLLINGER: No, I want to talk about even a little further with the tests we are talking about now, as they become licensed and could be utilized.

DR. JANSSEN: One of the things in the process of right now is modifying CDC's counseling testing guidelines. One of the parts of those guidelines that will not be modified is post-test counseling, particularly risk reduction, prevention counseling for people who are found to be HIV positive. So, there will be prevention intervention at the time of provision of the test result.

Beyond that, then people who continue -- and I think the idea behind SAFE is that a very important part of it is supporting HIV-infected people in adopting and supporting safe behavior. One of those ways is through something we call prevention case management, which is essentially case management with a counseling or prevention component to it. Those people, for example, who are HIV-infected and come in repeatedly with sexually transmitted diseases would be people we would want to get into prevention case management or other prevention interventions to try to get them to reduce their risk behavior.

It is a concern. I think you might have had a question that was sort of leaning towards intentional transmission. That clearly happens; it seems to be a fairly rare event. The vast majority of infected people reduce their risk behavior.

You asked me three questions --

DR. HOLLINGER: The treatment issue.

DR. JANSSEN: The treatment issue is one which we have thought a lot about. The question is do you wait for the services and then encourage testing and getting people into treatment, or do you get people to learn their status and push for the services? The decision we have made is that if we wait the services will never be there. But if there is more and more demand on the services, then more services will come about.

DR. HOLLINGER: Yes?

DR. OHENE-FREMPONG: I am trying to imagine the various settings in which we encounter patients in whom we want to know their HIV status. The sort of sensitive counseling that would be required if you receive the results -- if somebody is in the emergency department, they are planning to be there for a few hours and they will be leaving, not like, say, CBC where you get results and what you say about it is not that sensitive and there are not often long-term consequences -- I just wonder who will be

the counselors who will follow up on that?

DR. JANSSEN: The idea is not for the ER doc. to spend an hour counseling someone because that is not going to be practical in an emergency room, but to actually provide counseling through other people. During the day it would be easy to refer someone to a service that is ongoing in a hospital. At night I think it would be more complicated and at a very high prevalence hospital, like the Grady Hospital in Atlanta, you would want counseling services available 24 hours a day to be able to deal with this, depending on what the rate would be at which you would be identifying people.

You are right, this is not like a CBC result; it is not like a lot of test results, and you do need someone to sit down and talk to people when they initially learn the results.

DR. OHENE-FREMPONG: I know it is very important but in any of the clinical trials has the follow up also been looked at?

DR. JANSSEN: Yes, we are looking at how do you implement these tests in this setting. Although I personally am convinced, and part of it is based on my experience in hospitals at some work I did at University Hospital in Newark about eight years ago. There were no rapid tests then but routine testing in their emergency

room, and did it successfully. But we are looking now at what are all the factors that would make this a successful strategy. It is not a strategy to implement in every emergency room. It is a strategy to target toward those hospitals with high prevalence of HIV.

DR. HOLLINGER: I will tell you what I would like to do, we are going to take about a 20-minute break and then we are going to come back and we will have the open public sessions. I would like those who are going to present to limit their talks to about 5-7 minutes each. Then we will go into the other questions with the committee and so on. So, it is now about 3:55. So, at 4:15 we will meet again.

[Brief recess]

DR. HOLLINGER: Somebody said what we ought to do is have each of the manufacturers start their test and then just speak for the time limit of their test. When their test became positive they could sit down.

[Laughter]

Actually, I had a colleague who used to do that. When he got up to speak he would take a Lifesaver and put it in his mouth, and he timed it just perfectly so that when the Lifesaver was all dissolved, then he was over his talk. He never spoke over that until one day he reached in his pocket and pulled out a dime and talked too long.

[Laughter]

Dr. Wade had another comment she wanted to make. Is she here?

DR. WADE: This actually falls under public comment as opposed to my other role here, and it is just a very brief comment. In New York State, I think there is an urgent need for additional rapid HIV tests for use in the labor, delivery and newborn setting.

The New York State Department of Health is actively pursuing an application with the CDC for a treatment use IDE for access to three rapid HIV tests. FDA has recommended the treatment IDE mechanism to meet New York's urgent need for rapid tests in the perinatal setting, however, the treatment IDE is a research mechanism that invokes another set of requirements to be met by each of the 160 birth facilities in New York State, including IRB approval and single-project assurances. This will be exceedingly cumbersome and will likely delay implementation for more than a year. It would delay identification of as many as 200 HIV positive women, and the lack of two rapid tests would result in the unnecessary treatment of as many as 50 infants who would be false positive on the single test now available.

We feel that available data support the sensitivity and specificity of these tests, and have confidence in their use when used in combination. All rapid

tests performed during labor and deliver in New York would still be confirmed by ELISA and Western Blot. We feel that the tests should be approved, and could be approved in the same time frame that the treatment IDE could be implemented. Our Health Commissioner, Dr. Antonio Novello, has submitted two letters to the FDA, encouraging them to accelerate their approval process, and I just wanted to take a moment to kind of reiterate that.

DR. HOLLINGER: Thank you, Dr. Wade. Dr. Chamberland?

DR. CHAMBERLAND: Actually, Blaine, I am just checking up on you. You asked Rob Janssen three questions and I believe he answered two of the three, and I actually wanted to ask him if he would elaborate a little bit on the second question. If I can paraphrase your question, it went along the lines of just because rapid tests might be licensed, what would cause us to believe that the approximately 200,000 infected individuals in this country who do not know their status would then seek to be tested? My understanding, and Rob can amplify on this, is that the rapid assay is only one component of a much larger strategy that would allow public health agencies to be much more proactive in trying to go out and find these individuals.

DR. JANSSEN: The idea behind the use of rapid testing -- I think there are a couple of things behind it.

One, in studies we have done, asking people about getting testing in publicly funded facilities, they prefer rapid testing, which will probably increase the acceptance of rapid testing in those facilities.

But I think what we really see is expanding the availability of testing, and that expansion is through the use of these of tests in mobile vans, for example, by community-based organizations, at Gay Pride parades, in bath houses, in places where people at high risk for HIV congregate, in addition to which I had mentioned routine screening, routine voluntary testing in emergency rooms, and high prevalence hospitals, and other high prevalence medical settings. Those are settings where people are going in for some other problem.

Again to use the New York University Hospital emergency room, a high proportion of the neighborhood injecting drug users get their primary care in that emergency room, and men go to that emergency room at least once every 18 months; women use it about, I think, twice a year. It is a real opportunity if you offered routinely to everybody coming through the door an HIV test. There is going to be a number of people whom you are going to identify as positive who didn't know they were at risk.

We have a couple of studies, and Bernie and I were just talking about them also -- we have a couple of studies

looking at this. Carlo del Rio is doing it at Grady Hospital where he has increased from 4 percent to 35 percent the acceptance of HIV rapid testing at Grady. They have doubled the number of HIV-infected people they have identified. It is only from 4 to 8; it is a small pilot project but they are identifying more people. We are doing a similar type of study.

The other is to work with correctional facilities. Again, it is difficult by voluntary testing, increased voluntary testing in correctional facilities where you are likely to find a large proportion of infected people who don't know their status.

So, it is really not just living within the current publicly funded counseling testing system, it is really expanding that and going way beyond it.

DR. HOLLINGER: Are you looking at something like this in the future like a home test kit as well, or if somebody is going to have sex with something else they are going to look at this and do this test on their own to find out if their partner may be infected? Is this where this is going?

[Laughter]

DR. JANSSEN: Can I give my personal opinion? This is not a CDC opinion, this is a personal opinion. There are some data that Vina Verghesi and our group at CDC

has been looking at and modeling, looking at risk behavior, whether the partner is infected, the different sexual behaviors and condom use, and which of these are the most important in predicting transmission of HIV, what increases the probability of transmission of HIV in any sex act. It is clear the thing that drives it the most is serostatus. So, if somebody tests negative or is recently negative, then the sexual behavior or condom use becomes less important in those circumstances.

I think this is an area that we are beginning to talk about. I think it is going to require a lot of hard thinking. It is going to require some very sophisticated prevention messages. Whether or not this is where we need to go, I don't know. I think there is potential benefit to it, but I think there are also some real potential dangers as well that I think really need to be explored very carefully. I mean, these tests offer that opportunity but whether it will go there, I don't know.

DR. HOLLINGER: Thank you for your candid comments. Yes, Dr. Epstein?

DR. EPSTEIN: On the same question, Blaine, the issue of whether FDA would approve a home-use test was first raised in the late '80s. Initially there were policies promulgated which required professional use tests in medical settings, venipuncture samples etc. This was a Federal

Register notice in 1989. Then, as the technology for blood spots emerged, we ultimately relaxed that policy and permitted the home sample collection test system with mail order testing, performed in clinical laboratories and, although the results were provided confidentially and anonymously, they were provided with counseling by a live individual.

There is, to my knowledge, no formal policy position by the FDA that would preclude a home-use test. However, we do have policies that have been published, guidances from the Center for Devices and Radiological Health which generally review the considerations applicable to an OTC, or over-the-counter, diagnostic test, medical diagnostic. It shouldn't surprise anyone that these guidances suggest that there ought to be a very high level of concern both about the accuracy of lay use and also the ability to properly handle the medical information, including limitations to the ability to be referred to the medical system.

So, think that these would be very serious concerns. I agree with Rob that the technologies, in and of themselves, could potentially permit this as the methods become simpler and simpler. But, one has to look very critically about the circumstances of use and ask whether it is or isn't in the larger public health interest to enable

people to test themselves and get results in the home or, I should say, in the workplace without the benefit of any medical interface whether at the laboratory control level, whether at the operator training level, or whether at the counseling and referral level, and I think that those would all be matters for very serious scrutiny.

DR. HOLLINGER: Yes, Dr. Schmidt?

DR. SCHMIDT: We have on our list an FDA position on labeling. The first ELISA test was labeled, as I remember it, for blood donor use only and, of course, people used it for many other things. So, if there is a position on labeling, if these rapid tests come into being would they be labeled not for blood bank use or not for home use? That is one question.

The other question is if they are so good, why wouldn't they be allowed for blood bank use?

DR. EPSTEIN: First of all, would they be labeled restrictively? They would be labeled for intended use in healthcare settings by properly trained individuals. In other words, they would not be labeled as over-the-counter products. They would not be available for sale over-the-counter. In other words, they would have to be distributed through medical distribution channels analogous to other medical devices, and there would be oversight that they would be used with properly trained individuals. In other

words, the operators would have to meet some kind of training criteria as established by the product sponsors.

Now, on the question of whether they could or should be labeled as donor screens, that depends on whether the sponsor seeks that label. If the sponsor seeks that label, then the FDA's response would be that that test needs to show equivalence to previously licensed donor screens, and we would hold it to a higher performance standard than what we have proposed for approval as general medical diagnostics.

So, it is not that the FDA is saying that they can't be so labeled. Indeed, some of these products potentially could perform sufficiently well to be donor screens. But, we do think that they should then meet a standard of comparability.

Now, having said that, it is not just the performance characteristics that enables a test to be a routine donor screen. It also has to be capable of very high throughput and with an objective readout. In other words, we don't want to promote in the routine donor screening environment systems that can't handle, you know, thousands of samples and don't produce hard, objective data as the readout.

So, the way we have labeled rapid tests when used for blood donor screening is that they are suitable for use

only when the routine ELISA is either unavailable or impractical. That is the label that was put both on the Murex SUDS and the Cambridge Bioscience Recombigen. Use in that manner has occurred but has been infrequent, as might be expected.

DR. HOLLINGER: Miss Knowles?

MS. KNOWLES: Getting back to your question, Blaine, about other potential uses in terms of a home-test kit, I am going to say that I really think what Jay just said about training by providers of this test, even expanding to the potential SUDS that Dr. Janssen is suggesting, you still have to have trained people to do it.

Further, federal rules of 1997 require partner notification of all HIV-positive people. So, in our current setting right now, counselors have to encourage; they have to help make sure -- they don't have to actually do follow-up but they have to make sure that that person who is HIV positive is actually willing to go, seek and find and disclose. How can you follow that up in a home-test kit? It is very difficult.

DR. HOLLINGER: Thank you. I am going to move to the rest of the public hearing today. We have about three or four companies who want to talk. The first one is from Abbott Laboratories, and this is Bill Murray.

MR. MURRAY: Thank you very much.

[Slide]

I am Bill Murray. I am the product manager for Determine, and we have been asked by the FDA to come, speak to the committee today to outline our rapid HIV device, which is currently sold outside of the U.S., called Determine.

[Slide]

In coming here today, the real goal was to be able to provide a general overview of what the product is all about and how it is being used in various countries around the world. When we set out to build Determine, and we launched the product in 1998, we spent a great deal of time meeting with potential customers and in different healthcare settings around the world, with the simple goal of building a product that would provide HIV results to more people faster. With that basic premise under way, we wanted to make sure that we had a product that would certainly fit the needs in places that we would consider to be developing, but certainly that would offer a quality product that people could feel comfortable with the results.

[Slide]

So, these are some of the very basic things that we set out to do and that Determine offers. We have a product that does detect HIV-1 and 2 and subtype O, that is

flexible and it is sample typed, especially including whole blood and that can be done with finger sticks, as some of the previous presentations outlined today. Ease of use and fast results, as we would determine them, were something that we wanted to make sure we could deliver in a product.

One of the other interestingly important things that we found was the stability of the product to be used in various settings around the world. We find that the product is used a great deal in very extreme environmental conditions where temperature is a real issue. So, we are shipping product now that is stable for up to 15 months, and in some cases more, with some pretty extreme environmental conditions.

But one of the other things we did not want to lose sight of is to make sure that the product did perform as well as those methods that were used in settings around the world, both in a rapid format in some cases as well as ELISA tests that were used in certain parts of the world.

So, as I said, the product was launched in 1998. It is being used in approximately 100 countries around the world, and this would be both in what we would consider developing as well as industrialized nations around the world, which would include Germany, France, Brazil, Japan etc. So, the product has turned out to be a product that really exceeded our expectations from a performance

standpoint, and it has been very well received by industrialized nations around the world.

It is being used in a number of cases with UNAIDS and UNICEF, and a number of other international relief organization that we continue to work with on an ongoing basis. The bottom point is that we have recently started to sort of look at how many tests are being used around the world, and we have had well over ten million of these tests used in diagnostic settings around the world. So, just looking at the sheer numbers that have been used, it has gotten quite a good reception in its use.

[Slide]

I wanted to just sort of pool some data from published studies that have been done. By no means is this inclusive and you have seen a number of other pieces of data from Determine that were presented earlier today, but I wanted to pool the published studies that really lend themselves to fresh sample testing. We have spent a lot of time and effort in making sure that we optimized Determine for fresh whole blood testing, which was really the goal of the product. If we couldn't deliver a whole blood result, that really defeats the purpose of rapid testing. So, we wanted to make sure that, no matter what we did, we had a product that could do that very well, and to speak to some of the data that you have seen on Determine.

I think it is important to remember that, at least in this kit's case, fresh sample testing is very important. When you start looking at stored samples and things that have been freeze-thawed more than a few times, you do start to defeat the purpose of your rapid kit. So, we have clearly optimized it for running fresh whole blood.

As you can see, I have put up what we have as the current package insert for the kit that is sold outside the U.S. We did the studies in Vietnam and Thailand. We wanted to go to those places where we would be selling the kit and we wanted to make sure it was in the field, using samples that would ultimately be run on the test, once approved.

So, as you can see, we had very good performance on whole blood which, again, was our primary goal. I have also put up the World Health Organization recommendation -- Determine now appears in the WHO book -- and corresponds to the CDC study done in Malawi.

[Slide]

Additional studies highlight the use of whole blood and its performance versus serum plasma. As you can see, I have focused on the studies that were primarily done outside the U.S. exclusively. I think you have seen enough CDC numbers to show that the product is being used in their studies within the U.S. But the people who are actively using the product outside the U.S. are seeing the same sorts

of results. As you can see, they are very, very good. So, we are very proud of the test.

That is it. Are there any questions for me at this point?

DR. HOLLINGER: Any questions?

[No response]

MR. MURRAY: Thank you.

DR. HOLLINGER: Thank you. The next speaker is from Bio-Rad Laboratories, Scott Dennis.

MR. DENNIS: Good afternoon. My name is Scott Dennis, and I am manager of regulatory and quality assurance for Bio-Rad, formerly Genetic Systems Corp. We currently manufacture and distribute HIV-1, HIV-2, HIV 1/2 and hepatitis B surface antigen licensed test kits. And, we appreciate the invitation from FDA to speak today, and to present a brief overview of the Multispot HIV-1, HIV-2 rapid test kit.

[Slide]

This test kit is a membrane-based enzyme immunoassay for the detection and differentiation of HIV-1 and HIV-2 antibodies in human serum or plasma. This rapid HIV test kit was initially developed by Dr. Patrick Coleman, in the 1990s, under the name of Genie. The Genie rapid test kit as extensively studied by CDC and other groups both within the U.S. and other parts of the world. The

technology was then transferred to Sanofe Diagnostics Pasteur, now also Bio-Rad, facilities in France, where it continues to be manufactured and distributed to various countries around the world under the name Multispot.

[Slide]

The principles of the Multispot test kit are as follows: microscopic particles are individually coded with antigens specific for HIV-1 and HIV-2. The microparticles are adsorbed onto the reaction membrane of the test cartridge to form test spots. That is during the manufacturing process of course. Then, for running the test, the patient's sample is diluted in specimen diluent and added to the test cartridge. HIV antibodies present in the sample will bind to the antigens on the membrane.

[Slide]

Then conjugate is added to the test cartridge and will bind to antigen antibody complexes on the membrane. A development reagent is added, and purpose color develops on the test spots and control spot where antibody has bound. The appearance and location of colored test spots determines if the sample is reactive for HIV-1, HIV-2, both HIV-1 and HIV-2 or neither.

[Slide]

This slide shows the Multispot membrane configuration. You can see that spot 1 is designed as the

reactive control spot. Spot 2, in the lower left, contains an HIV-2 peptide. Spot 3 contains an HIV-1 recombinant. Spot 4 contains an HIV-1 peptide.

[Slide]

A little more detail on the spots themselves -- spot 1, the reactive control spot consists of an anti-human IgG from goat source. Spot 2 consists of a synthetic peptide which mimics the immunodominant epitope of the HIV-2 GP36 transmembrane glycoprotein. Spot 3 consists of an HIV-1 enveloped glycoprotein expressed from E. coli, GP41. Finally, spot 4 consists of a synthetic peptide which mimics the immunodominant epitope of the HIV-1 GP41 transmembrane glycoprotein. As noted earlier, each of these four biological materials are bound to the test cartridge membrane during the manufacturing process.

[Slide]

Quickly, the Multispot procedure -- in step one, serum or plasma specimen is pre-diluted in a sample diluent and added to the test cartridge. Notice that the specimen is added through a prefilter which is effective in minimizing specimen flow problems. At that point, the sample is incubated for two minutes at room temperature.

Step two, the prefilter is removed and 1 ml of wash buffer is added. In step 3, 3 drops of conjugate are added and a second 2-minute room temperature incubation is

performed.

[Slide]

Step 4 includes a 2 ml wash which involves simply filling the cartridge reservoir twice with the wash solution that is provided with the kit. Step 5 requires the addition of the development reagent, followed by a 5-minute room temperature incubation. Finally, in step 6 the reaction is stopped by the addition of 1 ml of stop solution, at which point the test result may be read. It should be noted that all liquids, including specimen and the kit components, are absorbed by a pad contained in the cartridge, thereby allowing for easy decontamination and disposal.

[Slide]

Getting on to the Multispot assay interpretation of results, you will recall that spot 1, the spot in the upper left corner of the cartridge must show color in order for the assay run to be considered valid. Therefore, the negative result shown here reflects control spot and no color in either the HIV-1 spot or the HIV-2 spot. An invalid result, shown down here, will have no color in spot 1. Similarly, any other test result which might show color in any or all of the HIV-1 or HIV-2 spots but no color in the control spot would similarly be invalid.

This slide also shows the positive results, including HIV only positives which show color in either or

both HIV-1 spots; the HIV-2 positive which shows color in the single HIV-2 spot; and finally the HIV 1/2 positive results which show reactivity in either or both of the HIV-1 spots and the HIV-2 spot.

[Slide]

The Multispot kit design has been designed to allow for testing and differentiation of HIV-1 and HIV-2 through the application of separate HIV-1 and HIV-2 biologicals to the test cartridge membrane and, as noted earlier, the reactive control spot provides an indication of assay validity for every test run.

[Slide]

Additional kit design features include a total incubation time of nine minutes. The test was also designed to avoid the requirement for any special equipment such as incubators and, as noted earlier, the test cartridge contains a prefilter to eliminate specimen flow problems.

Finally, as Bio-Rad does intend to submit a PMA application to CBER for this product, I wanted to briefly describe the manufacturing strategy that is employed currently for Multispot, and let you know that we intend to continue this strategy, initially at least, following PMA approval.

Again, the HIV biologicals are manufactured in the licensed Bio-Rad, formerly Genetic Systems Corporation,

facility in Redmond, under the quality systems employed for our licensed test kits. The cartridges and other kit reagents are manufactured by Bio-Rad in Les Ulis, France. This Les Ulis facility holds an FDA license for the manufacture of blood typing reagents and has, to date, undergone multiple FDA CBER inspections. So, we would intend that the final kit would be tested and released at that facility.

In summary, Bio-Rad intends to submit a PMA to CBER to obtain approval to market Multispot as a diagnostic test kit in the U.S. Our PMA will include all relevant chemistry manufacturing and control information, and also data from previous European studies, as well as data from studies conducted by multiple U.S. sites will be submitted in support of approval.

[Slide]

I briefly have some data -- you have seen a lot of data done by CDC people, the Army people, but we also submitted this product in France, and here is a brief summary of some seroconverted panels. As you can see, the number in each case represents the number of days from the first bleed at which the sample was first detected as positive by each test. Just for your information, the Genelavia test refers to an indirect ELISA which was approved for blood screening in France at the time of the

study, and the Western Blot data are taken from the seroconversion panel data from the manufacturers. Basically, you can see at this point basic equivalence between Multispot and the ELISA.

[Slide]

Finally, we also have some specificity data in a European study, 4230 normal donors. Fresh and frozen plasma and serum. Six were initial and repeat reactive, for a specificity of 99.85. We also did other medical conditions for cross-reactivity, 144 samples from a variety of non-HIV medical conditions and zero reactive. Thank you very much.

DR. HOLLINGER: Thank you, Mr. Dennis. Any questions? Yes, Miss Knowles?

MS. KNOWLES: What year were those studies conducted, please?

MR. DENNIS: I believe 1994.

DR. HOLLINGER: Thank you. The next speaker is for MedMira, Debrah Lynch and Hermes Chan.

MR. CHAN: Good afternoon. I am definitely Hermes Chan, not Debrah Lynch. I am a representative for MedMira.

[Slide]

I would first like to thank FDA for inviting us to such an important meeting. First of all, MedMira is a Canadian public company. We are the first and only rapid HIV test approved by Health Canada for the detection of HIV

type 1, 2 and group O antibodies in laboratory settings. We have submitted a full PMA for FDA approval for serum and plasma applications, and we have initiated discussions with FDA regarding whole blood HIV testing.

My central point of the presentation today is to share the excitement we have about the fact that we have developed a novel approach to overcome some of the limitations of a rapid diagnostic test.

[Slide]

Obviously, our rapid HIV test shares similar features with other manufacturers, as you have seen before. However, to ensure the excellent performance of our test we have done over 20,000 tests in Canada alone and also over 10,000 tests in the United States to achieve sensitivity and specificity of over 99.5 percent.

What I would like to share briefly with you is some of the procedures that we have. This is for our serum and plasma test. Basically, we are using a colloidal gold conjugate which can increase the stability of the test, and with a few simple steps we can achieve a test showing a positive with a single dot and a negative with a clear background within less than three minutes.

[Slide]

The second one that I want to share with you is our whole blood test kit. The whole blood test kit is very

similar to the serum plasma kit, except that we have a prefilter system whereby, within a few seconds time, we can separate the cells from the serum or plasma.

[Slide]

In the past year we have done clinical trials in three different locations, and they were all very successful and I want to share with you some of the results. We have done it in Nova Scotia, in Canada, with 154 real-time patients whole blood specimens, with matching plasma, and we have shown sensitivity of 100 percent.

[Slide]

The second studies were done with Newfoundland Public Health Lab, again in Canada. Here, we have 145 routine specimens for HIV screening, out of those there are 96 positive specimens, again with matched plasma, and 49 negative. The same as before, we have an overall agreement with the reference test of 100 percent.

[Slide]

The last one happened in the Bahamas while we are doing our serum plasma test. We happened to have 15 in-hospital patients and again we saw 100 percent sensitivity.

[Slide]

You have heard so much about all the wonderful things concerning rapid HIV tests today, and you can't help but wonder about what the catch is. It is too good to be

true, isn't it? This is a comparison of the routine ELISA system versus rapid assays. A rapid assay does provide a very unique advantage over the ELISA system in the time required to perform the test, as well as the portability compared to the ELISA system. However, there are two disadvantages of rapid assays. One is that it does only have a subjective readout. Secondly, it does not have computer data storage.

[Slide]

From MedMira's point of view, this is not a home test. Because of this, data storage as well as results and interpretation are a very important features when tests are not done in a routine, controlled environment such as clinical laboratories. As a result, MedMira does not just introduce a point of care rapid test, we give you a rapid HIV point of care testing system, and this is what our system looks like. It is a portable reader that can read out the result of a rapid test. The test itself takes about two minutes to do, and the result to be interpreted by the reader takes only about two seconds.

[Slide]

The interesting thing about this rapid reader system is that it does have the possibility of including all the patient information which the software can adapt to the clinical laboratory so that we can get all the information

directly.

[Slide]

Negative specimens take about two minutes and does offer a graphic interpretation saying it is a negative result. It also gives you numerical values as well as written, whether it is positive or negative.

[Slide]

On top of it, it also is able to provide you with the actual image of the test result which is stored in the database and you can retrieve it any time.

[Slide]

With a positive result, it gives you a similar thing except that now we have a positive graphic interpretation as well as numerical. On the right-hand side we also have the statistical data that you can use for any statistical analysis.

[Slide]

When we look at the comparison using the ELISA system as well as our Rapid Reader 2000 systems, again we can see the advantage of the rapid test, as has been shown, and also we can store our data in the computer, as well as having the test image stored on the hard disc.

[Slide]

I would like to conclude my presentation with the comment that Dr. Spencer Lee, the Director of Virology,

Public Health Lab of Halifax, Nova Scotia. He said that the MedMira rapid test and the rapid readers 2000 have all the testing performance characteristics of a test acceptable in point of care testing. I thank you for your patience.

DR. HOLLINGER: Thank you. any questions? If not, we will move on. The final person who has asked to speak is Mr. Raymond Smith, for the National Alliance of State and Territorial AIDS Directors.

MR. SMITH: Hello, and thank you. I have no slides and this will be brief. I am with the National Alliance of State and Territorial AIDS Directors. For those of you who are not familiar with us, we represent the heads of the HIV and AIDS programs in all the U.S. states and jurisdictions, and that is both in terms of care and prevention.

On May 18 of this year, we sent a letter from Wendy Craytor, who is the Chair of NASTAD and the AIDS director from the State of Alaska, and Julie Scofield, who is the executive director of NASTAD, to the Office of Blood Research and Review. We have received a very gracious reply, and I understand that there is a copy of this letter in the packets that were distributed to the committee. So, I will just very briefly read a couple of excerpts which highlight the position of NASTAD on the question of rapid tests.

On behalf of the National Alliance of State and Territorial AIDS Directors, NASTAD, we are writing to request expedited approval of rapid HIV antibody tests by the U.S. Food and Drug Administration. Public health agencies and their community partners must have available to them a range of testing technologies and approaches to maximize the number and proportion of clients who are tested for HIV and who receive their test results in a timely manner. Rapid testing technologies, in particular, would contribute to the provision of high quality HIV/AIDS services responsive to the needs of consumers and providers.

As representatives of the front-line HIV/AIDS programs in the jurisdictions directly funded by the CDC, NASTAD members are deeply involved with the full range of testing issues. We have been anticipating the availability of rapid HIV antibody testing for quite some time, and expect that it will have an important positive effect on our ability to deliver effective HIV counseling, testing and referral services. Although we recognize that rapid testing will require modifications to the existing systems of HIV counseling and testing, including providing assurances of appropriate confirmatory testing, we believe that it would not be problematic for us and other providers to implement such modifications in a relatively short time span. Given the demonstrated benefits of early medical intervention in

promoting health and delaying disease progression, as well as the key role that HIV antibody testing plays in a comprehensive approach to HIV prevention, it is critical that rapid testing be made available in the U.S. as soon as possible. NASTAD strongly encourages the FDA to expedite review and approval of these tests. Thank you.

DR. HOLLINGER: Are there any questions for the companies with regard to their tests?

I have just a couple of questions and I think this has probably been done, but I would like to know about a couple of issues about the various tests, and maybe the companies individually can remark about this. There are several things which might cause a false-positive test or even a false-negative test, and I would like to know if they have been looked at. For example, patients who are on heparin, where there is a very marked charged particle present, has this caused any problems in there. I would like to know about jaundice patients. I would like to know about hemolyzed samples, patients with hemolytic anemia or even cirrhotics who have cells which are quite fragile, and any other charged particles where they might be taking drugs, like the heparin. I think some of them have looked at lipids. But could each one of you at least let me know if you have looked at all of these things, and whether there are any problems associated with these particular aspects of

your tests?

MR. BERNSTEIN: Dave Bernstein, from Guardian Scientific. The Quix test has a prefilter. Badly hemolyzed samples, no problem. Icteric samples, no problem. Also all the anticoagulants -- we have looked at heparin, EDTA, ACD, no problem. The test is very versatile in terms of samples.

MR. MURRAY: Bill Murray, with Abbott. Concerning the Determine test, a couple of things -- we recommend EDTA in our package insert as an anticoagulant although we have had studies done to support other anticoagulants. Our clinical studies within the package insert show a full array of patient samples that we used, including hematocrit, etc. We looked at a battery of different sorts of potential interferences. So, we did include that and we can certainly make that available to the committee.

DR. HOLLINGER: Heparin?

MR. MURRAY: The samples do work using heparin, yes.

DR. HOLLINGER: All right. Yes?

LT. ZAHWA: Lt. Zahwa, from Walter Reed. Regarding the comments on hemolyzed samples, in most of the lateral flow devices, the color that develops is a reddish color and that is the interference substances there such as the red color in the hemolyzed sample will mask the view of the reader from that distinct line that might be present.

Some companies have done extensive studies on the hemolysis effect on the results of the test but the question remains whether that reddish background can be distinguished from the clear line that the individual reader is looking for.

DR. HOLLINGER: Yes, please?

DR. COLEMAN: My name is Patrick Coleman. I am from Bio-Rad, representing the same test that Scott Dennis talked about. The Multispot test, previously known as Genie, has been actually studied around the world for more than ten years. It has been very well evaluated with the same anticoagulants that the other gentleman mentioned -- heparin, ACP and other major anticoagulants, EDTA. Because it is a flow-through device and not a lateral device, most anything that is in solution will really not be impacting the test. It will go right through the membrane and into the absorbent cartridge. So, it will not reside with the test itself.

DR. HOLLINGER: Thank you. Yes?

MR. GEORGE: I am Richard George, from Epitope. We didn't make a presentation but some data has been presented about our test. I would just like to say that we have looked, as I think most people have, at all the anticoagulants that are frequently used in collecting samples. They don't interfere with the test, the OraQuick test that was presented.

In response to what Lt. Zahwa just said about hemolysis, our strategy for doing whole blood is that we actually lyse the blood but we only add 5 mcl of blood and it does not affect the test at all, and the color that is generated from the lysing of the blood is really not visible on the strip.

DR. HOLLINGER: Yes, please?

MR. CHAN: My name is Chan, from MedMira. I just want to point out that with our product we have extensively studied the interference, and anticoagulants and everything is no problem. However, as with any flow-through device, the only samples that will cause some sort of a problem will be heavily lipemic specimens. If there are heavy lipemic specimens the samples will not filter through the membranes. That is why the filter system that we put in does help to improve the sensitivity in that way.

Open Committee Discussion

Questions for the Committee

DR. HOLLINGER: Thank you. We have some questions but I want to just see if there are any other burning comments that anybody from the committee would like to make about anything. If not, why don't we see the questions that have been put before us? There are two of them.

The first question is does the committee agree with the FDA criteria for approval of a rapid test for use

in a diagnostic setting? Yes, Paul?

DR. SCHMIDT: It is not really clear to me what the question is. We haven't heard what the problem is, if any, with the FDA standards for approval. What is the issue here?

DR. HOLLINGER: Paul, are you asking about what are the FDA criteria for approval?

DR. SCHMIDT: Why do they create a problem for the licensing of what we have heard about today?

DR. POFFENBERGER: I want to switch over to the overhead slide because then I can present to you what we are proposing.

[Slide]

What is happening today is we are proposing to use a standard that is different from a standard previously used for licensing of blood screening tests. We are proposing to allow a test to be approved if it can show that it can meet the 98 percent sensitivity and specificity standard, which is that the lower bound of the 95 percent confidence interval must be at least 98 percent. For sensitivity, in addition, we are asking that the test be able to detect 11 out of the 11 positive samples on the FDA HIV-1 panel.

So, the difference is a different standard for sensitivity and specificity. Now, as you have seen some data shown today, a lot of these tests, we think, are going

to be able to meet or come very close to the same sensitivity and specificity that is already out there for tests that are licensed. However, at this point in time we don't have a lot of data in U.S. populations. So, we have chosen this point based on the preliminary data that the CDC has obtained in studies that they are performing.

Our goal here really is to try and include as many of the assays as possible, to do it on a rational basis, because we don't know, for instance, with multiple test algorithms which combinations might prove to be very beneficial. So, we felt that based on the data available this would be a reasonable standard for rapid tests.

DR. HOLLINGER: Yes, Dr. Nelson?

DR. NELSON: I am not clear about what the licensure would mean. In other words, would it mean that two rapid tests would then preclude the need for a confirmatory assay, or does this mean it would be a rapid screening test which would then be followed by a confirmatory assay? I am not sure what the licensure would mean.

DR. POFFENBERGER: That is a good thing to ask about. Approval, as I said before, will mean the test can be used in the intended sites. The users there will be able to choose how to use it. Approval will mean we say that this test meets the standards, is able to be made

consistently. At this time -- now we are sort of getting into the second question with your question here, and maybe we would want to separate it out. So, maybe we ought to postpone that discussion. Okay?

Right now, for this question, we are specifically asking does the committee feel that this 98 percent lower bound is acceptable for these tests for diagnostic use settings.

DR. HOLLINGER: Based also on the number that are required for the testing.

DR. POFFENBERGER: Yes, based upon the sample populations and sizes that are requested.

DR. HOLLINGER: Yes, Jeanne?

DR. LINDEN: Other the decrease in the number of samples that have to be tested, what is the other change from the present requirement for diagnostic testing for sensitivity and specificity? You are talking about lowering the standard?

DR. POFFENBERGER: The current blood screening tests, the lowest one for sensitivity out there has a 99.2 percent but the ones that are commonly used are typically performed at 99.9 percent levels.

DR. HOLLINGER: Is that a requirement? I think maybe what Dr. Linden was asking is, is that a requirement now for licensure of those particular tests which are

currently out there, that they be at least 99 percent, or are the same --

DR. POFFENBERGER: No, we are not changing any standards for licensing of screening tests. This pertains only to approving, under the PMA setup, diagnostic use tests -- if that is the question.

DR. HOLLINGER: Yes, Dr. Epstein?

DR. EPSTEIN: If I could also clarify, part of the issue is operational because we approve new donor screening tests by requiring that in clinical trials they be shown to be equivalent. The statistical equivalency standard is a more rigorous standard and it drives the requirement for larger trials. Additionally, we have had a more stringent requirement for showing geographical distribution of the samples. We have placed more emphasis on prospective studies under clinical use conditions, and we have had requirements for HIV-2 sensitivity. We have also requested that tests meet standards for HIV-1 group O sensitivity, although that is evolving for the donor screens. So, we have also eliminated all of those requirements except if a product sponsor wishes to make a specific claim for HIV-2 sensitivity or group O sensitivity. So, we waived that as a trial requirement or validation requirement.

Additionally, coming back to Paul Schmidt's basic question, why is there an issue here; why are we bringing

this? Of course, we hope there is not much at issue in your minds and you will concur. But the reason we are bringing this is because there are those who have stated that FDA has set the bar too high and that we are, therefore, impeding the development of these technologies for use in the United States. We don't believe we have set the bar too high. We believe that we have asked for the least burdensome validation consistent with tests that we think will be sufficiently accurate for the proposed use. But the underlying question is has the FDA set the bar too high?

DR. HOLLINGER: Yes, Col. Fitzpatrick?

COL. FITZPATRICK: I guess maybe I am being a little dense this afternoon but I don't understand, relative to sensitivity and specificity in paragraph (b) there, in relationship to Jay's last comments where is the bar now? You said tests are functioning at 99.9 percent but what is the bar?

DR. HOLLINGER: I guess I would say the same thing, if a test came in today to be licensed for donor screening and fit these criteria, would it be licensed --

DR. EPSTEIN: No, but the strategy for getting there isn't the same. See, in this case we have said the standard is a sensitivity and specificity determined from the point estimate of the clinical trial plus statistical analysis. For the donor screens the standard is defined

operationally. We are saying do a head-to-head trial with a licensed test and prove that it is equivalent -- not even not inferior; it has to be proven equivalent with statistical rigor. John is nodding because he knows what I am saying statistically. It is not the same standard. Now, if you ask me what is the statistical statement of the operational standard, it would be higher than this. I mean, I haven't computed it so I can't answer the question but it would be higher than this.

DR. HOLLINGER: Thank you. Any other questions before we vote? Yes, Dr. Mitchell?

DR. MITCHELL: Again, when you are talking about the sensitivity and specificity of the standard, that is for one test, is it not?

DR. POFFENBERGER: That is for each individual test to be approved, yes.

DR. MITCHELL: So, that, again, makes it much higher than if you are repeating it twice or three times -- repeating it once or twice.

DR. POFFENBERGER: It is possible that it could be. It would depend on the data from doing repeat testing but, yes, maybe.

DR. HOLLINGER: In fact, that is a good point. I guess the question is, is this based on repeatedly positive tests or just based on a single one?

DR. POFFENBERGER: The use of the test is primarily under the trials and what has been proposed, that I have been aware of, for testing by individual rapid test -- it is a single use; a single result. There are instances where a secondary or repeat result is recommended.

DR. HOLLINGER: So, it depends on how they come in and ask for it, but if they come in and they say these are based upon a single test --

DR. POFFENBERGER: If the clinical data will show that it meets the standard, then we are proposing that they can be approved.

DR. HOLLINGER: All right. Thank you. All right, if that is the case, then we will vote on the question. Based on these criteria, does the committee agree with the FDA criteria for approval of a rapid test for use in a diagnostic setting, as described herein?

All those that agree with that and vote yes, raise your hand.

[Show of hands]

All those opposed, voting no?

[No response]

Abstaining?

[One hand raised]

And, Mrs. Knowles?

MS. KNOWLES: Yes.

DR. HOLLINGER: And, Dr. Simon?

DR. SIMON: Yes.

DR. SMALLWOOD: The results of voting for question number one, there were 14 "yes" votes. There were no "no" votes; one abstention. Both the consumer and industry representative agreed with the "yes" votes. There are 15 members that are qualified to vote on this issue.

DR. HOLLINGER: Thank you. Now we will go to the second question. Again, I think we will probably have to have some additional information, if we could. Does the committee agree with the FDA approach to labeling rapid tests? Would you like to go ahead and tell us what the approach is that you have up there?

DR. POFFENBERGER: What you are seeing in front of you is the proposed labeling. The first statement, for use as an aid in diagnosis, is what is our current practice. The second statement is really what we are looking for input on, which is that this test may be used as part of a multiple test algorithm. What we are proposing is that when a test is approved, based on its individual merits, meeting that 98 percent sensitivity and specificity standard, we will also be putting the statement in the labeling that will in specific testing settings allow the use of the test in multiple rapid test algorithms.

DR. HOLLINGER: So, Dr. Poffenberger, what you are

asking from the FDA standpoint is that where these other tests are not feasible, supplemental tests, confirmatory tests, you could use it but in a multiple algorithm of some sort.

DR. POFFENBERGER: Yes, that is correct.

DR. HOLLINGER: Dr. Boyle?

DR. BOYLE: My question is related to the last part of the second labeling, which says in settings with the use of an approved supplemental test for HIV antibodies is impractical or infeasible prior to patient counseling. My question is are people going to interpret that the same way? I mean, is one emergency room going to say yes and another no? I mean, what exactly -- I know what you are intending it to say, but what does it say?

DR. POFFENBERGER: Well, I think you are probably correct, it won't be interpreted in quite the same way by everyone. What we are trying to do is open the door to meet the needs that you heard of before. We are trying to do that without imposing a lot of burdensome requirements for submission of data that is going to become exponential as the different tests overlap. We want to allow individuals at testing sites to be able to design their algorithms.

We are hoping, and I believe it is being planned, that recommendations will be issued, Public Health recommendations will be issued on the basis of studies, and

that these recommendations would be then available to the users in the settings that you have heard described. So, that is sort of the approach.

DR. HOLLINGER: Dr. Poffenberger, I am a little confused about this in some respect because, in the first place, I thought the object was that when you saw somebody for the first time in a setting and you do this test, you do it while they are there so you could counsel them. But now what this essentially is indicating, at least to me, is that it requires a supplemental test before you can do the counseling. It says "prior to patient counseling" which would mean you would then have to either do two tests to get to that point or you would have to have another supplemental test, or do something to get to that point.

DR. POFFENBERGER: It is not intended to mean that. What it is intended to do is to allow the use of the algorithm to increase the accuracy. With the overlapping test algorithms you might be able to tweak your specificity up a good bit higher so that when you do give the results there on site, you can essentially counsel them that this is your serostatus. At this point in time, the current recommendations for the sample to be further tested by the Western Blot as a confirmatory will still remain in place. These recommendations are still in place.

DR. HOLLINGER: Yes, Dr. Chamberland?

DR. CHAMBERLAND: I guess that is my question somewhat, and maybe I could ask Rob Janssen or others to elaborate on this, if in a clinical setting you are using only one of these rapid assays and it is positive, is the individual then going to be counseled or should there be a supplemental test performed, a Western Blot supplemental test performed?

DR. JANSSEN: [Comment away from microphone; inaudible.]

DR. CHAMBERLAND: But in the same clinical setting, if there are data that have been developed that demonstrate that two or more of these rapid assays are as good as an EIA and a Western Blot, or better, then you would still have to proceed to a traditional Western Blot, or does this labeling allow you to eliminate the need for a Western Blot? I just wanted some clarification on that. Rob, you indicated that CDC is developing these revised testing and counseling guidelines that are trying to incorporate the probability of rapid assays being available.

DR. JANSSEN: The way we have looked at the rapid test algorithms is as a replacement for Western Blot, as a replacement for EIA and Western. In terms of this, I think it is incumbent upon the Public Health Service to develop those algorithms and publish guidance for those algorithms, as we have done in the past.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: Yes, it is not really an FDA question. When we approve a test as a diagnostic, that test approval doesn't imply what you do next. The recommendation for performance of supplemental testing prior to counseling is a PHS recommendation, which I think has been on the books since about 1989. I think that the concept of validating the preliminary test result remains necessary. In other words, nobody really wants unconfirmed results reported.

The distinction that is being made here is between confirmation through supplemental testing and, if you will, improvement of accuracy on a statistical basis by performing multiple tests with essentially similar technology. When we have approved supplemental tests, the concept has always been that there is what is called an orthogonal method. In other words, the nature of the signal is different than what you did with the first test. Those differences can arise because of differences in format or differences in the underlying principle of the test. For example, the Western Blot operates on a different principle than the EIA because it separates the antigen and enables you to see the signal independent of the surround. So, the concept of confirmation through supplemental testing is that on each and every individual sample tested it yields a definitive result, whether it is a true positive or a false positive.

Now, the concept that is being put forward here is a little bit different. The concept is that the accuracy can be increased on the basis of test concordance which is, therefore, a statistical validation of accuracy. What has been argued, based on experience and mainly the studies in Africa, is that the two test method using rapid diagnostics can produce in the end results that are, on average, as accurate as with confirmatory testing. But that would never be known with the same degree of certainty as if one had come back and tested with an orthogonal method.

So, what we are saying here is we are faced with a situation in which we believe, based on the available data, that the accuracy of reported results can be significantly increased by using multiple independent diagnostics, each of which is, as it were, a preliminary test or a screening tool, although we don't label it for screening because by that we mean donor screening.

So, it is a rapid diagnostic. No one of them is definitive in its own right. Because it is useful to combine them, we think we should move in that direction. But we don't want to find ourselves in the position where we don't allow it without sending manufacturers out to collaborate with each other, or having clinical investigators study all the possible test combinations and then bring the data to the FDA. FDA thinks that if we can

set a high enough standard for the individual tests, then we shouldn't have to entertain applications for all the possible combinations.

So, what we are asking the committee is do you concur that if we have put the approval standard is place, we can then let the tests be labeled as suitable for use in multiple testing algorithms without the FDA reviewing trials for those combination algorithms? We do envision that such trials will be done, and we do envision that guidance will be published by the Public Health Service on optimal combinations, such as choice of the test sequence; such as, you know, true hits; is it positive or best out of three; or test sequence proposals, particular test followed by a particular test. We do think that guidance of that sort will be necessary. We just don't think it should rise to the level of FDA approving every such combination and every such algorithm. So, we are asking whether you concur with generically labeling the tests as suitable to be combined to improve accuracy on a statistical basis.

DR. HOLLINGER: Yes, go ahead, Paul.

DR. SCHMIDT: Unless this is defined some place else, to me, a multiple test doesn't necessarily mean use two different reagents. It could mean you do the same test twice. Is that defined some place else, what a multiple test algorithm is? Is it really two different manufactured

products?

DR. HOLLINGER: There was data, I think, presented in the material that was handed out that did suggest that if you combine the test and you use as your first test the most sensitive test, and then combined it with a more specific test at the end, that this would be comparable to or close to perhaps the EIA and the Western Blot --

DR. SCHMIDT: I agree, but the requirement doesn't say that.

DR. HOLLINGER: No, it doesn't.

DR. SCHMIDT: So, is that the right label?

DR. HOLLINGER: If I understood what you said, Dr. Epstein, you said that you may not require -- and I agree with you, we don't want to get into should you combine this test with that test; I don't think that is what we should be talking about, but I do think there needs to be some requirement because someone could combine a less sensitive test with another test and end up with some erroneous results on that basis. Yes, Dr. Simon?

DR. SIMON: I think we need to keep in mind the difference between licensing a test and approval process as a diagnostic. When a test is licensed, licensed organizations like blood and plasma organizations have to follow exactly the instructions. But as I understand it, this test will have labeling that will indicate something

but once it gets out in the public health arena it will be used as directed by appropriate physicians and professionals. So, I think that the agency is trying to give the flexibility that the public health professionals have requested to be able to use these rapid tests in a situation that would be helpful to them.

DR. HOLLINGER: Yes, Dr. McCurdy?

DR. MCCURDY: My question is why does the label have to say anything about multiple tests? Why can't it just say for use as an aid in diagnosis and let the guidelines that are in preparation, I guess, deal with how you should use them?

DR. HOLLINGER: Dr. Macik?

DR. MACIK: I had the same question, and I would like to ask currently, do the tests that are being used for diagnosis have on their labeling that you have to do the second supplemental test? Or, is that being done only as part of the guidelines from the Public Health Service?

DR. POFFENBERGER: It is being performed as part of the guideline for the Public Health Service but most, if not all, of the licensed tests also include language to recommend that a positive test proceed on to a supplemental test. So, it is really in both places.

DR. MACIK: So, it would be similar to having this labeling on it? I mean, are we going to be labeling the

Point of Care test in a manner different than the current test that is being labeled?

DR. POFFENBERGER: Yes, this will be a difference in labeling, but it is a difference that is necessary really because of where it is going to be used and how the test is going to come to market, that is, as an approval.

DR. MACIK: Then it kind of gets back to the question again, when Jay started off he said determining whether you need a supplemental test was not done by FDA; that is guidelines, Public Health Service. Then, in a way, by putting this label on there it looks like the FDA is saying that you have to do something.

DR. EPSTEIN: In the setting of blood screening, FDA does have standards to recommend and/or require supplemental tests. Currently, they are only required under HIV lookback regulations, and not for all tests. We published a proposed rule on testing last year which would create a regulatory requirement to follow all screens with licensed supplemental tests whenever available. So, in the donor screening setting it is either already required or to be required. In the medical diagnostic setting there is no such requirement. However, there are PHS recommendations which are long-standing, which call for the performance of confirmation, by whatever means, before notification. That is why if you, as a physician, order an HIV test you always

get it back both with the screen and confirmatory. You get back the ELISA and the Western Blot. The reason is because the clinical laboratory is complying with the PHS guideline, or should be.

Now, what we are trying to do here is address the fact that we have existing guidance which calls for supplemental testing, but we are going to permit algorithms that don't use those tests. So, what we are trying to do is indicate in the test label how you might comply with the available guidance.

Now, you know, I would agree that we could drop it from the test label but I am not sure that that would add any help for users. Whereas, putting it in the test label suggests that, you know, you are not done as a clinical laboratory, and we still do want that message.

DR. HOLLINGER: Dr. Boyle?

DR. BOYLE: Since I started picking on the thing, I would like to come full circle and say, although I think I can wordsmith it better, the intent I think is reasonable. The fact that there is going to be follow-up guidance on exactly what is meant by some of the phraseology where we basically said, beyond the use and diagnosis, is that it could be used in a multiple test algorithm and we don't have to go through a new approval process to get that added to the label. Since that will simplify everybody's lives, I am

willing to forget what I said earlier and just -- you know, I think it works pretty well with follow-up guidance.

DR. HOLLINGER: I certainly agree with that, and maybe you can help me out of this, Jay. The problem I have with this is, I mean, the whole idea with the rapid test was that you could talk to people and give them information before they left a clinical setting somewhere. And, then we are hit with a label that says you have to have this other possible thing, a supplemental test prior to patient counseling. Am I missing something?

DR. EPSTEIN: Yes.

DR. HOLLINGER: Well, then help me.

DR. FINLAYSON: Let me say something because this is almost instant replay. I had the same problem when I first encountered this, and my reaction was, well, you can do the first test in three minutes or five minutes or seven minutes, and then you are going to make them wait for a Western Blot? The answer is what Dr. Poffenberger is proposing that you have another test there which will also take only five minutes, or seven minutes, or ten minutes. So, in a span of about 25 minutes you can get your answer with enhanced accuracy. Maybe Dr. Poffenberger would like to show that slide again in which she showed the worst case. If you combine two tests together, the worst that you could ever come out, in as much as you have already voted on

question one and said both sensitivity and specificity must be at least 98 percent -- the worst you could ever come out with is 98 percent/96 percent, or 96 percent/98 percent.

DR. HOLLINGER: John, I don't have a problem with that. I mean, I totally agree with you but then essentially what it is asking us to do, or me as I view it, is to vote that there is a requirement for these multiple tests. I don't have a problem with that either, but that is basically what it is saying because, you are right, you do one test and then you do another test and then you can do patient counseling. But that is basically what it would say, that we are not going to license a test just for a single test only and then follow up with patient counseling. It is saying you are really going to have to do both of these tests and you are going to have to have another test. That is what I am having a problem with.

DR. FINLAYSON: I don't work in this area so, see, I have the overwhelming advantage of consummate naivete when it comes to HIV test kits. But I read this as saying this test may be used. It is not a requirement; it is a recommendation, and it is not an FDA specific recommendation; it is a Public Health Service recommendation. And, this is saying this may be used this way to fulfill that overall recommendation.

DR. HOLLINGER: I just wanted you to say that.

Yes, Dr. Macik?

DR. MACIK: I guess that is what I am kind of getting back to. I understand Jay saying you want to get across to them that you are not finished. But, how do we want to put that? And, I think putting something like it should be recognized that this diagnostic test must be used in a way consistent with current Public Health, or whatever, recommendations for validating the test before you counsel a patient, or something like that -- in other words, still get the message across that this test by itself doesn't end but without bringing up the exact -- leaving it open to whatever the reigning guidance is from the appropriate authorities that this test should be used in concordance with that guidance.

COL. FITZPATRICK: I am having the same problem you are, Dr. Hollinger, with some of that, and that is helping but is it feasible to drop the "prior to patient counseling" part, and that fixes it?

DR. HOLLINGER: Well, that is basically what I wanted to do, just take that last portion out. I guess we could vote on it, and if the committee doesn't want to do it, then they can decide not to. So, I will propose that we modify or revise this -- that for the purposes of the vote we revise this by taking out "prior to patient counseling" and then vote on that. So, I would like to propose that as

a revision and if there is not a second we can go on from t there. Is there a second to that motion?

COL. FITZPATRICK: Second.

DR. HOLLINGER: So we will vote on that. The vote is to remove from this approach "prior to patient counseling." Dr. McCurdy?

DR. MCCURDY: Blaine, I am continuing to have the problem that I mentioned before, and I am not really sure that helps. My suggestion is to split question two into 2(a) and 2(b), and 2(a) would be labeling for use as an aid in diagnosis, which I think is pretty common for all diagnostic test kits. The second one would then say you should use some other kind of test. I think at one time it was fairly common to use more than one liver function test, but I doubt if the labeling of the kit said this may be used as part of a multi-test algorithm. And, I think this is basically clinical medicine and PHS guidelines, if they are not too far delayed, would take care of this.

DR. HOLLINGER: Dr. Simon?

DR. SIMON: I a thinking that the FDA was trying to be permissive and helpful to the public health sector with this wording. Is that true? Because, if that is the case, then I would want to be supportive and vote for the wording.

DR. CHAMBERLAND: I agree with you, although I

think we need to hear from the folks at CDC who have been working in this. This document that is in process about testing and counseling, as I see it, I mean, again maybe there would be words to wordsmith this a little bit better but I see that second statement basically as saying that this test can be used either as a single test where the confirmatory test would be a Western Blot, and there may be settings -- and other people in this room may know that there may be settings where it is a better sequence to do a rapid assay and do a Western Blot as the supplemental confirmatory test, or it can be used as one of a series of multiple rapid assays.

Maybe what people are reacting to is that there is a sense that the first part of that is missing, that if you use this as the sole rapid assay you need to have a supplemental confirmatory test performed, the traditional Western Blot or whatever. Are people feeling that this somehow is missing that element? Because I don't feel as strongly as others do on the committee about the need to delete the language. I certainly would have no problem with FDA or others maybe rethinking the language, and I don't think we need to think that this is the final, final version of the language. It seems like it is up for discussion, and I think what they are trying to do is tell us what their intent is, and maybe the feedback we are giving them is you

might need to work on the wordsmithing a little bit better because it is not as clear as we would like.

DR. POFFENBERGER: I think you have really captured what we were intending. We were intending to make it an "or" situation. That is, you can either use it as a single, initial rapid screening test or you may use it in a combination. The recommendations, if it is used as a single test, would still be in place. That is, the site would be under Public Health recommendations to go on and do a confirmatory Western Blot. So, what we are trying to do here is be flexible and offer the option, and let it be up to the testing site and the health professional running that site as to which path they are going to choose.

DR. HOLLINGER: Which would mean that they could counsel patients before they do that other confirmatory test.

DR. POFFENBERGER: Yes, they can counsel the patients but those recommendations are part of the PHS recommendations. So, they would be following that and presumably following the counseling recommended by the CDC.

DR. HOLLINGER: Well, with that understanding, I would withdraw my -- if Col. Fitzpatrick will withdraw his second.

COL. FITZPATRICK: I will certainly do that, yes.

DR. HOLLINGER: Let's vote on the intent of this

question. Does the committee agree with the FDA approach to labeling the rapid tests? All those that favor that question and are voting yes, raise your hand.

[Show of hands]

All those opposed, or voting no?

[No response]

Abstaining?

[No response]

Consumer representative? Mrs. Knowles?

MS. KNOWLES: Yes.

DR. HOLLINGER: And Dr. Simon?

DR. SIMON: Yes.

DR. HOLLINGER: Thank you.

DR. SMALLWOOD: Results of voting for question two, unanimous "yes" votes. The consumer and industry representative both agreed with the "yes" vote.

DR. HOLLINGER: Thank you. This concludes today, but let me just mention about tomorrow. Tomorrow we start at 9:00. The first three updates are going to take a little bit of time, so I am hoping we are going to get out at 12:30 but it may be 1:00. So, you need to know that. So, we will see you all tomorrow morning.

[Whereupon, at 5:45 p.m., the proceedings were recessed, to reconvene at 9:00 a.m., Friday, June 16, 2000.]

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