TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

59th Meeting

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Pages 1 thru 230

Rockville, Maryland
June 18, 1998

MILLER REPORTING COMPANY, INC.
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Washington, D.C. 20002
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

59th MEETING

Thursday, June 18, 1998

8:00 a.m.

Doubletree Hotel
Plaza I and II
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
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Donald H. Buchholz, M.D., Industry Representative

GUEST

Mary E. Chamberland, M.D.

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Statement of Conflict of Interest

DR. SMALLWOOD: Good morning, and welcome to the 59th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary of the Committee, and at this time I will read the conflict of interest statement, for your hearing pleasure.

[Laughter]

This announcement is made a part of the record at this meeting of the Blood Products Advisory Committee on June 18th and 19th, 1998.

Pursuant to the authority granted under the Committee Charter, the Director of the FDA's Center for Biologics Evaluation and Research has appointed Dr. Paul McCurdy as a temporary voting member for all Committee discussions.

In addition, the Acting Commissioner of the FDA has appointed Drs. Ralph D'Agostino and Lemuel Moye as temporary voting members for the discussion on the review of clinical trial design for alpha-1 proteinase inhibitors.

Based on the agenda made available and on relevant data reported by participating members and consultants, it has been determined that all financial interests in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the Committee's discussions

have been considered.

No waivers under 18 USC 208(b)(3) were necessary. In addition, Mr. Dubin disclosed a potential conflict of interest which has been deemed by FDA as not requiring a waiver, but does suggest an appearance of a conflict of interest. On March 9, 1998, the Agency approved a written appearance determination under 5 CFR Part 2635.502 of the Standards of Ethical Conduct for this appearance. The determination is relevant for this meeting and Mr. Dubin is permitted to participate and vote on all Committee discussions.

With regard to FDA's invited guests for Topic IV on standard testing for HIV variants, the Agency has determined that the services of these guests are essential. There are reported interests which are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants. The interests are as follows:

Dr. Michael Busch reported that he was involved in the past in clinical trials of assays developed by Murex Diagnostics, Inc., Abbott Labs, Bio-Rad Labs, Cambridge Biotech Corp., Cellular Products Inc., Coulter Corp., Epitope and Genetic Systems Corp. He has received speaker fees from Abbott and serves as a scientific advisor to Abbott.

Drs. Bernard Branson and Mary Chamberland had no financial interests to report for the discussion on standard testing for HIV variants.

Also, with regard to FDA's invited guests and speakers for Topic V on the review of clinical trial design for alpha-1 proteinase inhibitors, the Agency has determined that the services of these guests and speakers are essential. There are reported interests which are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the guests and speakers. The interests are as follows:

Dr. Mark Brantley reported that he is an employee of the National hart, Lung and Blood Institute, NIH. As part of his federal duties he has associations with alpha Therapeutics, Bayer and Centeon. In addition, he is a member of the Board of Directors for Alpha One Foundation and Co-chairman of the alpha One Foundation Registry Research Network. Also, NIH has received a gift from Bayer to support an NIH phenotyping lab.

Dr. Edward Campbell reported that he one of five principal investigators on an Alpha Therapeutic study on alpha-one proteinase inhibitor deficiency. He also has an interest in a firm which operates a detection center to provide alpha-1 antitrypsin deficiency testing. The detection center receives some support from Bayer.

Dr. Ronald Crystal consults with Centeon on alpha-1 proteinase. He receives remuneration. In addition, he is also involved in the design and manufacturing of therapeutic vectors.

Dr. Robert Stockely receives research funds from Bayer to study unrelated issues.

Dr. James Stoller reported that he is the principal investigator on an alpha Therapeutic study; has received speaking fees from Bayer and Alpha Therapeutics; and is a scientific advisory to Bayer, Alpha Therapeutics and Centeon.

Mr. John Walsh reported that he is the president and founder of the Alpha One Foundation and its subsidiary, AlphaNet, non-profit organizations that provide consumer and patient advocacy to the Alpha community.

Drs. Asger Dirksen and Mark Schluchter had no financial interests to report for the review of clinical trial design for alpha-1 proteinase inhibitors.

In the event that the discussions involve specific products of firms not 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.

Screenings were conducted to prevent any

appearance, real of apparent, of conflict of interest in today's committee discussions. Copies of the appearance determination addressed in this announcement are available by written request under the Freedom of Information Act. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

At this time, I would like to introduce the members of the Committee. I would like for those members, when I call your name, to please raise your hand. Following that, I will make another brief announcement and then we will proceed with our meeting for today.

The Chairman of the Blood Products Advisory Committee, Dr. Blaine Hollinger; Dr. Marion Koerper; Mr. Corey Dubin; Dr. Richard Kagan; Dr. John Boyle; Dr. William Martone; Dr. Jeanne Linden; Dr. Norig Ellison; Dr. Joel Verter; Dr. Paul McCurdy; Dr. Buchholz; Miss Katherine Knowles.

We will also have participating as temporary voting members Dr. Ralph D'Agostino and Dr. Lemuel Moye, who will be in attendance tomorrow. If they are here, if you would please raise your hand.

We will also have guests of the Committee, Dr. James K. Stoller and Dr. Mary Chamberland.

At this time, I would like to announce that there are proposed workshops for 1998. There should have been a listing outside on the table. I will just read the name of the workshops quickly, to inform you that for each of these workshops we will ask that there will be participation from our Blood Products Advisory Committee in these workshops, and that participation will be determined through the Chairman of the Committee.

The workshops are as follows. There will be a stem cell workshop, one day, to be held on September 10, 1998. There will be a one-day granulocyte workshop, to be held on September 11, 1998. There will be a one-day PCR workshop, to be held on September 16, 1998; a one-day platelet workshop, to be held on September 28, 1998; a public meeting on the rewrite of blood regulations for one day, held on September 16, 1998; a donor suitability workshop, to be held for two days, December 7th and 8th, 1998; and a blood licensing workshop, to be held for one day on December 9th, 1998.

As I said, that information is available at the outside table. Yes, Dr. McCurdy?

DR. MCCURDY: I would like to note for the record that the donor suitability workshop occurs right in the middle of the annual meeting of the American Society of Hematology.

DR. SMALLWOOD: Thank you, Dr. McCurdy. So noted. If there are no declarations to be made at this time, I would like to turn the proceedings of this meeting over to the Chairman, Dr. Hollinger. I would just like to remind everyone that we do have a full agenda today. I know that we got started a little late but I would ask, in the interest of fairness and time constraints, that we try to adhere to our time frame, and I will assist Dr. Hollinger in that task. Thank you.

DR. HOLLINGER: Thank you very much, Linda. This is the 59th meeting of the Blood Products Advisory Committee, and most of the things that we are going to be doing this morning are going to be informational. Then, this afternoon there is more discussion and a question for recommendations, and so on.

So, I think with that in mind, let's go ahead and get started. I think there are some very important issues that we need to be apprised of. So, let's start out with the first update, and that is on hepatitis C recipient notification. I think Dr. Mied is going to do that.

Committee Updates

Hepatitis C Lookback Notification

DR. MIED: Thank you, Dr. Hollinger.

[Slide]

This is an update for the Committee on hepatitis C

recipient notification, or lookback for hepatitis C. A guidance for industry on HCV lookback, supplemental testing and the notification of consignees of donor test results for antibody to hepatitis C virus, anti-HCV, was given notice in the Federal Register 63 FR 135.75, and provided on the Internet at CBER's home-page for purposes of comment and implementation, on March 20, 1998.

This guidance was issued in response to recommendations of the PHS Advisory Committee on Blood Safety and Availability, made subsequent to its meeting in August, 1997. This guidance supplements the July 19, 1996 guidance document, entitled, "Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus, HBV, Hepatitis C Virus, HCV, and Human T-Lymphotropic Virus Type 1, HTLV-1."

The notice of availability regarding the HCV lookback guidance document gave a recommended date for submissions of the comments by May 19th. However, written comments and suggestions regarding the document may be submitted to FDA at any time.

My next three slides summarize the guidance document recommendations, and reiterate the recommendations made in the product retrieval guidance document, issued on July 19, 1996, which also pertain to lookback for HCV.

[Slide]

When a repeatedly reactive result on a licensed multiantigen anti-HCV EIA is currently obtained, or is a historically repeatedly reactive result found as a result of a retrospective review of records, FDA recommends that prior collections be quarantined, and consignees be notified so they may quarantine prior collections that they hold. FDA recommends that the current sample be tested using a multiantigen supplemental test.

[Slide]

This multiantigen supplemental test may be either a licensed RIBA 2.0 or an investigational 3.0, and FDA recommends that lookback be carried out on a positive or indeterminate RIBA 2.0 unless an indeterminate RIBA 2.0 is followed up with a RIBA 3.0 and the result is negative or indeterminate. Lookback is recommended for positive RIBA 3.0 whether the RIBA 3.0 was run initially or was performed to resolve an indeterminate RIBA 2.0

Now, lookback, as I am referring to, is the identification of previously distributed units from the same donor dating back 10 years for a current repeatedly reactive result, or dating back to January 1, 1988 for a previous repeatedly reactive result for a donor with a record of prior donation, or in either case to the date 12 months prior to the most recent negative licensed multiantigen

screening test, whichever is the later date. The lookback process also includes the notification of consignees of the screening test result and the supplemental test result when it is available.

This chart summarizes whether lookback should or should not be carried out, depending on the supplemental test result obtained. It applies both to prospective lookback for a current repeatedly reactive EIA result and to retrospective lookback for a historical repeatedly reactive result. For each of the testing outcomes the indication is also made whether to destroy or label quarantined prior collections or to release them, as discussed in the July 19, 1996 guidance on product retrieval.

Blood establishments should identify previously distributed units and notify consignees, and transfusion services should trace and notify recipients of prior collections through the patient's physician of record when the test results are as indicated, a positive or indeterminate RIBA 2.0 or a positive RIBA 3.0.

The guidance states that the notification of consignees in the retrospective lookback should begin within 6 months of the date of the guidance and be completed within 1 year of implementation of suitable procedures.

[Slide]

If the supplemental test was not done on a

historical repeatedly reactive donation, that is, a repeatedly reactive donation from a donor with a record of prior donation dating back to January 1, 1988 which was found as a result of a retrospective records review, three options are recommended to the blood establishment, as summarized on this slide:

Option one is to test a stored frozen sample from the repeatedly reactive donation on a supplemental test. Option two is to test a fresh sample from the donor by a licensed multiantigen EIA and, if repeatedly reactive, to perform a supplemental test.

For options one and two, whether or not consignees should be notified so that prior recipients may be notified depends upon the result of the supplemental test which is to be performed within 6 months of the date of the guidance, as shown for the various supplemental test outcomes on the last chart that I showed you.

Option three is to proceed with notification of consignees of the repeatedly reactive result if neither a test on a frozen sample from the repeatedly reactive donation nor a test on a fresh sample from a donor is performed.

Comments on the guidance which have been received that may necessitated significant changes in the guidance encompass several major issues. First of all, time frames

for consignee and recipient notifications: The retrospective lookback is to involve an estimated 500,000 components, and difficult lookback situations may be anticipated for some blood establishments. As a result, a request has been made to extend the time period to complete the retrospective lookback to two years from the date of the guidance. The guidance currently provides six months for notification of consignees to begin, and then one year following the date of implementation to complete the notifications, for a total of up to 18 months. FDA's current intention is to make this change to the guidance document.

Due to the large number of notifications which are anticipated in the retrospective lookback effort, industry additionally has requested that transfusion services be given a year to carry out notifications of recipients identified in the retrospective records review rather than eight weeks, as provided for prospective notifications. FDA's current intention is to clarify the guidance so that a year will be permitted for the retrospective notifications of transfusion recipients.

The blood banking community has also requested that prospective notification of consignees be required within 30 calendar days after receipt of the supplemental test result, or within 45 or 60 days of the repeatedly

reactive screening test result, whichever is sooner, rather than within 30 days of the donor's repeatedly reactive screening test. At this time, FDA does not believe that notification within 30 calendar days of a repeatedly reactive screening test constitutes an undue burden. However, we will consider additional comments on this issue.

The guidance states that if a donor is repeatedly reactive on a multiantigen screening test and then indeterminate on RIBA 2.0, the blood establishment could retest using the investigational RIBA 3.0, and that lookback would not be required if the result is negative or indeterminate. Due to difficulties surrounding the ability of investigational RIBA 3.0 kits, the blood banking community has suggested for RIBA 2.0 indeterminates that the lookback be waived if an EIA 3.0 is performed and the result is negative.

Data have been obtained to suggest the validity of obviating the lookback for a negative result on the EIA 3.0 even in the face of a RIBA 2.0 indeterminate. Recent studies have shown that for RIBA 2.0 indeterminate, EIA 3.0 negatives the probability that the result would be positive on RIBA 3.0 is about 0.8%. Two out of two such samples identified in research studies were both PCR negative, suggesting that the prior donations might not have been infectious in any case. This low rate of RIBA 3.0

positivity and absence of PCR positivity suggests that it would be valid to override RIBA 2.0 indeterminates with a negative EIA 3.0. It is our current thinking to permit the use of the EIA 3.0 to resolve RIBA 2.0 indeterminates.

First-generation EIA: Other comments include the proposed use of repeatedly reactive results on the first-generation EIA, now frequently referred to as EIA 1.0, dating back to 1990, as a trigger for lookback. The military and some private sector blood banks have indicated that they are considering doing lookback on all first-generation EIA, or EIA 1.0, repeatedly reactive donors.

In the reissuance of the guidance, we will reiterate the FDA recommendation at this time that lookback should be triggered by a repeatedly reactive result on a multiantigen screening test, an EIA 2.0 or EIA 3.0, in conjunction with certain supplemental test results, as I have described. This recommendation is made with the expectation of a concurrent public education campaign, including a recommendation for testing all blood recipients prior to July, 1992.

I should add that there will be evaluations by the Public Health Service to determine the utility of extending the targeted lookback to encompass EIA 1.0. But, at present, we are only recommending multiantigen screening tests as the basis for HCV lookback.

Other changes to the guidance document will also be considered. FDA intends to revise the guidance for industry document and reissue and mail the guidance to blood establishments. In addition, the FDA intends to follow the guidance process with rule-making. I would like to emphasize that the Agency is committed to the rule-making process for promulgating HCV lookback.

Now, Dr. Hal Margolis, from the CDC, will provide the Committee with a summary of the PHS program for hepatitis C prevention and control, including an educational campaign targeted both to healthcare providers and the public. I will be pleased to take any questions the Committee might have. Thank you.

DR. HOLLINGER: Thank you, Paul. Do we want to go ahead and have Hal comment first? Hal, why don't you go ahead? Dr. Margolis, from the CDC Hepatitis Branch.

Hepatitis C Prevention and Control Program

DR. MARGOLIS: Thank you. What I am going to do this morning, and it is something that was triggered by the Secretary's letter of concurrence to the Blood Safety and Availability Committee, back in January, that, in fact, CDC should put together a plan for the Public Health Service, outlining those activities that would both deal with identification and prevention of HCV infection in recipients of blood transfusion who may have been infected, as well as

other high risk groups, groups at risk for HCV infection.

[Slide]

Basically the components of the plan, and I apologize I don't have the plan to hand out to you at this point because it is still in the Secretary's office going through some of the approval issues so it is really not out for distribution -- it begins with prevention and detection of HCV infection in the very large population of approximately 4 million people who are chronically infected, looking at activities to control HCV-related product disease, including chronic liver disease. There is an evaluation component to it. Then, as importantly needed, a surveillance and research component.

[Slide]

Probably most importantly, and I will focus on what is really what is pertinent to this group here, and that is secondary prevention activities which is really identifying infected individuals and, as I say, given the estimates of 4 million infected individuals in the country, that is a daunting task which involves identifying HCV-infected persons and really providing appropriate testing and medical management as specified and, I think, guided now by the NIH consensus conference statement on management of hepatitis C.

[Slide]

In terms of some of the testing activities that, again, this Committee and participants are most interested in are clearly the ongoing and continued testing of blood, organ and tissue donors. What I am really going to focus on now is the issue of both targeted lookback and general notification of transfusion recipients.

In putting together the plan and in discussions that have been held in various advisory committees and comments by industry to the Health Service, basically it has been our perception and our assumption that, in fact, the targeted lookback is something that is primarily going to be conducted by the blood industry, both by the blood collection agency as well as the transfusion services. In fact, as far as public sector programs, that is something that PHS, other than the guidance and much of the supporting educational material, has not put together a major effort or plans for conducting.

Where our area has been focused is that of what one might call general notification. I think the most important part of this, and I think as those of you who may not have seen this week's "US News & World Report," of which the cover is hepatitis C and the statement is, "you may have the silent killer that even your doctor wouldn't know."

[Slide]

We have focused a tremendous amount of attention

on the education of the health professional. This was started late last year with a Public Health Service-sponsored satellite teleconference and, in fact, now the audiotape from that has been produced and the PHS is planning to mail to every primary physician in the country. This is going to go on this summer, with a little box that, hopefully, all of you are going to get and there will be special mailings to blood banking and blood industry.

This is my "show and tell." Basically, it is going to have the logo of that satellite conference. In it you are going to find about an 80-minute audiotape and, probably most importantly, a card that a physician can put on the wall, his pocket or wherever that tells them who they should be screening for HCV, and on the back of that is a very simple algorithm for HCV testing that one would use, again, as a primary care physician.

In addition to that, there are two educational pamphlets, one for the HCV-infected individual and the other on prevention of HCV infection. These are the ones that we, at CDC, have had for a number of years. Then, a list of resources for both physicians and patients in terms of where you can get additional information. It includes various government agencies, national health, volunteer agencies, websites, hotlines, and all of that type of information. So, basically you are looking at close to a quarter of a

million physicians and residents in training who are going to receive that beginning this summer. We see that is, you know, the most important for getting the message out.

Clearly, after that comes education of the public and, again, CDC and other PHS agencies but with CDC having the lead, we are in the process now of beginning to put together general media information -- this is the new word, media advertising, basically public service announcements and those types of activities. As I say, given the strong interest by the news media, with articles such as you are seeing in "US News & World Report," and which I think was fairly balanced except for the statement that if you want to find out your status, you know, go, donate blood. You have to realize we didn't have the final right of refusal on this article. We tried to get most of the facts of information correct in it. I think others in this audience who may have participated with the various reporters -- you know, it doesn't always come out right, and those are the things that we will try and deal with. I presume some of us going to write some letters to the editor, hopefully, to correct that in terms of the magazine.

But that is basically the plan. You are probably saying, "well, where is the line item in the congressional budget for this?" As I had to speak to all of our state and territorial health officers last week, the bottom line is

that Congress is only becoming aware of this. CDC will have modest funding for this in the 1999 fiscal budget, and we are hoping that by the year 2000 there are going to be much more resources in terms of at least public sector testing and counseling. Clearly, the HIV prevention and counseling infrastructure that is out there in everybody's community right now is going to be heavily leveraged at least in terms of part of this activity, and I think with that I will probably stop and answer questions.

DR. HOLLINGER: Thank you, Dr. Margolis. This whole issue is so important, particularly to the blood banking community, the American Red Cross asked if they could make a statement, and I am going to allow that for about five to seven minutes so that we can hear their viewpoints. I don't have a name, but is there someone from the American Red Cross?

DR. DAVEY: Dr. Hollinger, I believe there has been some error. We don't have a statement to make on that today.

DR. HOLLINGER: You have withdrawn from that? Thank you. Are there any particular questions that anyone wants to address?

DR. BOYLE: I have a general question. That is, how do they plan to evaluate the effectiveness of the patient notification? In other words, what percentage of

patients actually receive these notifications?

DR. HOLLINGER: Dr. Mied or Dr. Margolis?

DR. MARGOLIS: There is currently a collaborative effort between CDC, FDA and ACPR to put together a population-based evaluation. Protocols are actually in the pipeline and being written. Clearly, we think targeted lookback would be the easiest. General notification is going to be the most difficult. And, we are planning to use somewhere between 4 and 8 sites around the country that would represent both blood collection agencies or Red Cross and ABC, and try and look at all the components including nested studies that would look at why an individual who receives a letter may or may not then act upon it. So, you know, that is all in the pipeline. We are all scurrying to try and put this together. Some things can begin to happen by this fall.

MR. DUBIN: First of all, we are glad to see you looking to the HIV counseling and testing program. I chair California's Prevention Working Group. It is something we have been very successful at. But I am wondering if actually implementing that, which we think is most important, is going to take a specific increase in budget from Congress and, if so, if we could get a discussion going between some of us who are doing that in terms of Congress on prevention issues to try to lend CDC a hand, because our

biggest concern at the Committee of Ten Thousand is that people get the information and then the counseling and testing program is not in place for them to understand and be able to plug in, which is kind of what happened when Chairman Shays released the press release and there was all this noise but nowhere to turn yet, and we have concerns about that.

DR. MARGOLIS: At least within CDC, having met now with some of the HIV counseling and testing groups, clearly there is going to be need to be a tremendous amount of training. CDC can work internally to deal with that through the various national training networks but, as you point out, when you really get down to testing, counseling and referral there is going to be need to be a lot resources and we would welcome that support.

DR. HOLLINGER: Dr. Margolis, I know they have talked a lot about supplemental testing, and maybe even Paul might answer this, but why haven't they considered using ratios? I mean, there is a lot of information out there that suggests high ratios, three or above for the anti-HCV test is very concordant with the supplemental tests. Of course, it is a lot less expensive to use that. You are going to miss some anyway. There is already data here that the indeterminates for the RIBA 3.0 might be PCR negative about 5%. But even if a patient is negative by PCR now, it

doesn't mean that they weren't positive before. We already know that about 15% patients actually lose all markers of their hepatitis C later on and wouldn't even be detected in the first place. So, with all those in mind, I am not sure why these issues from the REDS data or other data have not been considered.

DR. MIED: Dr. Hollinger, we would like to see data that, you know, accurately describes what you are talking about. The use of the EIA 3.0 is an instance where we have seen the data and feel that it can be used to exonerate RIBA 2.0 indeterminates or to resolve them, but the situation you are talking about is one in which we would welcome a review of the data.

DR. HOLLINGER: That is good. Thank you. Yes, let's have one more question and then we will have to move on. Go ahead.

DR. STRONCEK: Will any of this monitoring follow the patients through to see how many get treated and what the outcome of that treatment is?

DR. MARGOLIS: That, again, in terms of the formative stages of the evaluation would be done in some nested study that, again, hopefully could be generalizable.

DR. HOLLINGER: Thank you very much. The next piece of information we are going to discussion is deferral of xenotransplantation recipients and partners. Actually, I

think those of you who have read the FDA guideline for xenotransplantation -- I thought it was an excellent guideline, by the way, and a lot of thought has gone into this based on a lot of information -- but this issue of xenotransplantation and deferral of recipients and partners will also become an issue. Dr. Dayton is going to -- yes, Andy?

Deferral of Xenotransplantation Recipients and Partners

DR. DAYTON: Good morning. I am Andy Dayton. At the last meeting of the Blood Products Advisory Committee we presented a summary of the xenotransplantation issue and of primary concern, obviously, was the deferring from blood donation of xenotransplant recipients. Of course, the thorniest issue was the question of deferring from donation of close contacts of xenotransplant recipients.

The Committee was advised that xenotransplant recipients were counseled, under current protocol, that they were at risk of harboring and transmitting to sexual partners novel, unknown and potentially serious pathogens. Before deciding on whether or not to recommend deferral of close contacts, the Committee wanted clarification as to whether or not xenotransplantation recipients were counseled to use barriers during sexual intercourse, and elected to table the issue. Not taken into consideration at was the likelihood that, regardless of counseling, recipients and

their partners would be expected to fail to use barriers quite often, even if counseled to use them, given that the nature of the risk is hypothetical and largely unknown.

In the draft Public Health Service guideline on infectious disease issues and xenotransplantation, a copy of which is in your pre-meeting materials, the informed consent guidelines require that the recipients be informed of, and I quote, potential risk of transmission of xenogeneic infectious agents to the recipient's family or close contacts, especially sexual contacts. Close contacts are defined as household members and others with whom the recipient participates in activities that can result in exchange of bodily fluids. The recipient should be informed that transmission of the agent can be minimized by the use of barriers. Of course, it goes on further but that is the critical excerpt.

Recently, CBER has developed a xenotransplantation action plan, led by Dr. Amy Patterson. This follows largely on the guidelines in the same document. The highlights of the xenotransplantation action plan are essentially that xenotransplants are to be considered biologics and to be regulated under IND. There will be establishment of a registry and monitoring of xenorecipients xenodonors, and archiving of patient and donor samples.

There will be very strongly encouraged counseling

for partners. This counseling will be voluntary but it will be strongly advertised in the recipient setting and strongly encouraged, but it does remain voluntary.

The plan also calls for the deferral of close contacts as well as recipients. Close contacts are defined as household members and others with whom the recipient participates in activities that could result in exchange of bodily fluids.

It is hoped that these guidelines will be published in the Federal Register in the late fall of 1998. In compliance with the CBER xenotransplantation action plan, the Office of Blood Research and Review had developed a xenotransplantation guidance document which will soon be put out for comment. A draft copy of this document is in your pre-meeting materials.

[Slide]

The key point in this document highlights for your concerns the deferral issue, which is handled as follows: Under the donor deferral section, persons who have received xenografts should be permanently deferred from donating whole blood, blood components, source plasma and source leukocytes. Persons who have had repeated close contact with recipients of xenografts, including sexual partners, household members and any others with whom the xenograft recipient participates in activities that could result in

exchange of bodily fluids should be permanently deferred from donating whole blood, blood components, source plasma and source leukocytes.

With respect to what we are going to put in the donor questionnaire, potential donors should be asked the following two questions: Have you or your sexual partner or any other close contact ever received a transplant of living cells, tissues or organs from any animal source? And, have you or your sexual partner or other close contact had your blood returned to your body after perfusion through an animal organ or through any device containing animal tissues or cells?

Potential donors answering questions 3(a) or 3(b) affirmatively should be permanently deferred unless in the medical director's judgment the nature of the reported close contact is unlikely to result in intimate exchange of bodily fluids.

In closing, there is one point I should make with respect to these donor questions in the donor questionnaire. We have given some thought as to how to make them fairly simple and not too complex, but it should also be remembered that anybody who would be targeted by these questions has been through a transplant procedure and has been highly educated in the nature of their disease, and we feel that will enable them to respond appropriately to these

questions. Thank you.

DR. HOLLINGER: Thank you, Dr. Dayton. Are there any questions of Dr. Dayton on this issue? We are obviously going to hear more about this as time goes on as porcine organs and other things are going to be used more in transplantation. It will become a very important issue and we will have to discuss more closely some of the issues about close contacts as well sexual partners.

DR. DAYTON: It will definitely come back.

DR. HOLLINGER: Yes, I am sure it will. The next item is on unusual HIV-1 variants. That will be presented by Dr. Hewlett.

Unusual HIV-1 Variants

DR. HEWLETT: Thank you, Dr. Hollinger. Good morning.

Today, I will discuss briefly the identification of a new and unusual variant of HIV that appears to be somewhat distinct from HIV groups M and O.

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As you know, the genetic diversity of HIV viruses is an evolving and well documented phenomenon, and we have been monitoring this scenario primarily from the standpoint of their impact on HIV diagnostic assays that are currently in use.

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I just thought I would give you a slight background on the issue. Genetic variation of HIV may be best understood within the context of lentiviruses that infect both human and non-human primates. HIV-1 and HIV-2 are both lentiviruses that infect humans, with the HIV-1 viruses clustering closer to the chimpanzee SIV viruses and the HIV-2 viruses clustering with the other non-human primate viruses. There are two groups of HIV-1 viruses, the major HIV-1 subtypes, referred to as group M, and the genetic outliers, referred to as group O.

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Why do we have so much diversity in HIV? These are just some of the possible reasons that might contribute to diversity, and I will quickly run through them. One hypothesis is that these viruses may represent cross-species transmission of related viruses found in non-human primates, and multiple cross-species infections could have led to new lineages of human viruses. A second reason is recombination within and between subtypes. The third reason is the high mutational rate of this virus, which is approximately, as shown on this slide, about 3×10^{-5} nucleotide substitutions per base pair, per replication cycle.

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A few features of the phylogenetic relatedness of the HIV viruses are listed on this slide. Basically, the

group O viruses are equidistant from group M and the chimpanzee SIV viruses. While the group M subtypes appear to be equidistant from each other, the viral strains from group O also seem to be somewhat equidistant from each other and they produce what is referred to as phylogeny, and I will show you what that looks like on the next slide. The finding of two separate star phylogenetic clusters of HIV viruses suggest that groups M and O may have had two separate ancestors and may, therefore, have resulted from two separate zoonotic transmissions into the human population.

[Slide]

This just represents a phylogenetic cluster and, as you can see here, this group of M viruses have a well-defined star cluster, with the result of which you have distinct subtypes among these viruses. At this point, I think there is about a total of 9 types, some of which are actually recombinants among and within some of these subtypes.

In regard to group O viruses, one does design a star-like structure but the distances and the star formation are not as well defined, partly because of there being fewer viruses identified in the whole subtype.

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At the fifth international conference on

retroviruses and opportunistic infections that was held in Chicago, in February of this year, Francois Simon and his colleagues, from Paris, France, reported on the isolation of a highly divergent non-M, non-O HIV strain, termed YBF30, which was isolated from a Cameroonian AIDS patient, interestingly who had never left the country. This patient was diagnosed as having AIDS in June, 1995 and died in December, 1995. So, this virus was pathogenic and resulted in the death of the individual. The virus was isolated from blood and subjected to nucleotide sequencing.

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Genetic characterization of the virus revealed that t he viral gene was related to both HIV M and the chimpanzee SIV virus depending on the region of the genome that you are looking at. I should mention that this virus hasn't been completely sequenced at this point.

Genetic characterization also revealed proviral DNA could not be detected using group M and group O specific PCR primers, but it could be detected using high conserved primers from the integrase region.

Regarding the structural genes, the gag and pol genes appear to be highly similar to the chimpanzee SIV where there was some differential relatedness in the regulatory genes. So the tat, vpr and the nef genes appeared to be equidistant between the HIV group M and the

chimpanzee SIV, whereas the vif and the rev sequences were more closely related to the HIV-1 M.

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The vpu, interestingly, is highly unique in this virus and is more divergent from both HIV-1 and SIV_{cpz} than the other genes. In the envelope region, however, these two viruses, the YBF30 and the chimpanzee SIV appear to be very closely related, suggesting a possible shared origin of the two strains.

There appears to be no evidence for this virus having been a result of recombination between known HIV strains, although there is some limited recombination in certain regions of the genome.

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From a virologic standpoint, this virus could not infect human CD4 positive T cell lines, but adapted to culture in chimpanzee PBMC very quickly. It was capable of using the CCR5 receptor but not the CSCR4 receptor, which is consistent with the fact that it did not induce syncytia in culture. This virus could also be inhibited by nucleoside and non-nucleoside inhibitors.

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A diagnostic evaluation of the specimen indicated that serum from this patient was weakly positive on third generation assays based on mixtures of recombinant antigens

and peptides. However, it was strongly positive on viral lysate based assays. It was non-reactive on assays that are based on peptides from M and O, that is, assays that are based solely on peptides. It was also weakly reactive but positive on Western Blots. So, one could design the various bands, but each of these bands was not as intense as one would see in an HIV M specimen. Viral RNA was not detected using current versions of nucleic acid tests.

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In an effort to track emerging HIV variants, the French have set up a collaborative study in Cameroon and Central Africa, and in this study 1200 sera were collected from HIV-infected patients in Cameroon from 1987-1997, and 90% of these samples were typed as group M and 8% were O based on analysis using specific peptides for each of these groups. What they did was to design peptides and PCR assays for the YBF30 virus, and analyzed all of these sera.

At this point, this is actually data that was shared by Francois Simon. It is not published as yet. It has been reported at meetings. And 2 out of actually 1200 sera were reactive using this YBF30 V3 peptide, and 3 sera, collected in 1992, 1995 and 1997, were positive using the PCR assay that was specific for YBF30 and not for any of the other viruses.

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So in summary, an unusual and highly divergent variant HIV-1 has been isolated from a Cameroonian AIDS patient who had actually never left the country. YBF30 is the first reported counterpart of SIV_{cpz} in humans, and the emergence of such unusual strains, I should say, although rare does stress the need to maintain an ongoing surveillance program for variants, particularly in light of implications for diagnostics and vaccine development.

I would like to acknowledge Francois Simon and his colleagues for sharing some of the unpublished data at this point, and I know that a manuscript has been submitted and they are waiting for comments. So, hopefully, we will be able to have more details in the future. Thank you.

DR. HOLLINGER: Any questions? Is the PCR in the integrase region conserved enough that it can be used for all these agents, and would be a better choice for detecting these agents in terms of that kind of detection assay?

DR. HEWLETT: Yes, in fact that is what the authors have concluded, that perhaps the degree of conservation is in the integrase region and that these variants, although they are divergent, could possibly all be detected when designed primers, such as those from the integrase region for detection. So, it appears that in this particular case they were able to identify a set from this integrase region that actually detected all the other

strains that they surveyed in the study involving the 1200 samples.

DR. HOLLINGER: Thank you. Yes, Dr. Nelson?

DR. NELSON: They were positive with viral lysate-based assays?

DR. HEWLETT: Yes.

DR. NELSON: And those are the ones that are commonly used in screening in blood banks now?

DR. HEWLETT: Not exactly. I think that there has been a move towards the use of more defined proteins like recombinant antigens and peptides. They are easier to make. You can put more on the plate. It cuts down on the non-specificity of the assay. Certainly from a manufacturing standpoint, you have a better way to QC and to produce them in a more defined and consistent way. So, there has been a trend over the last couple of years towards using recombinant antigens and synthetic peptides, and that is the reason why there is concern about variants because some of them are missed by assays based solely on peptides.

DR. HOLLINGER: But to follow up on that, didn't one slide show that it was weakly reactive to recombinant and peptide assays?

DR. HEWLETT: These are third-generation assays and, as I understand it, you know, certainly they are not assays currently in use in the U.S. But these are assays

that are modified for group O and so on. So.

DR. HOLLINGER: Thank you. Thanks very much, Dr. Hewlett. So, this ends then the Committee updates for this morning. We are now going to move into two other areas where there is going to be more open Committee discussion. The first one is on the blood action plan and Dr. Feigal is going to discuss that.

Blood Action Plan

DR. FEIGAL: Good morning. Going back several years now, there have been a series of oversight hearings looking at the blood program, looking at the safety of the blood supply in the United States. It is actually a process that continues and is intended to be ongoing.

But there has been very focused review by the Institute of Medicine, congressional hearings, in particular from the subcommittee chaired by Congressman Shay, by the government Accounting Office which is the investigational branch of Congress, and by the Inspector General of Health and Human Services, which is the Department's investigational body. These groups have broadly looked at the decision-making process around blood safety. They have looked at how advisory committees fit into that function. They have looked at the way that FDA communicates requirements to industry, and the effectiveness with which they are brought in place. There have been very focused

looks at very specific problems, including hepatitis C, product shortages, pool size, specific guidances. There have been examinations of the way that FDA organizes and conducts inspections of blood and plasma collection facilities, of manufacturing and of the distribution chains.

Some of these have been focused enough that, as you may know, they have examined the issue of saline contamination of plasma in congressional hearings -- a very technical, focused and specific problem.

There have been questions about how well FDA and industry respond to emergencies. How do we deal with withdrawal, recalls and those types of issued, and how well are people notified about those issues?

I think if we were to kind of group the concerns into broad areas across these different oversight groups, one way of grouping them would be there is a group of questions that ask how responsive has the Agency, has the industry been to problems that have arisen? And, the problems include dealing with new infections, or new tools to discover old infections. How well have we dealt with specific emergencies and needs to institute rapid changes?

Beyond the issue of how fast and how responsive we all are, there has been the issue of how are things communicated. Some of that deals with the fact that the regulatory guidance and guidances for blood products are

complex, but also there is a broader issue than has been dealt with by numerous groups which is going beyond the issue of blood safety per se and dealt with issues that I guess I would characterize as the right to know. As an example, you may be using a screening test that has false positives. That may be perfectly adequate for the public health mission of protecting the blood supply but it doesn't give accurate information to the person who donated that unit. So, there has been focus on does the donor have the right to know whether or not they have a true positive, which gets into the issue of requiring supplemental tests, for example, beyond the public health contribution. There has also been the issue of the right to know at the consumer level in terms of notification.

Then a third broad area beyond responsiveness, beyond communication, there are many things which could be grouped under inspectional practices of the FDA, and I will talk about those in a little bit.

One of the changes that occurred because of all of this oversight has been a fundamental reorganization of the way that blood safety is assured within the Department of Health and Human Services. Secretary Shalala, with some of the functions delegated to the Surgeon General and Assistant Secretary of Health, David Satcher, are the chief blood safety officers for the Department. They have taken on the

responsibility for blood safety for the Department of Health and Human Services.

In many ways this is appropriate because there is a multifactorial effort to work with blood products that involves many departmental agencies, not only FDA but, as you well know, CDC, HCFA and other parts of the Department. Advising Secretary Shalala is the Blood Safety Committee. This is actually an internal committee that is made up of agency heads. It is a committee that is meeting this morning, unfortunately, since many of us would be directly there. But this is the committee that make recommendations to Dr. Satcher and Secretary Shalala.

The advisory committees have evolved in the last five years, and advising the Blood Safety Committee is the Blood Safety and Availability Committee. That is a committee many of you have attended, but this is the committee which is Department-wide. It advises all of the departments in Health and Human Services.

Then, as you know, the committees within the FDA have gotten more complicated in recent years. We have the TSE committee which addresses the issues of the spongeoform encephalopathies FDA-wide since there are issues that affect food products, drugs and biologics and, of course, blood. There is the Xenotransplantation Committee, which is a subcommittee of the Biologic Response Modifier Committee.

Then, of course, there is BPAC, which is the grand-daddy I think of all of these committees.

One of the real challenges as the Department and the FDA have responded to the need to find more ways to seek advice and communicate in open public hearings, is to actually keep the role and the missions of the various committees straight to make sure that we are not bringing things to two committees and then having to find a third committee as a tie-breaker.

[Laughter]

About a year ago, we were asked to systematically go through the oversight reports, some of which were book-length, bound as books, and identify the recommendations and put together an organized effort to deal with these issues. Last summer we proposed the formation of six teams, some of which extend beyond the FDA. We began implementing the plan for these six teams, but, because we were asking for Department-wide support, we brought this plan up through the Department and asked for endorsement and acceptance of the plan by the Secretary. In fact, that was completed about a month ago after review by all of the agencies.

But even though we had an approval process, we actually have gone ahead during the last year. We set goals for these teams during the last year, and the goals that we set for ourselves were all met.

So, what I would like to do is go over the teams and illustrate a little bit how we are trying to deal with the oversight from the different committees. The first team, and in some ways one of the largest efforts, is the team that is looking at updating the blood regulations. As you probably know, there are over 60 guidances that we currently consider to be in force. Many of these deal with issues that belong in regulation, and one of the challenges for us is the fact that the cycle of instituting even a relatively non-controversial regulation is typically about two years. So, there are issues that, to remain current, need to be in guidance. On the other hand, there are things in guidances that clearly can be in regulations, and there are regulations which are out of date. There are also areas where we can consolidate guidance and regulations and simplify and streamline the advice.

So, this team was asked to really review, revise and rewrite the blood regulations from start to finish. We began by creating a database listing all of the regulations, guidance and other instructions for industry, and identifying the ones that we knew didn't exist and hadn't been written yet but were needed. We prioritized that list and we have put together over a dozen teams that have begun drafting regulations and in some cases it will probably also mean redrafting regulations.

Our options when we write regulations are three-fold. If we are simply doing technical corrections in areas that aren't controversial, or just correcting facts or doing things which we think are well accepted, we have a mechanism called a direct final rule. We can propose a regulation and say here it is; there is a comment period. At the end of the comment period, if there is not substantial objection to the rule, the rule will be in place as announced. If during that comment period there are substantial objections then, in fact, we will revise the rule and reissue it.

The second type of rule that we can issue is a proposed rule. That has also a comment period. Typically the comment periods are three or four months. Then the rule is revised. The final rule will explain and describe the comments that were made and how the revision addressed the comments, and then you will have a final rule.

Then the third mechanism where the process is most controversial of all is for us to have advance notice of proposed rule-making. There is quite a bit of flexibility in how these notices look. Sometimes they are published actually as a proposed rule. Other times they are actually published more like an essay, discussing different options, discussing the pros and cons of going in different directions, and asking for comments. That is often the area where it is not clear how to even start with the proposed

rule.

I think if you look at how these teams will bring forward the new regulations out of the old guidances, out of the ongoing issues that arise, you will see all of these mechanisms being used, and it is a time that you should be very active in communicating with us your comments on how to do these things.

Our time frame is that we have intended by the fall of this year -- in fact, one of our stretch goals was to even have some of these regulations completed this summer. What I mean by completed is that they will be out of FDA. There is an additional review process that we don't control before they are published. And, we will begin the comment process and, you will see as we issue these first sets of regulations, some of the areas that we prioritized.

What we think will be the outcome when this group, which will be a multi-year process, finishes its task is that we will reduce the number of exemptions that are needed for outdated regulations. We will be able to reduce the guidance documents that lack the enforceability to regulations. That doesn't mean that there still won't be guidances because there is a very important role for guidance, and the clarity from having more modern and concise regulations will improve industry compliance.

The second team that we have put together is a

team that was asked to look at how we could reinvent blood regulations, not just to rewrite the regulations but are there ways that we can do things differently. One of the tasks that this group was asked to do was to continue the implementation of an initiative that the Center for Biologics proposed under the REGO, the reinventing government initiatives that Vice President Gore launched in the first term of the administration.

This is a process of simplifying the older system, which had separate establishment licenses and product licenses, into a unified license, and simplify the application process.

A second area, and this is an area where we are going to be doing a pilot because we are not sure if this will help or not be helpful, but a second area is to take a look at some of the types of products and some of the manufacturing that is very repetitive where we see the same applications for the same types of products, for example, an irradiated blood product that is coming from multiple different manufacturers.

One of the things that has occurred to us is that the Agency very successfully uses monographs and standards. It does this in devices. It does this in over-the-counter drugs. It has done this in antibiotics. The concept here is that if we can identify an agreed standard that is

acceptable good manufacturing, good standards for that product that is sort of a consensus way that a given product is manufactured, we can simplify the application process because people can reference the standard and they can say we are making the product in accordance with the standard and, of course, there will be ways that they can verify both in terms of their application and when we inspect that they, in fact, are doing that. Of course, they will have the option to do it in a new way, or a novel way or a slightly different way by describing the processes as they do now.

But we are going to do a pilot of two product areas that we selected, and this will be rolled out sometime in the next year, where we will look to see if this really works. We will look for a pilot on one area, in the area of blood products, and in the other, in the area of plasma products. Again, we need to find out if this really does work; if this really does help before we move on and apply this in other areas.

The hope is that we will be able to streamline or reduce the number of things that require applications and decrease the number of submissions to FDA, and the degree of standardization will actually, again, improve the compliance.

The third team that we formed is a team that was asked to deal with the issue of emerging infectious

diseases. This is a team which cuts across the Department to involve the CDC, the NIH, and this is a team that has been asked to take a look at known and potential threats to the blood supply, for example, new HIV variants which we are discussing today; new hepatitis agents; human herpes virus type A; the TSE family of problem agents; parvovirus; bacterial contamination of blood and so forth.

The way that we asked this team to organize this work was to develop a catalog, a database of the different potential threats, and together with the NIH and the CDC develop a strategy appropriate to the level of what we know about the level of threat and the technologies that we have available for each potential threat. There have already begun to be quarterly face-to-face meetings, and this group also uses an ongoing mechanism, an internal PHS conference call which occurs every month where many of the discussions involve emerging infectious disease problems. I think this will be an ongoing effort, and I think it will help us coordinate the efforts across the Department.

A fourth team was put together to look at the compliance of plasma fractionation establishments. One of the issues that many of the oversight committees dealt with had to do with the historical origins of CBER and how it differed from FDA. CBER, as you know, has just had its 25th anniversary as being part of the FDA. Prior to that time

the Division of Biologic Standards -- I am probably not getting the name right -- was part of the NIAID at the NIH. As a body which was not part of the FDA, it did not use the FDA field resources for inspections. All the inspections were done by CBER staff and, as you might expect, with both agencies having a half century of inspection history different inspectional cultures emerged. The tradition of the field, ORA, the Office of Regulatory Affairs -- the tradition of the field has been to strongly emphasize a common theme to manufacturing of all FDA products, which is good manufacturing practices. The CBER tradition, on the other hand, was much more product specific and emphasized the expertise of the reviewer.

So, a new concept of how to blend the two regulatory traditions was put in place and called team biologics. This has already been implemented for blood products. It will actually be implemented for all CBER products. It takes advantage of both of these cultures. Instead of having any of the 3500 field staff be available for a blood inspection we have, in fact, identified a specifically trained cadre of teams that will specialize in specific products. There is a team that has been trained to inspect plasma fractionation establishments. There is a team of about 120 who will do blood and plasma collection facilities. There is a team that will do in vitro

diagnostics, and this will be expanded to vaccines and other biological products as time goes on.

These teams have members that come both from CBER and from the field. They are conceived of as national teams even though many of the team members are based in the districts. We actually think this is a paradigm that will work not only for biological products but also for other types of products in FDA, particularly products that are high risk and vulnerable to manufacturing problems.

So, at the time this action plan was written, this team was asked to complete the team biologic plan itself. That has been done. To implement the team blood part and that has been done, and to begin with the training. We now have the inspection of plasma fractionators all being done by this specialized group.

The fifth team is a team that looked at the issue of notification and lookback. One of the real issues that has developed around blood products is the consumer's right to know, both the donor and the recipient. I think these are issues that are well known to this Committee and to this audience. But this team has been the team that has worked to develop the new guidance that was needed for the hepatitis C lookback. We are working at translating that guidance into regulations. And, they are working with the issue of how to do direct notification to consumers about

problems with products.

We anticipate that some of these issues will arise for other infectious agents, and that this team will be asked to address those agents as well. But what we think will be the outcome of this is that donors who are permanently deferred for infectious reasons will be notified of that, and that recipients who have received potentially infectious material will also be notified.

The final team, the sixth team is a team that has been asked to internally review and train and update the way that FDA responds to Class I recalls, the recalls for imminent hazard, and for other types of blood emergencies. The things that we proposed that we do, most of those have been done and put in place. We have finalized an emergency procedure. We have trained FDA staff. We have had staff-wide training. There is also an oversight body, an internal oversight body that reviews responses to emergencies, and this has all been put in place.

One of the challenges for us is that the signal that there is a problem out there can come to us in any number of different number of sources, including reports to other parts of the FDA that are not directly parts of CBER. We have tried to find and identify these to make sure that serious problems are recognized and promptly dealt with.

So in summary, I think one of the things I hope

you will appreciate is that this is an ambitious effort. This is also something that is being done largely by the personnel and staff that were already here, people who are already busy with many other things. But we think that this will have a large payoff and result in addressing many of the concerns that have been raised about the way that blood products are regulated, and will continue to assure that we have a safe and available blood supply.

Let me stop and ask if there are any questions.

DR. HOLLINGER: Any questions from the Committee regarding these issues? Clarifications or anything? Yes?

MR. DUBIN: First, congratulations. This is a good process. We are, of course, glad to see this. I gather the workshops scheduled for the 16th November will be a chance to dialogue more on that.

DR. FEIGAL: Which workshop are you referring to?

MR. DUBIN: The proposed workshops for 1998.

DR. FEIGAL: Sure, that is part of the process.

MR. DUBIN: And, in an ongoing way, are you taking comments from organizations such as ours?

DR. FEIGAL: Yes, absolutely. We have spoken in the past year about some of these processes but we haven't really explicitly laid them out as a plan because we asked the Department to accept it as a Department plan before we starting saying we had this Department-wide plan. Now that

they have accepted it, it is something that is a dynamic process. It needs to be modified as we go. Some of our ideas undoubtedly will be over-ambitious; some of them won't even be good ideas and new things will arise that will need to be taken into account to change the process.

The one thing that I think the team as a whole is quite proud of is that it has set a series of specific time frames for delivering this. It has been a very busy year; they have met all of those time frames. We were smart enough not to be very specific about the second year. We had a good idea of what we could accomplish working hard the first year, and part of the input that would be helpful, as we get more specific and set our goals for the second year, is that we have some input on where our priorities and focus should be.

MR. DUBIN: Yes, we don't seem ever to be tired of input but, again, the process sounds like a good and a positive one, and the breakdown into teams seems like a very good approach. It sounds very good. Thank you.

DR. HOLLINGER: Thank you, Dr. Feigal. The next topic is on the IGIV supply issues, which we have heard a great deal about and there is a lot of concern among the community. So, we are going to initiate this by Dr. Golding, who will provide us with some information.

IGIV Supply Issues

DR. GOLDING: Before I start, I would just like to make two comments. The first one, I was diagnosed as having acute labyrinthitis yesterday so if I get disoriented, at least I have an excuse.

[Laughter]

The other is that a lot of people at the FDA, including myself, have been working on this IGIV shortage issue but the actual presentation was put together by Mark Weinstein who would have been here today but was called away to represent the FDA in Europe.

[Slide]

So, what we are going to be talking about is an update on the IGIV shortage. This is a summary of the presentation: The evidence of the shortage; the causes of the shortage; the FDA actions to alleviate the shortage; the current situation; and considerations for the future.

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The FDA doesn't routinely monitor the supply of blood products, and the evidence of the shortage had to come through other means. What happened is that during 1997 there were sporadic calls to the FDA complaining about shortages of various products including IGIV. So, there were complaints about some of the coagulation products, albumin and IGIV. But towards the end of the year, around about November, these reports became very numerous and

persistent, to the point that we were receiving 30-40 calls per day, and these calls were coming not only from frantic physicians but they were also coming from directors of major medical centers across the United States.

When we contacted manufacturers, we found out that their inventories were really low which supported that there wasn't any material available, and an indirect line of evidence was that the price of IGIV had gone up considerably, and had doubled, and in fact there were even reports of the price having tripled in various parts of the country.

First I am going to go into some of the reasons for the shortage. One possible reason was the increase in demand. We now have some data from a group called the Market Research Bureau, who have been surveying blood product supply, and they have documented that there has been a 10% increase in IGIV demand over the past 5 years. So, part of the problem is that there has been an increase in demand. As you know, there are certain FDA approved indications for use of IGIV, but there is also a multitude of off-label uses for this product. This product is used for neuromuscular conditions, for autoimmune diseases and for a whole variety of conditions, some of which have been shown by careful studies that these conditions should be approved, used as standard of medical care in major medical

centers, but other conditions have not been shown by adequate trials to be efficacious and it is based on anecdotal reports or a few case reports, and some of these diseases are very rare. But the outcome is that much of the use of the IGIV today is for off-label use. We don't have hard and fast numbers for this but speaking to medical directors at major medical centers, their impression is that 50% to 70% of the use is for off-label use. I would like to reiterate that some of this is well justified but this really needs to be looked into if we are going to solve this problem of the shortage.

Another issue is compliance. A moment ago you heard Dr. Feigal talking about compliance and inspection issues and the fact that CBER has been looking much more carefully at these fractionators partly because there have been major compliance violations, and most of you are probably aware of the albumin incidence thing in which two patients nearly died because they received albumin that was contaminated.

But as a result of our heightened inspection and attention to compliance issues, this has probably resulted in decreased production. So, manufacturers attempting to come into compliance have needed to take steps which have, to some extent, slowed down production. We have made a concerted effort to work with manufacturers to try and help

them to facilitate their coming into compliance without this having a major impact on the shortage. But, obviously, this is a balancing act and it has to be done carefully.

The other issue are CJD issues. It is very clear that over the last three years there have been withdrawals, and these are voluntary withdrawals by manufacturers who discovered that one of the donors was either at high risk or developed CJD. As a result, they have had to withdraw material from the market.

Now, the effect on the IGIV shortage is a little more complex because in most cases, because of the shortage, by the time the withdrawal occurs most of the product is actually consumed. So, that doesn't have much of an effect. There was one exception with one manufacturer in particular where a large number of lots were affected before they were distributed but, for the most part, the withdrawals occur after the product has been consumed.

But there is another aspect of this, and the other aspect is that when the withdrawals are made, the pools that were used to make those lots were also used to make intermediates that hadn't been further processed and are in storage at the manufacturers. As a consequence of the withdrawal, those intermediates are not processed further. So, it is clear that some of the CJD withdrawals have resulted in contributing to the shortage situation.

[Slide]

This is a graph pointing out the IGIV distribution in the United States in kilograms. We have this data because in 1994 regulation was enacted which asked manufacturers to provide their distribution data in the United States. So, if you look at this graph and you look at the amount of material distributed over the years, you see that between 1995 and 1996 there was an increase in supply but in 1997 there was actually a decrease in supply. What I told you earlier was that because of a 10% increase in demand, in order to keep up you do have to have an increase. So, in order to prevent a decrease we would have predicted that this had to be the level of supply to avoid a shortage. In fact, there was a shortfall, and this shortfall is explained on the next slide.

[Slide]

So, that amounted to a 20% shortfall. If you now look at the IGIV distribution in the United States according to year and different manufacturers, you see that some of the manufacturers had maintained the supply. For some of the manufacturers there was a decrease, and in some cases this was precipitous. Clearly, these factors led to the shortage and the factors, again, were partly CJD withdrawals in the case of some manufacturers, and in the case of other manufacturers due to compliance issues.

[Slide]

So, in fact, if we look at this pie diagram and consider the 20% shortfall for 1997, a large percentage of it, perhaps 60%, was due to compliance issues related to good manufacturing practices.

Another high percentage was probably due to CJD withdrawals, and there are other issues which are hard for us to quantitate. For example, how much of the manufactured material is exported. We have no way of monitoring or knowing this. And, there are other possibilities such as distribution to various wholesalers who, for whatever reason, are keeping the product.

[Slide]

Another factor that may have played a role is that it was noted that in 1997 the amount of material placed in a vial was increased on average. So, if we actually look at the distribution in the United States, especially if instead of in kilograms we now express it in terms of vials, we found that between 1996 and 1997 there is not a drop of 10% but there is actually a drop of 20%. This is accounted for by the fact that more material was placed per vial. So, there was about a 10% increase in material added to the vial. We are not sure why this was done. Was this required by consumers? Was this a marketing ploy? But this is something that could be looked into because it may result in

a less efficient usage of the product if you put in more per vial and it is a single-use product.

[Slide]

So, what has the FDA done to try to alleviate the shortage? So, getting back to late November, December, 1997, what did we do when we found out that there was a shortage? Well, we were impressed by the number of calls and by the situation and our group contacted the Office Director, Dr. Epstein, and arranged a meeting with the upper management at the FDA. What was decided was that they would actually call the CEOs of the various companies to convey the FDA concerns to try to learn about the reason for the shortage, and to try to think of mechanisms to alleviate the shortage. One that was discussed was the potential of using European approved product for emergency use in the U.S. under IND and, importantly, to establish hotline numbers, 1-800 numbers that would allow emergency use of IGIV.

[Slide]

In addition, FDA worked with manufacturers to try and facilitate increased production and distribution without compromising the safety and efficacy of the products. This comes back to the balancing act that I mentioned earlier to make sure that companies were coming into compliance but still trying to make sure that this did not impact on the shortage situation.

From the point of view of our lot-release program, we expedited lot release and reduced the time spent on the lot release from two to three weeks to a few days, and worked long hours to expedite review of license supplements which are related to IGIV products and which would allow increased production and distribution of IGIV.

In addition, a "dear doctor" letter was written to provide guidance for prioritizing the use of IGIV. This letter also included the 1-800 emergency numbers that could be used by physicians or medical centers for IGIV in an emergency situation.

[Slide]

The FDA has also instituted methods to try and increase the monitoring of the supply. One of the actions that was made that released quite a large amount of IGIV that was placed on hold was to release some IGIV that had been made with albumin which was potentially contaminated with CJD from an at risk donor, and this was set aside for emergency use only and with appropriate labeling.

[Slide]

Well, what is the current situation? Well, there has been a dramatic decrease in the number of complaints regarding the shortage, and we now have 5 to 6 phone calls a week compared to 30 to 40 per day. But there is no question in our minds and in the minds of the manufacturers and the

people that we talk to who are looking after patients that the shortage does continue. Many of the underling causes have not been resolved, and one of the issues that remains is the compliance issue. Another issue that I referred to earlier is that the increase in demand for off-label use remains an issue. There are 1-800 numbers in place for emergency purchase but in some cases product is available only for consumers who enter into contractual obligations with a particular manufacturer. We have actually tested these numbers and spoken to physicians, and it is clear that a physician may have to spend six hours to obtain IGIV for emergency use by going from one company to another until he finds a place where they have some IGIV which they can supply for a particular patient.

[Slide]

So, what are the future directions? FDA is considering updating the "dear doctor" letter to include new hotline telephone numbers, and we are working on an idea of establishing central distribution points for emergency IGIV. We are also trying to increase the monitoring of product distribution to trend the data; to modify current CJD recommendations, particularly by encouraging labeling of products according to CJD risk.

[Slide]

The FDA continues to meet with plasma

fractionators on an ongoing basis to investigate ways to further improve product availability. This relates in the main to compliance issues. And, also to facilitate the development of IGIV from new sources. So, this involves talking with established manufacturers who already have licensed product to try to work out ways to increase production, but it also involves talking with manufacturers that have IGIV product in other countries and trying to determine if there are ways of having their products licensed for use in this country.

The shortage problem will be reduced most substantially as manufacturers come into compliance with GMPs and production is increased. Thank you.

DR. HOLLINGER: Thank you. Any questions of Dr. Golding? Yes, Dr. Verter?

DR. VERTER: I just have one question. On one of the slides it looked like you are about 4000 kilograms short from the projection and about 50% to 60% of that shortage seemed to occur from one manufacturer. Can you identify what the issue is with that manufacturer, and has it been corrected?

DR. GOLDING: Well, you know, I don't know in a public hearing to what extent I want to talk about what happened with that particular manufacturer and identify the issue, but in general terms, those were serious compliance

issues which were identified, to the extent that the manufacturer found it necessary to shut down production for several months in order to come into compliance. When we consider the types of changes that needed to be made, such as changing equipment, processes, and on, and on, and on, we can understand why this was a major problem for the company. The actual request by the FDA was not to shut down the company but that they come into compliance. We worked with the company, and are still working with the company, to try and ensure that they return to full production as soon as possible. In fact, several months ago they did come back on line and the increase in production that we have observed over the last few months -- what I didn't mention and this gives me the opportunity to say that since November there has been an increase in supply in terms of the amount that is released by the FDA. There has been a 40% increase per month, and that is mainly because of certain manufacturers coming into compliance and being able to return to full production.

DR. ELLISON: You started your presentation by saying that you do not monitor the supply routinely, and this is an example of responding to a shortage that occurs. Has any consideration been given to try and monitor and act in advance when you see something like this?

DR. GOLDING: Well, you know, I think that is a

very important issue. Before this occurred, what we had in place was six-monthly reporting to us of distribution of product within the U.S. So, we were finding out after the event and not in real time what was happening with the supply. To try and actually monitor the supply more carefully -- we have some ideas about how we can do this, but this is also a tricky situation. In other words, you know, how do you find out exactly how much material is being distributed by a particular company? It often goes out to distributors who then can hold on to the material or can release the material. The whole setup of the FDA and the control of this industry at the moment does not have in place, as far as I am aware, a proper monitoring system for this material or for any drug and it has largely been left up to the industry at large to produce enough material to satisfy the consumers. You know, there are certain steps that we can take, but it may require more than just the FDA's action -- you know, legal action, congressional action -- in order to get a very rigid monitoring and control of the supply, if that is what we want. But that is the major problem that we have been thinking about.

MR. DUBIN: I think a couple of things, and this was a very hot discussion at the HHS Council on Safety and Availability, it has obviously been our contention that FDA already contains within the Food, Drug and Cosmetic Act the

steps toward authority to monitor supply. If more is needed, certainly I think some efforts can be made to do that. We have had this problem in terms of factor concentrates over the years, not getting the data and then being asked to make decisions. I think for the first time industry, to their credit, came forward at the Council meeting with some preliminary data, and the request was made that that be done by company on an individual basis monthly or bimonthly, whatever it takes. This is clearly something we need to make intelligent regulatory decisions, be they about CJD or immunoglobulin or factor concentrates, for that matter.

I think we saw the criticality of it this time in the shortage with primary immune patients. We have seen it in the past in shortages with hemophilia patients, and from our perspective, certainly, we would like not to see it again. It is pretty clear that with some solid monitoring we can get some clarity.

I think another thing we learned is that while CJD is a serious issue, it was not the primary force driving this shortage, which we had been told it was. So, I think we have a window into some of the things we need to do. Obviously, FDA has made an attempt to do them. And, I think we should ascertain what it takes.

The Council made some recommendations. One of

them was for regular data to be turned over by independent third-party, or to be monitored by that third party, however all of everybody's interests get protected but that we get that done so we don't face these situations where patients who need product are not getting it.

The last comment I made is, and I don't know how to put it other than that we were outraged at what happened with the 800 number. There is enough markup in this industry; there is enough profit being made, and we have never debated people's right to make a good profit on their investment but when we hear things like patients in critical need calling up and having to be, you know, slit into a contract to get service, that is just downright gauging. It is outrageous. From our perspective as a consumer group, we will do everything in our power to see that not happen again. We think most of the responsible home-care companies do not behave in that way. We don't want to make this an indictment -- or the manufacturers, for that matter, but that is something we all need to band together to ensure it does not happen.

DR. KOERPER: I think that the need for FDA to know what the supply is and where the supply is going is in a very timely fashion, as underscored by one of your points, which was that in an attempt to alleviate this it was considered to import IGIV from Europe. Yet, at the same

time, we heard that American-produced IGIV was going to Europe. So, it seems that we need a better way of knowing where the product is going and not reach this situation where American product is going to Europe creating an emergency whereby we need to bring product from Europe to the United States.

DR. GOLDING: Well, just a quick comment on that, my understanding when we tried to get information is that there was no regular or organized way in which we got information regarding exports, and it was just based on speaking to manufacturers and asking them and, in good faith, they would tell us, you know, how much they exported. The impression we got from most of the manufacturers is that it varies from zero to 25%. That is, it could be as high as 25% or as low as zero. But we do not have a good way of monitoring this. You know, I think your point and the previous speaker's -- you know, we should have better ways for monitoring this and I think we would need to enact certain regulations in order to do this.

DR. MARTONE: If the use of this product is anything like the use of antibiotics, while we surely don't want to stifle off-label use some of the use is probably clearly inappropriate. For example, with vancomycin, because of the problems with vancomycin-resistant enterococci, when surveys were done in institutions up to

60% of vancomycin use in hospitals was totally inappropriate. Hospital epidemiologists and others instituting programs of education and control are generally successful in limiting this antibiotic use up to 30% and 40%, with 30$ and 40% reductions.

I am glad to see that in part of your "dear doctor" letter you listed some priorities for IGIV use, but I would encourage you to follow up on this and do some epidemiology on the use patterns because I am sure you are going to find some that is clearly inappropriate.

DR. GOLDING: Well, you know, we think that is a major concern but we are not quite sure what we, as the FDA, can do. In other words, we can't dictate to physicians how to use the product. I think what we can do besides a "dear doctor" letter is to communicate to groups that have access to large numbers of physicians and try to get them to make policy statements regarding this. We have had contact with various medical directors at large hospitals and several of these hospitals have instituted prioritization schemes in the hospital, either before they spoke to us or after we had some discussions. So, we have gone to that level to do it. But I agree with you that this is something that we should try and find more ways to pursue because I think this is a major contributing factor to the shortage.

DR. HOLLINGER: Dr. Golding, you said that the FDA

lot-release process was shortened to about two to three days. How did you do this without compromising the integrity of the evaluations?

DR. GOLDING: Well, the usual process involves the company sending, either electronically or manually, a protocol which describes their final container testing. Our group in the Division of Hematology and another group looks at these protocols and determines whether any additional testing has to be done at the FDA. Now, for the most part, these are manufacturers that have been manufacturing these products for a long period of time and they have a track record. So, it is relatively rare that we will get a sample and say, well, we now have to go back and really test it. So, what we are really doing is checking their paper record to make sure that their final container testing was within specification so that we can then release the product. Several of the companies, by the way, are not under surveillance. In other words, they do not have to wait for FDA release. They still submit their final container testing results to us but, because they have had a track record over a long period of time, they can release the product without FDA release. But companies, especially companies which have had compliance problems, have been placed back on this release protocol.

So, you know, I don't think that in any way we are

taking chances with the product. I think the review is as complete as it was before, but we are just making sure that it gets to the various people that need to review it in a much more expedited fashion, and using electronic means to a large extent to facilitate quick review.

DR. HOLLINGER: And along those same lines, if you are going to use European produced product, if you are considering that, again, how would the lot release process go and how would the evaluations go for those kind of products?

DR. GOLDING: Well, for any new product, I mean we have a system in place that would apply to a European product, and we have certain regulations that would have to be applied. For example, the plasma has to come from U.S. approved centers. The product that is made has to -- they have to submit a license application which has to contain all the usual information. What we are proposing for some of these situations is an expedited review of that and working with the companies to make sure that they have all the material. Some of them haven't submitted PLAs to the U.S. FDA. We work up the IND studies so that they have all the information so that when they submit it, it can undergo an expedited review. But we are not going to cut any corners in terms of allowing them to market this product unless we are convinced that it is safety and efficacy, and

won't allow any approvals which would be different to the approvals that we gave to the U.S. manufacturers.

Several of these situations, by the way, are American manufacturers or manufacturers that already have product in the U.S. and have IGIV in the U.S., but also have a sister product in Europe and we are considering whether we can have that also licensed in this country. So, they have done parallel studies which are not very different from those that are required for U.S. licenses.

DR. HOLLINGER: Thank you. Yes?

DR. MITCHELL: I am very concerned about CJD and the compromises that apparently are being made in the balances. I understand the need for balance, but I think there needs to be more information about the risk of CJD, and then also that needs to be communicated to physicians, particularly when we are talking about off-label uses versus CJD risk. I think it is very important to portray that and, you know, maybe reserve that for off-label uses, if people feel they need to use IGIV for off-label uses.

DR. HOLLINGER: Thanks, Dr. Mitchell. Yes, Dr. Stroncek?

DR. STRONCEK: Does Europe have a shortage of this product, and are there any marked differences in price between Europe and the U.S. that might explain some of this? Also, I would just like to comment, I understand that people

that need the product need to get something so there is a reason to release some product that may not have been quite up to standard concerning CJD, but I am involved in a transfusion service and it puts everybody in a very difficult position to be giving product that does not meet all the standards.

DR. GOLDING: Well, maybe somebody else can answer the question regarding the price of the product in Europe. I don't know how much it costs in Europe.

But regarding the CJD issue, the point that I would like to make is that the only IGIV that was released for use was released for emergency use only. It had to have separate labeling. And, the decision to release the product was made after a large number of discussions within the FDA and also included the TSE advisory committee whose recommendation was that we could use IGIV and other blood products that had albumin or other excipients which came from individuals who were at risk or had CJD. So, there were a lot of qualifiers on the actual release of that product.

DR. HOLLINGER: Yes, could you state your name and your organization?

MR. BABLAK: My name is Jason Bablak, and I am with International Plasma Products Industry Association. I just wanted to briefly respond to Mr. Dubin's comment. As

he correctly stated, at the April HHS Advisory Committee on Blood Safety and Availability, our association came forward with some data on the IGIV supply. At that point, we committed to providing that on an ongoing quarterly basis. We are currently looking at ways to expand that data production to include other plasma-based products as well. I think it was important to bring that forward in response to that comment.

DR. HOLLINGER: Dr. Boyle actually has asked, not as a Committee member but as a representative of the Immune Deficiency Foundation, to make a brief statement of response to the IGIV shortage, and particularly to a patient and physician survey that they have made. John, you can do it there or you can come up here.

DR. BOYLE: One of the points that Dr. Golding made and that was made in the prior meeting was that it is hard for the FDA to have some information, other than complaints, about the extent and magnitude nature of this particular shortage.

Since I was one at the previous meeting that was demanding harder information so we can made some decisions, the Immune Deficiency Foundation went out and conducted two surveys, one of physicians and one of patients, to try and get some handle on, if not the causes, at least the current nature, extent and consequences of the shortage.

Since I didn't expect to be presenting today I don't have slides but I will walk the Committee members through their handouts. This was presented at the HHS committee about six weeks ago, at the end of April.

First the physician survey -- the Immune Deficiency Foundation has identified approximately 1500 physicians who treatment about 24,000 immune deficient patients. So, it makes a good sampling frame to be able to identify what types of problems, if any, physicians are encountering. Now, of those 1500 physicians, about 221 treatment about 15,000 patients, more than half of those that we have identified. We took those 221 physicians with certainty and then did about 1/50 random sample for the remainder of the physicians, sent them a one-page form and asked them to fax it back to us to be able to know the nature of this thing.

First we identified now many in fact treated patients with IGIV, then of that group, we asked them a series of questions. What we were able to identify is that in every state that we have a physician treating in the sample we have one or more physicians reporting shortages. Overall, 87% of the physicians that we surveyed said that during the past six months they had had difficulty in obtaining intravenous gamma globulin for their patients with primary immune deficient diseases. That is 87%.

We asked them, as a result of shortages in IGIV supply during the past six months, which of the following, if any, has happened to you? Of those 197 physicians treating patients with IGIV, 64% had to contact new suppliers to get it; 42% had to contact manufacturers directly; 75% had to change their usual IGIV product; 49% did not receive IGIV orders from their usual sources; 48% received less IGIV than ordered; 49% made special arrangements for access to IGIV; only 2% said none of these; and 13% were blank, who were the ones who already said they didn't have a problem.

As a result of shortages in IGIV supply during the past six months, which of the following, if any, has happened to your patients? And, 68% of the physicians treating IGIV patients said they had to postponed scheduled infusions; 71% switched to different IGIV brands; 51% switched to less preferred IGIV brands; 55% changed the interval between infusions, increased it; 38% reduced the dosage at infusion; 17% were unable to obtain product for indigent patients; 18% substituted alternative therapy for IGIV; if I put the "blanks" and "non" together only about 16%, 17% of physicians said none of these things happened.

This is the end of April. You know, we heard about the November, December, January shortages from the complaints but how bad is it in April? In April, we asked

how much difficulty are you experiencing now in obtaining normal supplies of IGIV product? And, 40% said a lot f difficulty; 42% said some difficulty; less than 1/5 said no real difficulty.

We didn't anticipate this but we did ask the question, to date, has the shortage of IGIV supply had a negative effect on the health of any of your patients? And, 45% of all physicians who are treating patients with IGIV say that yes, it has had an adverse effect on the health of their patients.

At the same time, we were in the middle of a patient survey so we included a similar form in the patient survey. At the time that we did this we had 158 patient responses. The sample, because it is early, is not going to be as good as the physician survey but of the 158, 25 don't use IGIV, 133 do. Of the 133 IGIV users, 80% reported problems in obtaining IGIV. Of the 107 who reported problems, 56% reported adverse health effects as a result of the shortage. Of those 60 patients, 31 reported more infections; 9 reported adverse reactions to the new brand of drug; 6 reported specifically pneumonia, bronchitis, lung infections. A small number, 7, said their effect was stress and anxiety and 7 didn't tell us exactly what the health effects were.

But one of the striking findings is from the

physicians, over 40% of whom say that their patients are already having adverse health effects, and of the patients, over 40% are reporting that they are having health effects as a result of the IGIV shortage.

We would conclude that the shortage is widespread, affecting every state in the country. It is affecting the vast majority of physicians that treat IGIV patients. That continues, and it does already impact upon the health of patients with IGIV usage. If you think about immune deficient patients and if there are, as we estimate, about 50,000 in the United States and probably about 35,000 are using IGIV, and you take any number, even if it isn't 40% but even if it is 20%, and project the health effects on that you have a major public health problem. Thank you very much.

DR. HOLLINGER: Thank you, Dr. Boyle. Any questions? Yes, Dr. Verter?

DR. VERTER: I just wonder if you could clarify a few things, Dr. Boyle --

DR. BOYLE: Sure.

DR. VERTER: I have absolutely no doubt that there is a problem, so let me start out by saying that. I wonder if you could tell us a little bit about the survey technique. Roughly, I can see that about 13% of the physicians and about 3.5% of the patients were sent in

surveys and about 20% of the patients responded, which is not a great response to date --

DR. BOYLE: It is still early --

DR. VERTER: I understand. So, I am wondering if you could tell us how the patients and physicians who were sent the survey were selected, and what effect you think the estimates, especially the patient survey if and when you get a better response, will be.

DR. BOYLE: The physician survey was a fax survey but if we didn't have a fax number we mailed it. It was done over a three-week period. Among the physicians with 25-plus patients we had a response rate, a completion rate, of about 70% despite the fact that we only had 2-3 weeks. Among those with fewer, we only had 2 mailings and we had a response rate of about 45%. So, overall, we got 50-something percent, which for a physician survey is tremendous. What I have not included here because more came in, we actually have updates on that.

In terms of the patients, we have an ongoing survey of about 3000 patients. What happened is we had an outgoing mailing of 800 which we slipped the form into. That mailing occurred in, I believe, the first week in April and we skimmed these results in the third week of April. So, we took the first 158 that came in. My guess is the first 158 are going to have more problems than the rest of

them because it is an incentive to respond. And, we are only presenting this as the only available data we have to date on what is the basis of probability sample. Over time we will have a better measure.

DR. HOLLINGER: Just following up on what Dr. Verter said, I think one of the key issues is you have 3000, how were those 3000 selected in the first place? There are 15,000, you said, getting product and yet you selected 3000. How are they represented? Are they representing the group as a whole, or what?

DR. BOYLE: The patient survey -- basically the sample frame for the 3000 are 3000 immune deficient patients who completed a short form so we have been able to identify them. That group was identified by circulating the forms to doctors that we knew from a previous survey were already following them. The doctors will not disclose names; the doctors will only distribute forms to patients. To date, we have 3000 out of what we estimate, from these physicians, is probably 25,000. So, we have a combination of doctors who don't want to give out forms; patients who only come in irregularly to receive those forms; patients who don't fill out those forms. But basically we have the only sampling frame that I know of that exists that is national. It is 3000; it is self-identified. Of the 3000 who have completed the survey and we know their diagnosis is an immune

deficient diagnosis, that 3000 then receives a longer form that collects information upon dosage, frequency of infusion and a variety of other things.

DR. HOLLINGER: Thanks, Dr. Boyle. We are going to take a break at this point and we will reassemble at eleven o'clock for the discussion of plasma inventory hold. Thank you.

[Brief recess]

DR. HOLLINGER: The session today is on plasma inventory hold, a quite controversial issue. This is mostly for information. The Committee is not being asked to make any recommendations at this time, but it is a critical issue about what one might do to make the window period safer. So, we are going to have an overview of this problem. Then there are going to be data presentations from the American Blood Resources Association. There will be three presentations. So, Robin?

Plasma Inventory Hold

Brief Overview

DR. BISWAS: Thank you. At this year's March Blood Products Advisory Committee meeting and also at the September meeting, the International Plasma Products Industry Association, or IPPIA, described voluntary measures for increasing the safety of plasma products. In particular, two IPPIA measures are intended to decrease the

number of window period units entering pools, and this was discussed in some detail at the last BPAC.

[Slide]

One of these two measures is the applicant donor and qualified donor procedure, and the other is the inventory hold procedure. Both measures have been implemented by most U.S. fractionators. I should mention that IPPIA's procedures are for source plasma only. Source plasma is obtained by plasmapheresis from donors who may donate up to 2 times a week and with a minimum of 48 hours between consecutive donations.

In the qualified donor procedure an applicant donor is a first-time donor or a previously qualified donor who has not donated within the past six months. So number two, the previously qualified donor, is considered as a first-time donor.

These individuals are screened and tested, and a donation is collected if all criteria are fulfilled. Donations from these applicant donors who do not return to the blood establishment are not used to make plasma derivatives. I should have told you that from these applicant donors, when the unit is collected it is held. I will go into that a little bit later.

[Slide]

A qualified donor, according to IPPIA's

procedures, is a donor who must pass two history interviews and have two negative sets of screening tests within a 60-day period and thereafter must have donated at least one time within the prior 6 months, otherwise the donor goes back to number one. Plasma only from these qualified donors is used, so the only collections that are pooled.

But in one above, the two negative donations and histories could be as close together as 48 hours. Nevertheless, plasma from an individual who is a one-time donor is not used in this procedure.

[Slide]

The second procedure, intended to reduce window period units from entering pools, is the inventory hold. Collected source plasma is held in inventory for 60 days. If the donor returns within 60 days and is positive for viral markers for HIV, hepatitis B, hepatitis C, the donor's positive unit and the prior negative units in inventory are not used.

However, if the qualified donor does not return after 60 days the units are used. So, a donor who is within the window period of, say, hepatitis C could return several times after the first donation, go through the testing and screening procedures, the units would be collected and those units that are collected would be used if the donor didn't return one day. However, some window period units would be

intercepted when donors return.

Now, at the previous BPAC meeting in March, the Food and Drug Administration described a possible alternative approach involving a plasma quarantine and release procedure as a theoretical gold standard for inventory hold. In this procedure a collected unit is placed in quarantine. The donor, after donating and fulfilling both suitability criteria, must always return after a minimum period of time based on the window period and meet all suitability criteria again prior to release of quarantined collections. The key here is that the donor must always return.

At the March BPAC meeting there was discussion about the scientific and technical issues involved, and the Committee decided to table the questions asked by the FDA. Committee members requested follow-up at this BPAC meeting based on the opinion that additional information was required and because IPPIA stated that industry required more time to gather and analyze the requested additional information.

IPPIA will now present this information. The FDA will not request Committee recommendations today as it is not clear whether sufficient scientific data will be available for decision making. It is also thought desirable that the Committee and FDA should have sufficient time to

consider the data presented. That is the end of my presentation.

DR. HOLLINGER: Thank you, Robin. We are going to go on then to the next data presentations, and Dr. Alan Liss is going to initiate this first round of talks and he will introduce the speakers to follow him.

Data Presentation, American Blood Resources Association

DR. LISS: Good morning. Thank you very much. Again, my name is Alan Liss, and I represent the American Blood Resources Association, ABRA.

Before I begin, if I could just comment briefly on one of Robin's remarks, the definition of qualified donor as far as the testing is two tests within six months, not 60 days. It doesn't affect the end results, I don't think, but a slight change.

[Slide]

Well, I want to thank again the Committee for allowing us to present this informational data. There are several points I would like to put down onto the table initially and then have the details given by our two speakers.

[Slide]

This very important topic is being presented so that we can begin to provide a comprehensive picture of viral marker safety among source plasma donor populations.

This is in response to Committee requests for complete data sets, and they include incidence and inventory hold effectiveness calculations. Perhaps more importantly, this is the beginning of a demonstration of the industry's commitment to data collection and dissemination. It is not stopping here.

[Slide]

Just as a reminder, understand that there is a long process from which we take source plasma to eventually our patients, and through this process there are a number of significant steps that affect safety, and we intend to go through these steps in our ongoing process of data collection. For today, we are talking about these early steps: Viral removal and inactivation, obviously a manufacturing step, should be included in our discussion but won't be discussed in detail in our numerical models.

[Slide]

Yes, we will be seeing data. We will have numerical models. We will be seeing these numbers which have very critical significance in our discussion. For these, we have asked our statistician to go over the details for you. That is the best person to do it. I am a biologist and I get trapped after too many zeros, but it is very significant for us to understand these.

[Slide]

We are also going to be discussing the impact of the 30-day quarantine. We feel, as you will see, that currently there is no meaningful safety improvement. We will have a significant loss in donations, which also means an impact on product supply, and there is also going to be other logistic and quality costs, that you will hear in detail about, that we think are critical for us to evaluate the need for such a change.

[Slide]

Perhaps in my mind, again, one of the most important things is that we are committed to have a future for data collection and analysis. We are going to be continuing science-based analyses based on our industry volunteer initiatives. We are going to be quantifying and analyzing the effect of viral inactivation and elimination steps, and we are going to be moving towards measurable safety improvements supported -- and this is important -- supported by real time data.

[Slide]

So with that background, the details are going to be presented by two very important people in this effort. One is Dr. George Schreiber, who is a consultant, representing Westat. He is going to be presenting the data collection and validation, how we analyze these data, and present a model which generates reasonable numbers.

We then will follow up with Dr. Toby Simon who is going to try and put this into context of not simply numbers but what it means to industry in regard to true risk, viral inactivation or partition and impact on quarantine. Again, the safety of our product is of prime importance to us and to our end users.

So with that, I will ask Dr. Schreiber to please present some data.

[Slide]

DR. SCHREIBER: We are really pleased to be here, presenting and helping out ABRA. They came to us with a request to help them develop their data monitoring and to develop some independent estimates of the safety. So, this is what Westat has done on behalf of ABRA but it is an independent effort.

[Slide]

The aim of this presentation is to calculate the probability of a non-reactive but infectious source plasma donation entering a manufacturing pool. We all have heard this probably ad nausea in terms of equations and prediction models. What I have tried to do, since I am just a simple country epidemiologist, is to refine this into some little charts that I hope everybody can follow more easily. I have to apologize for the sets that you all had before. There is one that has an error in it, which might have confused it a

little bit, but there is another set.

In the model that we are also going to talk about we are going to describe the data collection and validation that ABRA has undertaken, and we are going to describe the methods used to calculate the incidence and residual risks, and then the results that come out of these models.

[Slide]

The data collection was actually a very substantial effort, conducted over the 4-month period. We collected data from 370 collection centers who reported information; a little over 4 million total donations. This data collection effort has continued and we are now into it for another 4 months, but we haven't cleaned that data yet but those will be used to substantiate and refine the estimates.

We have donation histories for 215 confirmed positive qualified donors for HIV, B and C and we have donation histories for a sample of approximately 16,000 non-reactive donors. That represents over 300,000 donations. So, as you can see, it is a substantial data set that we put together in a relatively short period of time.

[Slide]

The data monitoring system starts with the laboratory test results. What we do, we collect information from the testing laboratories and what we get from that is

reports of seropositives and then the total number of donations processed. This is where we get the number of donations that have come through in a 4-month period. There were about 4 million donations.

We then go back to the donation centers and ask them to review the histories. We do this to make sure that nobody is in the system twice; to make sure that there are only qualified donors. Then what we are doing, we are collecting the complete donation histories, and we have asked them to send them to us from the beginning of 1997. These come directly to Westat. What we are using those for is to answer the FDA question about what the impact of the 60-day hold would be. So, we are using historical information and actual empirical data as opposed to just the modeling. Then we review all of this data and do data entry. So, this is what we do on the positives.

[Slide]

For the negatives, again, we collect from the centers a sample of donors, and we have collected about 16,000 donors. We then review, edit and enter this data. Some of it is given to us on disc form but most of it is hard copy, paper and pencil. Then we edit it. We look for inconsistencies, clean it and compile a database. This database then is used for the subsequent calculations, as you will see.

[Slide]

I have already mentioned this. This is the process that we go through. The labs confirm the positives and the donation histories. We review it for qualified donor status and, in fact, there were some that came in, about 65 out of 300,000, that had longer intervals. So, those long intervals that they would have had to requalify as donors were then removed from the data set, and that is because those donations wouldn't have been used because they were requalified. What we use that for is the calculation of the inter-donational intervals, and 65 out of 300,000 doesn't make too much difference. Then, as I say, we enter and verify the data.

[Slide]

Just to go back, the residual risk represents the probability that any given donation is in the window period and released for pooling. Our model includes the probabilities of both the known seroconverting donors and the probabilities for seronegative donors. These are the donors who, at the end of the observation period, we don't know their actual history, impending history, and some of them could have been within the window period. So, those are added into the calculation and that makes it parallel to the system that we have used to predict residual risk in the whole blood donors.

[Slide]

In our models we have also accounted for industry 60-day hold, and in the model that we used -- just as a point of clarification -- we have 4 months of data but we have broken it down into 2-month periods. The first 2 months are the observation and then the second 2 months for calculating the 60-day hold are used to look at the projected impact of the 60-day hold. The reason we did that, we figured that at the end of the observation period the people had to have at least 60 days to come back. So, then what we did, we went back and calculated the impact of the 60-day hold on the negative donation.

[Slide]

You have seen assumptions parallel to these, the one Satten presented, and as the population incidence rate for all donors is constant, unlike the Satten model, we use a fixed window period because we think that the projections are more accurate. Then we also are using the steady state assumption that the donors who leave the pool are equal to donors that enter the pool.

[Slide]

These are just the terms that you will see in some of the other slides. Everybody is already familiar with window period and incidence. The t_o on the slides that follow will always be the last donation, and t_i is the

donation that is under consideration. In the slides later you will see T, which is the inventory hold, and these are probabilities that we then calculate.

[Slide]

These are the slides where I have attempted to simplify to show what goes into the model. This is the first case when the last donation, here, is positive. What you can see from this slide is that here is the donation under consideration. We don't know when the person seroconverts. So, what we are calculating is he has to serconvert sometime between t_0 and t_1, and if you calculate or track back the window periods what you are looking at is that there is some potential risk within this box for a donation. For the first example the donation is outside this box. So, that means that it has absolute 0 probability of being within the window period. So, in all of these cases the probability assigned to that donation is 0. These would have a different probability, as you will see on the next slides.

[Slide]

This slide, again, the same thing; the same box. Here is a donation now within the window period. This one, now we know, is within the window period so it has a probability of 1. Again, we go through them and we add all of those up.

[Slide]

The more interesting ones are the ones that fall within this box. What we are trying to do is estimate how many days at risk there are, and it is the whole width of this box and what we are trying to estimate here is what percentage of the time it would be within the window period. So, the calculation really refines to the ratio of this orange box to the total box and that is the assigned probability. As you can see, the further out the donation is from the initial donation, the closer it is to be 0. So, it is right on this line, here, that it would have a 0 probability of being within the box and if it is out here, again, it is the first example. If it is to the right of the box, as you move further the probability increases that it is going to be within the window period. As soon as you cross the line it is a probability of 1. That, again, is parallel to the models that you see with the whole blood.

[Slide]

Now what we are looking at is the probability that the last donation is non-reactive. Again, it is very parallel and easy to see. Here is the last donation which is negative. Here is the window period and a donation way back here. So, that has a 0 probability of being in the window period and that is assigned a probability of 0. These are important because, as you see, we had 330,000

negative donations and we only had 215 positive donations so in many instances the negative donations contribute the most of the estimate to the residual risk.

[Slide]

Again, here is one that is within the window period and, again the same thing, we are calculating the proportion of the window period that would be at risk. As you move further towards the t_0 it becomes more like the whole blood situation. The whole blood situation assumes that everybody has the risk of the window periods times the incidence rate. What we are calculating here for these donations is that the window period is reduced. So, in this one there would only be a small risk period. As you move forward it approaches the window period. So, the interval is bigger and the risk becomes bigger.

[Slide]

These are very parallel because now all we are doing is we are superimposing a hold period. Again, if it is outside the window period and outside the hold period, the probability is 0 that it is going to be within the window period or be infectious.

[Slide]

If it is within the window period but also within the hold period, from here over, the probability still is 0 that it would be released and be infectious.

[Slide]

Again, this is parallel and what you see here is that this donation is outside the hold period, within the window period, and we calculate exactly the same the probability. So, the probability is the orange part of the whole box. That then translates to that versus the area here, which is the area of that box, and that gives us the probability estimate for this particular donation being within the window period and being released. Again, as you move further the probability is decreasing.

[Slide]

This is again parallel to the whole blood situation. It is within the window period and the donation is negative. So, what we do is we calculate a probability, and the probability is a function of the distance that it is outside from the window period and, again, it is the area of this small box which translates into days. That is what is then used for calculation of the probability.

[Slide]

With all of that then, what you can see from this equation is that the window period of residual risk is a function of all of those probabilities that I mentioned summed, and this is the probability of the positive donations. This is the probability of the negative donations over all of the number of released donations. So,

it is a relatively simple calculation once you get to this step.

[Slide]

Now just a couple of terms, the incidence rate is a conventional definition. It is the rate of new infections in the qualified donor population. We use person time. To calculate the person time we are calculating the number of donations times the mean inter-donational interval. The incidence rate then becomes the number of seroconverters times 100,000 so that we don't have to look at all of those zeros, divided by the person years of observation.

[Slide]

The next slides just show you where we are in terms of some of the parameters. The average inter-donational interval -- again what we did, we summed up for the 300,000 donations all of the inter-donational intervals the times and then we divided by the number of intervals. That gave us an average inter-donational interval of 5.3 days. So, you can see that the donors come back fairly rapidly.

Standard deviation -- I probably shouldn't show this since, as you can tell from the range of 2 to 178 days, it is really skewed and to a statistician it wouldn't mean anything. But the reason to put that up there is just to show you that it is very skewed and that it is way down at

the level of the 5 days donations.

We were worried a little bit about the impact that we had different numbers of observations for the negatives for companies, and we were worried that some companies may have people coming back more quickly than other companies. As you can see, the range of them coming back for the different companies, or which there are 16, ranged from 4.8 to 8.1 days. So what we did, we calculated weighted average for all of the donations and we came up with a weighted average of 5.4 days. Since that was so close to the average, we then decided to use the 5.3 because statistically it becomes a lot easier to handle and we don't think it would add very much in the interpretation of the data.

[Slide]

You have all been eagerly waiting to hear the 4 data slides. For HIV we had 36 seroconverters. The inter-donational interval is 5.3 days. Total donations is the same, and we have an incidence rate of 61.9 per 100,000 person years. Here is the confidence interval around it. So the confidence interval is actually pretty tight.

For HCV we have 37 and for hepatitis B, by far the most prevalent, we have 143. Now, if anybody can remember, the first number that I showed was 215 and it is obvious that these don't add up to 215. It is 216. So, one of

these people was co-infected and is represented in this table twice. Unfortunately, I can't remember what the co-infection was but we calculated them independently.

[Slide]

This is the question that was initially asked about the impact of the 60-day hold. So what we did, we took the positives and we went back using the 60-day holds and we used 2 window periods. For example, for HIV we used the window period of 11 for PCR and the 22-day EIA and we looked at how many would have been interdicted, and we found that we would have interdicted with the 60-day hold 59/59. So, 100% of those that were in the window period would not have been released, for an interdiction rate of 14.7. We just took the numbers and divided it by the total number of donations. You can see that eve with the EIA we were still interdicting 100% for the HIV. That is because the window periods are relatively small. As the window periods get bigger then more will slip through, as you can see down here with the biggest window period of 82.

For HCV we again looked at PCR, and I just got a news flash from Mike Busch that this number is by far an overestimate and it should be somewhere between 7 and 12 days. So, our subsequent residual risk rates should be modified and will come out to be lower. But we were taking a 23-day PCR. Using the EIA too, we are only interdicting

about 55% of the HCVs.

For the hepatitis B we are interdicting about 91%, and the interdiction rate is still quite high. The rate is also, as you can see, a function of the longer window period here than in these cases. So, you really won't gain very much unless you can shrink this window period by a bit.

[Slide]

This is translating the data into the empirical calculation of the residual risk. As you can see, for the HIV with 11-day PCR we are calculating a residual risk of about 0.49, and this is about 1/2 million. If you look at the EIA and the 22-day period, it is about 1.47 and this is about 1/680,000 compared to the whole blood situation where we calculated about 1/450,000. So, we are fairly comparable with the 60-day hold.

Here are the comparable estimates using the HCV. With the HCV, I believe that since the industry does pooled PCR in addition to the EIA and since the ramp-up of viremia is very fast for the HCV, I think that the pooled PCR testing is probably comparable to doing single-sample PCR testing. So, I think that somewhere around here is probably the true estimate of the HCV residual risk, and I think it is closer to here than it is using the longer window period. In fact, the window period used is a little bit of an overestimate even for this because this is from infection to

test and it is not just the period of infectivity.

[Slide]

This slide shows you the impact of the model. The point that I would just like to make is everybody keeps on saying, "does your model include negative donors and positive donations?" If you look here, what you can see is that for HIV the sole contribution to the residual risk is made by the negative donations. The positive donations are all captured so that you have the majority of the risk due to the negative donors.

In hepatitis B, for example, the situation is the opposite. The majority of the risk is due to the positive donors with some smaller risk due to the negative donations. You know, it is 86% due to the positive donations. So, you can see that by including the negative donations you, in fact, come up with a larger estimate of your residual risk. That is probably a more accurate estimate than some of the models that we believe were shown or talked about last.

That is our data presentation. Thank you.

DR. HOLLINGER: Thank you.

[Slide]

DR. SIMON: As Alan indicated we are moving from the data reflecting the way things are now to what they might be if we go to a quarantine system, and trying to compare and see what is in the best interest of safety.

[Slide]

First, we have the factors that affect the residual risk, the donor screening and the viral marker testing; then the effects of viral inactivation, the viral reduction and the clinical experience we have had with that. Finally, we will spend some time looking at the analysis of what the impact of a quarantine would do and where we wind up with ultimate safety.

[Slide]

Just to remember that this is where we are starting with the data that Dr. Schreiber showed you of what the risks are today and our best analysis.

[Slide]

I think it is an important point to make that this is a theoretical model of the probability or the possibility that units in the window period might be entering the pool. We don't know if such units are entering the pool, and we believe that this model which is based on the test result overstates the true risk.

The reason for that is that we are interdicting units during the 60-day inventory hold for reasons other than a confirmed viral marker test. Primary among these is the medical screening deferral option that we have when a donor returns and a reason for deferral is found that could impact product safety. The manufacturer would be informed,

a lookback conducted, and all units would be interdicted and removed from possible manufacturer. So, any new events that would occur and would be revealed in the medical screening, such as a new diagnosis in the spouse of a disease that could be transmitted by transfusion, or change in life style habits or anything of that sort.

Some of the companies are also interdicting based on increased ALT, although this is a variable practice. In addition, the companies will be, of course, removing units which also have indeterminate confirmatory testing, which are not included in the analysis and, of course, would be informed about all repeat reactives that would make a determination even when there is negative confirmation.

Finally, there is this major issue of post-donation information. We come across a great deal of post-donation information and whenever that information indicates there could be a problem with the safety of the unit that was shipped for further manufacture, the manufacturer would be informed and would have the opportunity and would, indeed, go ahead and remove that unit from the pool. So, we have a variety of other factors that allow us remove units that could possibly impact safety.

The problem with the interdiction, as was brought up by Dr. Biswas and Dr. Hollinger at the last meeting, that we can't be sure that every donor returns during the 60 days

is true. So, it is not a zero risk situation. But the flip side of that is that every unit that we remove in the interdiction, we have reason to believe could impact the safety of the product, as contrasted with the quarantine where we may be removing very many units that we have no reason to believe there is a safety problem. So, this is a mechanism that allows us to remove units which reduce supply but units which we know or we feel could have an impact on safety of the final product.

[Slide]

We are not going to present a detailed analysis of the viral attenuation procedures which both inactivate and remove virus, but I think it is important to point out before we move on that all the data that you have seen and many possible window units would go into a pool that is subject to various viral reduction measures. These measures have been validated, and various estimates have been made of their effectiveness. I believe claims are allowed for up to a 4 log reduction although it is felt that it is actually much greater.

We do have an extensive clinical history since the implementation of the validated methods. Since sometime around 1987 in the treatment of hemophilia, there is a lack of documentation of any transmission of disease from Factor VIII, Factor IX products that have been appropriately

treated, and since we dealt with the hepatitis C problem and IGIV in the early '90s and have been applying appropriate methods since around 1994, we have million-plus vials of that product that have been administered without known transmission. So, we have good clinical history to support the safety of the product as it is finally distributed to the patients due to these additional measures.

[Slide]

Now we look in contrast or in addition to this at what could be achieved by a 30-day quarantine. We have chosen 30 days arbitrarily but in consultation with the Agency on the assumption that at some point PCR testing would make that a reasonable period of time to use for a quarantine to pick up units that might be in the window period, and in order to do this analysis in a rapid fashion to bring back to this meeting we have made a number of assumptions which we believe are valid assumptions for this analysis. Individual unit release would be the criteria, which means it would be the responsibility of the collection center to maintain the quarantine and to release for shipment across state lines for further manufacture only when the quarantine measures have been satisfied.

We are allowing units to be held up to 45 days or donations through 45 days. There will be a few extra days to get test results back. So in other words, if a donor

were to donate on June 1, that donor would have to return between July 1 and July 15 for the June 1 unit to be shipped under the quarantine hypothesis that we are examining. We have chosen the 45 days somewhat arbitrarily but we believe that is a reasonable period for this analysis and, as you will see, it will be logistically problematic even at that level, but the extent to which this can be tracked and also to which these units can be stored before release dictates to some extent how far we can go in waiting for the donor to return.

Units for which the donor has not returned, for which we do not have retest results after 30 days would be destroyed, and this is based on the assumption that the quarantine might be a gold standard.

[Slide]

We are looking in our analysis at these areas of impact: Of course, the supply one which we know the Committee is very concerned with; also issues that relate to logistics and cost; unit tracking and computerization; retention and storage capability; impact on center personnel and on the products.

[Slide]

In terms of supply, our best analysis indicates that something in excess of 30% of the donated units would need to be destroyed in a quarantine program, which we think

would not result in a measurable increase in safety based on the data we have shown you.

This is based on donor return rates at 77 centers that are owned primarily by two companies that have excellent computerized systems and were rapidly able to give us the data for this analysis. It does represent approximately 20% of the industry total and is, in our mind, fairly representative. The return rates are measured by totaling the number of donors that return between 30 to 45 days after a given donation date.

[Slide]

The actual data which is the basis of the conclusion is shown here. Basically, each of these companies chose a donation date in 1997, and then one early 1998 which, as you see, tracks a fairly substantial number of donations because these are large companies, and then looks at the percentage of donors who did not return for another donation that could be tested 30 to 45 days after the donation on the date shown. For the 10/13/97 donations at one of the centers it was 31% that were lost. For the other October number it was 34%. The two '98 came up with almost identical percentages of 37%. So, that is what we come up with, somewhere between 30% and 40% or, more conservatively, something more than 30% of total donations we estimate would be lost to final supply based on this.

What I want you to keep in mind is that as we discard these units, these would be units from donors in many cases who have donated for years but happen to be working overtime and being unable to return, or have moved to another community or have developed a new diagnosis that is unrelated to safety, like coronary disease or diabetes, and couldn't donate any further, as well as newer donors. But, in general, we would be discarding units about which we have no information to suggest that they are harmful based on the fact that we couldn't confirm that we had a test result during the window period.

[Slide]

There are other impacts as well. Unit tracking and computerization -- not all of our companies are fully computerized but they are moving in that direction, and we asked one of the companies to do an analysis with their programmers of the cost of reprogramming to achieve this, including the design and development of new systems, their validation and 510(k) clearance by the Agency.

[Slide]

The estimate based on that is between 50 and 100 million dollars, 10 to 20 million for this one company alone; 50 to 100 million dollars by the industry as a whole would be spent in order to redo existing systems or systems and design or in work right now in order to achieve this

tracking. That would be for implementation, validation, and regulatory authorization and would be in a time range of 3 to 5 years.

[Slide]

Perhaps the biggest one in terms of feasibility in the short term would be storage capacity. Right now, most of our companies try to ship every two weeks. So, the truck comes every two weeks for the units that have been moved out of quarantine and are prepared for shipment, and they would have left as a residual another one to two weeks of supply on which there weren't complete test results or for which applicant donors had not returned. To extend this out to 45 days we estimate would be an approximate 5-fold increase in current storage capacity for these collection centers, which would mean an investment in modifying the facility, relocating in some cases where there wasn't space for additional freezers, and building new freezers, and this would also require ELA and BLA modification to be submitted to the Agency.

[Slide]

Our cost estimates for this is something in excess of 50 million dollars for the total capital investment and equipment facilities and the regulatory compliance requirement, with a time scale of two to four years for completion.

[Slide]

In order to track this and ensure that all the quality and GMP requirements would be met, we estimate that it would require approximately 3 new personnel for the average for a large size center, with new packing, shipping and inventory management processes, which would result in multiple layers of additional QA/QC functions, and we are estimating that this cost would likely exceed 80 million dollars per year.

[Slide]

As we indicated, there would have to be additional QA/QC functions in the center, but there would probably be some requirements for the manufacturers to meet in order to qualify these units and to assure that all the quarantine requirements have been met with redesign of inventory management and unit tracking and the flow.

[Slide]

So, remembering that our comparison of what a quarantine would achieve is something to improve safety beyond these numbers and the additional steps that are taken.

[Slide]

Therefore, we would conclude that a quarantine such as has been proposed would have drastic effects on the final supply of source plasma to the manufacturer and the

supply, therefore, of final product with a reduction of something in excess of 30% using a 2-week period for the donor to return after the 30 days.

We also have very significant logistic and financial issues that would compound the situation and create major feasibility issues in terms of instituting this over a period of time.

We believe that, given the data that we have presented and that are available, the quarantine would not meaningfully -- or said another way, would not measurably increase plasma product safety above what is in the current standards.

However, I do want to emphasize that while we believe, based on our analysis, that a quarantine is both unfeasible and would compromise supply and not significantly increase safety, we do recognize that complacency is the enemy and that continued vigilance is required to ensure safety. So, we do appreciate the opportunity the Committee and the Agency have given us to do this analysis, and we agree on the necessity of continuing to look at options to increase or maintain the safety standards that we have, and we are committed to a continued science-based database assessment of safety and a dialogue with you on that basis.

Before turning it back to Alan for questions, I would like to take this opportunity to acknowledge the

support of the companies that helped us get this data and the people there, as well as our staff at ABRA, particularly Bobby Whittaker and Chris Healy and also, of course, George Schreiber's staff at Westat.

DR. LISS: Again, just in closing before asking if there are any questions if there is time permitted for that, just to remind everyone that this is just the beginning and that these are ongoing promises to continue science-based data gathering for us all to reach the safety and quality and supply issues that we all demand. So, thank you again.

DR. HOLLINGER: Thank you, Dr. Liss. Any questions now for this group? Yes, Dr. Mitchell?

DR. MITCHELL: I have several questions. You talked about the increased cost of tracking. I guess I am curious as to how you currently track for the inventory hold, and how that would be different under the quarantine.

DR. SIMON: The inventory hold is an interdiction so that the inventory hold occurs when we have either a new event that triggers it, in other words new information, a positive test result, and all those analyses would go to the regulatory departments of the companies that would analyze them, and when they are significant would then send information to determine where the units were shipped and send them to the manufacturer. So, prospectively we don't track each unit. It is a retrospective thing that when we

get information of concern, then we go back to those particular units that are involved.

The difference here is that each unit would have to be prospectively tracked. That is, no unit could be released until someone determined that the donor had returned and had negative test results 30 to 45 days after the previous donation. So, say, on July 1 somebody would have to physically look at all the units donated on June 1 and what was left from before that date and then determine in each case whether the donor had returned, and they would have to keep on doing that until such time as we arbitrarily cut it off and removed the units.

DR. MITCHELL: Okay, but first of all, you don't hold it on site, you send it --

DR. SIMON: Right, it is not a quarantine for release so the units are sent to the manufacturer. The manufacturer holds it actually for 60 days --

DR. MITCHELL: But the manufacturer has to track it.

DR. SIMON: Right. The manufacturer then would have to keep units at least in storage for 60 days. So, the manufacturer moves them out of storage into the manufacturing line. We have to determine that at least 60 days had elapsed and they have the systems instituted for that.

DR. LISS: Perhaps to add to that, first of all, each company does it differently and there are variations on the theme. I think what Toby was saying is that currently tracking is more temporal tracking either at the manufacturing site or the collection center. Adding the complexity of the data entry not being at a particular time but being essentially spread out through the entire hold period, you know, the addition of when the data would come in that would initiate the interdiction event would be different for each unit. So, it is trackable but trackable using a computer system which currently isn't used by the industry versus the current issue, which is perhaps you have a lot of different units, all marching to the same temporal time beat. Did that clarify it?

So, the complication, I believe, is that the timing for the data could be any time throughout that period. It is another event in addition to a holding period versus a calendar hold.

DR. HOLLINGER: Any other questions? Yes, Dr. McCurdy?

DR. MCCURDY: If the average inter-donation interval is between 5 and 6 days, and it is permissible for donors to come back as soon as 2 days, I believe, after the donation, and there is an appreciable number that might come back in there in order to give you the average that you have

come up with, and in that period of time you might get 2 or 3 donations possibly within a window period that may be 10 or more days. So, I am curious, if a donor comes in maybe 2 or 3 times in a week or 10 days and then stops coming in, which I think is conceivable in this model, why are you interdicting 100% of the infected units by a simple hold without a requirement for retest?

DR. SCHREIBER: That is a good point. I think the two slides were actually a little bit conflicting. The question that the first slide addressed where we interdicted 100% was of those known positives. The other question that you are raising, what happens to those that you don't know, that is what contributes to the overall residual risk. As you can see, even though we interdicted 100% of the known positives, we still had a residual risk for HIV and that was due to the point that you just raised, that we don't know the outcome of that particular individual but his units are contributing something. If we knew further down the line, which may be in 6 months, we could project what the ultimate history of that person is and we can refine that number. But you are absolutely right, that is the difference between the two, the theoretical and then the calculation of just what we actually interdicted on that small number.

DR. HOLLINGER: Dr. Biswas, I think you had a couple of points, and then we will come back to the

Committee again.

DR. BISWAS: Actually, I wanted to respond to Alan's comment. So, Alan, if I got something wrong I would just like to have clarification. If plasma is only being taken from qualified donors, then an applicant donor who comes in -- if you combine that with the inventory hold, the 60 days, if you are only pooling plasma from the qualified donors, then an applicant donor who comes in should surely have to go through two history interviews and two negative tests within the 60-day period, otherwise you would be pooling that first unit, right? And, that would be from an applicant donor.

DR. LISS: May I respond? Robin, that is an excellent point. I mean, the alternative may be the opposite. Some organizations might be holding the unit forever or six months -- that is the end of forever, but we certainly wouldn't use it. And the reality -- you know, I can't speak for everyone but I am guessing that logistics would say that you would throw it out if they don't come back within 60 days, but certainly not use it. So, you are conceptually right, but there is the possibility someone would want to hold that for 6 months but certainly that is a good point.

DR. BISWAS: Thank you very much. I just wanted to say that we are studying IPPIA's procedures and we will

consider whether any regulatory steps would be taken for those that are scientifically valid.

DR. MITCHELL: I forgot to say that I certainly appreciate the industry's efforts to respond to our questions. I think they have done a phenomenal job in providing real data rather than theoretical data. So, I think that you deserve some recognition for that.

I have also looked at a lot of the cost figures that you have presented. The data that you presented shows the risks are very, very, very low and theoretical the quarantine risks are close to zero. You also presented about the cost, and I think you need to distinguish between the one-time cost and the continuing cost of production, and we will have to look at that.

DR. NELSON: Are there any data on how genetic diversity in the various viruses that we trying to screen for and prevent -- hepatitis C and hepatitis B etc. -- affects the window period in those who eventually are detected? Certainly, that is a theoretical issue and it is real, but what I can't tell is how important it is with the current distribution of viral infections in potential donors. Do we know any data on that? I mean, we always give just one figure with fairly narrow confidence limits around it but I think that viral genetics may substantially affect those, and I guess we are going to hear about that

this afternoon a little bit.

DR. HOLLINGER: Yes, host response and concentration and a variety of things probably do play a role. Anybody have any response to that? Any information about the genotypes etc. and their effect on the window periods? Any data? Yes, Mike?

DR. BUSCH: I will show this afternoon some data on HIV, but there is reduced sensitivity of the current generation assays to non-clade B infections. It is a very good question, and we now have very good data from plasma donor screening programs where they are picking up a fair number of these donors and following them over time, and there is quite a distribution in the duration of the viremic seroconversion window periods and it would be very interesting to subtype those to see the different subtypes in prolonged versus shorter windows. I have never seen data on that.

DR. HOLLINGER: Where are all these hepatitis B cases and C cases in donors who receive blood in the window period? It always amazes me that we have such a large number that we suspect but it is the same issue with hepatitis C that we had before but, still, you would think you would see something coming along the way. Yes? Could you give your name?

MR. NAGLER: My name is Rick Nagler, and I

represent the Hemophilia Federation. My concern is the figures up there look like it is just a small fraction, but when you take 235,000 pints of blood and mix it together, that figure goes up greatly. It only takes one. In the late '70s and early '80s one of the arguments made was costs -- costs, costs, costs. Now, you know, at least 10,000 people from the hemophilia community are going to die. So, when the blood industry does present figures such as that, I would also like to see an independent organization study the matter and come up with whatever findings they get from the figures.

DR. HOLLINGER: I think though, in fairness, we should also not forget that there are viral inactivation and removal procedures, and I think we need to at least retain that as an indication of a different step and a different place, but the risks are still there, as you said, and we have to consider that as well. Thank you. Dr. Busch?

DR. BUSCH: We saw for the first time today I think incidence rates derived for the source plasma industry, and the incidence rates, you know, were substantially higher than for the whole blood sector. I think the interdiction of the 60-day hold combined with PCR testing, I agree, from the analysis has brought those incidence rates down to a comparable level.

I think the comment about the clinical experience

is very important. I mean, we have been in the last ten years for HIV and for the last years for HCV transfusing blood without the benefits of these additional safety measures, the 60-day hold and the PCR screening, and therefore, it seems that it is presumably entering pools at those incidence rates with those contributions of high titer viremic donations without any transmissions. My understanding is that the hemophilia community has been fairly well monitored on an ongoing basis. So, I think it speaks very strongly to the efficacy of the inactivation of procedures. They have essentially been completely effective during the period when a moderate number of window phase units were probably entering pools, and now with the additional safeguards that have been described dramatically reduce that issue. So, I think it is really dramatic improvement and I think the inactivation procedures have been proven to be extraordinarily effective.

DR. HOLLINGER: Thank you, Mike. Dr. Verter, a last comment?

DR. VERTER: Actually, it was more of a question to either you or Linda. While I appreciate and really admire the efforts that were shown here today, if it is going to come back, I was wondering if we could have some input into the next presentations as far as some other estimates that probably are easy to calculate actually. I

don't know if that is appropriate or not.

DR. HOLLINGER: Yes, I would also like to see some examples, simplified examples, reality, real time, exactly what would happen if you had a person in; the number of samples and what happens; something you can really sink your teeth in. It makes it a lot simpler for us. Right, I agree, Dr. Verter.

Dr. Smallwood wants to make a few comments about this afternoon's topics and what is going to happen, and then we will break for lunch. Dr. Smallwood?

DR. SMALLWOOD: For this afternoon, if you notice on your agenda, there will be a closed session. I just want to make a few comments regarding that. The closed session is scheduled, according to the agenda, to begin at 3:00 p.m. I would like everyone to be prepared to move quickly and quietly, which would mean that you would need to remove all briefcases and luggage. All recording equipment must be turned off and unplugged. There will be no one allowed in the room other than the transcriber, the presenters and their identified guests, FDA personnel with an ID or a recognition factor, Blood Products Advisory Committee members who have been cleared under the conflict of interest review. There will be a break immediately following the closed session, until 3:45, and it will be appreciated if you would follow these instructions as best as you can.

I would also like to ask if the presenters in the open public session for the afternoon would be seated to my left so that you will be available to the podium. Thank you very much.

DR. HOLLINGER: Thank you. We are going to take a break then, and we will return to begin at one o'clock. Let's make it 1:15.

[Whereupon, at 12:00 noon, the proceedings were recessed to be resumed at 1:15 p.m.]

AFTERNOON SESSION

DR. SMALLWOOD: For this afternoon's discussion, I would like to make a disclosure for the record. Dr. Paul McCurdy is making a disclosure that in his previous employment with the National Heart, Lung and Blood Institute he was the supervisor of a project officer that worked with a contract with one of the sponsors that will be presenting today on this topic. He would further like to let it be known that currently he is in a consulting arrangement with the National Heart, Lung and Blood Institute, and is continuing that relationship with that sponsor.

Before we broke for lunch I had given instructions regarding the closed session, and I would just like to remind you of what was previously said. We will provide assistance to anyone that has any particular problem at that point.

At this time, we will continue with the afternoon session. Dr. Hollinger?

DR. HOLLINGER: Thank you, Dr. Smallwood. Well, we already had some discussion this morning about the HIV variants, but we are going to be dealing this afternoon with the group O HIV variants particularly and how that impacts on the sensitivity of manufacturers tests for detection of patients with HIV in this country. So, we are going to start out initially with an introduction and background by

Dr. Koch. Then we will move forward with some of the other presentations.

Increased Sensitivity of Manufacturers' Tests for HIV Variants

Introduction and Background

DR. KOCH: Good afternoon.

[Slide]

We have a pretty full plate for the next hour so I am going to keep the introductory comments and background pretty brief. Most of this is information that has been presented to BPAC at some previous point.

The main issue before us this afternoon in this session is whether the FDA should continue to require that rapid tests, intended for use in detection of HIV-1 antibodies in diagnostic settings, have a demonstrated sensitivity for HIV-1 group O.

[Slide]

Reports of the inability of some HIV serologic assays to detect all HIV-1 group O clinical samples have raised an issue of substantial concern. In 1994, evaluation of 10 FDA licensed tests, using a panel of 8 confirmed group O positive samples showed that 6/10 tests, including the one licensed rapid test, were unable to detect all of the samples. To date, 2 cases of HIV-1 group O have been identified in the United States, both in 1996. Since that

time, no additional cases have been identified.

[Slide]

In 1996, the FDA asked manufacturers, or manufacturers of licensed test kits, new tests under IND, were requested to modify their kits to incorporate specific group O viral antigens. In 1997, FDA wrote manufacturers to inform them of changes in the review criteria that would facilitate licensure or approval of test kits that included group O-specific antigens. Manufacturers of tests to detect HIV-1 antibodies are in the process of modifying their tests to be sensitive for HIV-1 group O in clinical specimens, and some of the manufacturers will present information and data in a progress report to the Committee in the closed session.

FDA is seeking recommendations from the Committee regarding the need for manufacturers of rapid tests, used in diagnostic settings for detecting antibodies to HIV-1, to demonstrate sensitivity of their tests for HIV-1 group O in clinical specimens.

This effort is being driven primarily by a recent PHS recommendation that preliminary positive results of rapid tests for HIV-1 be provided to the person being tested before confirmatory results are available in situations where tested persons would benefit. For example, in settings of high prevalence with a low percentage of persons returning for their results, such as sexually transmitted

disease clinics.

This recommendation is based on research which demonstrates that persons who receive preliminary results understand the meaning of their result and prefer rapid testing, and that the overall effectiveness of publicly-funded counseling and testing programs would potentially be increased. When additional rapid tests become available for use in the United States, the Public Health Service will reevaluate algorithms using combinations of two or more rapid tests to improve the predictive value of rapid testing for HIV antibodies so that the public can derive the optimal health care and health benefit from technologic advances in HIV testing.

FDA's position is that it is in the interest of public health to facilitate licensure of additional rapid tests for use in the diagnostic setting. Therefore, it is our current thinking that the requirement for group O sensitivity for rapid tests to be used in the diagnostic setting be waived.

[Slide]

The question which we will pose for the Committee later in this session, following additional presentation, is the following: With regard to rapid tests used in diagnostic settings, should FDA relax its current policy to require, as a condition of approval, that all new tests for

antibodies to HIV-1 have demonstrated ability to detect HIV-1 group O?

DR. HOLLINGER: The next speaker is Dr. Branson, on public health basis for HIV counseling and testing using rapid tests, which deals with this issue for which the question is being asked.

Public Health Basis for HIV Counseling and Testing Using Rapid Tests

DR. BRANSON: This is Branson. I apologize. I didn't realize I was next on the agenda. It will take me just a moment to get my slides.

[Slide]

I would like to present the background for the recommendation that the Public Health Service made in March of 1998, related to the use of rapid tests for screening based on strategies for rapid testing.

[Slide]

The Pubic Health Service began to reconsider this recommendation on the basis, in particular, of the high rates of persons who did not return for their test results. In 1995, in publicly funded HIV counseling and testing 33% of the people who tested negative and 25% of the individuals who tested positive did not return in order to learn their HIV serostatus in publicly funded testing.

Additionally, the CDC had received requests in

circumstances where there was need for immediate information in order to make treatment choices, especially in perinatal settings, potentially when a woman would be presenting for delivery at high risk for HIV but have undocumented status, and in circumstances such as healthcare exposure where decisions for treatment needed to be made for post-exposure prophylaxis.

[Slide]

The Public Health Service considerations were made on the basis of the experience with the licensed test for HIV-1 in publicly funded sites, and considerations were the potential impact on the number of persons who would learn their HIV status. We also considered what the particular value would be in settings of different prevalence and did additional analyses of cost and cost effectiveness. I will be talking primarily about the first two issues, the experience in publicly funded sites and the impact on the number of persons who would learn their results.

[Slide]

The field evaluation of the SUDS rapid test was conducted in an anonymous test clinic and an STD clinic in Dallas County, comparing a 10-week period when we followed the standard current algorithm for testing, which is to obtain a sample at the time of pretest counseling and then provide no results to an individual until confirmatory

testing could potentially be done in a positive sample.

The nature of this algorithm, I must say, results in all individuals who are tested for HIV to have to make two visits because it was impractical to be able to potentially provide results to an individual from a negative test but to tell other individuals whose reactive test was positive that no result will be given. This effectively precluded the use of rapid tests in most publicly funded settings.

[Slide]

In this particular study during the standard protocol period there was approximately a 2.5% prevalence; in doing the rapid protocol period there was a 3% prevalence. In the standard period overall in the anonymous counseling and testing site, as you see here, as the experience is across the country, between 86% and 95% of individuals returned to receive their test results. Even in this setting there is an increase of 99% for HIV-negative individuals and 100% for HIV-positive individuals when individuals were given their negative test results on the day of testing and were given a preliminary positive test result after their rapid test was repeatedly reactive.

The experience in the sexually transmitted disease clinic was considerably more dramatic. As has been the experience across the country, the return rates during the

current two-step protocol was 30%. In 1995 the return rates for HIV-negative individuals averaged 48% across the country. And, 79% of the individuals who tested HIV positive during the second protocol period did receive their test results, however, only approximately only half of them returned on their own, and 34% required active outreach efforts in order to locate them, and approximately 21% of the people who tested HIV positive did not receive their results.

When the rapid test was employed in the STD clinic there was a substantial increase. Up to 93% of the individuals who were HIV negative received their test results, and 97% of the individuals who were HIV positive received their results, only one of whom required outreach visits. So, 94% of people who were given a preliminary positive result returned on their own in order to receive confirmatory results.

[Slide]

We developed a decision model looking at the potential impact of using rapid tests in various U.S. settings based on the data that was reported to the CDC through a counseling and testing data base in 1995, using the prevalence at different types of testing sites including anonymous testing sites, STD clinics, drug treatment centers and family planning settings. The prevalence at those

different sites ranged from 0.4% overall at family planning clinics to 2.9% at drug treatment sites. For each of these sites we also used the rates of return for test results of individuals which ranged from 48% for HIV-negative individuals at STD clinics with outreach efforts up to approximately 85% for individuals who were tested at counseling and testing sites.

[Slide]

These are the results. At anonymous counseling and testing sites, where we experienced the highest rates of return, an additional 1,970 individuals tested in 1995 would potentially have learned that they were HIV positive if a rapid test had been used, and the experience was similar to that which was observed in the studies in the publicly funded sites. An additional 106,000 individuals would have learned that they were HIV negative.

Because there was only one rapid test available and no additional method was available to improve the predictive value, approximately 2700 people would have received a false-positive screening test result, their preliminary result, before they returned for a confirmatory result.

[Slide]

At the STD clinic the results would have been significantly more dramatic. There was approximately a 43%

increase or about 2,700 more individuals who had already been tested would have learned that they were HIV positive. If rapid tests had been implemented, an additional 288,000, nearly a doubling of the number of individuals who would have learned that they were HIV negative. At the STD clinic the tradeoff would have been giving 2,200 people an initial false-positive test result on the basis of a single repeatedly reactive rapid test.

[Slide]

The difficulty in low prevalence settings was illustrated by the results at family planning clinics. Although there still would have been an increase of 168 individuals who would have received a positive test result, a false-positive preliminary result would have been given to 951 individuals at family planning clinics which experience the lowest prevalence in publicly funded testing, an average of 0.4%.

[Slide]

On the basis of this data, CDC combined the figures from all these sites and overall projected that the potential impact for using rapid tests in publicly funded testing, on the basis of the 2.1 million tests that were included in the client record database from CDC, would have been an increase of 8,170 individuals who had already been tested who would have received a confirmed HIV positive test

result. This represents approximately 23% of all individuals who tested positive in publicly funded testing. There would have been an increase by 50% of the number of individuals who had learned that they were HIV negative, and significantly, approximately 2.1 million individuals, would have been able to receive their negative HIV test result by making only a single visit instead of the currently required two visits. Overall, 8,300 individuals would have received a false-positive screening test.

[Slide]

All these figures in the right-hand column reflect the number of individuals who would have received a confirmed positive test result, and we believe that an additional advantage is that these individuals, as well as the 1,115 individuals who had received their initial positive HIV test result who did not return to the same clinics for confirmatory test results would not only have received positive results and advice on changing their behavior in order to prevent transmission, but would have received this information considerably sooner.

In many of the settings where individuals are notified of their test results there is a substantial delay between the time the person is tested and the time that outreach efforts successfully locate and notify these individuals.

As a summary, the tradeoff cost would have been 8,301 individuals who had received an initial false-positive test result from the single available rapid test.

[Slide]

As a result of that, a meeting was convened at the CDC on October 24 in order to seek expert advice, in 1997, looking at the issues related to the use of a single rapid test. At that time, it was decided to change the recommendation which had been issued in 1989 to withhold preliminary positive test results until they had been confirmed but, at the same time, attempted to take additional steps in order to make additional rapid tests available in order to improve the predictive value.

Our experience basically in other settings, and I will present a little bit of this data, in the use of two different rapid tests suggested that this would substantially reduce the difficulty with false-positive tests. We have gained additional experience, which I will not have time to present today, about counseling on the basis of a single rapid test, as well as patient interest and acceptance of rapid test results, which indicated that this was a prudent step to take because of the potential benefits for the number of people who would learn their serostatus.

[Slide]

The difficulty with predictive value at rates of different prevalence is illustrated in this slide, in that with a test with the approximate sensitivity and specificity of the currently available test is published at 99.6%. There is a substantial difference at different testing sites in the United States, ranging from a 96% predictive value positive for individuals in testing sites with a high prevalence, such as STD clinics in major urban centers where prevalence is as high as 10%, but overall in the United States our average prevalence is between 1% and 1.5%, which would give us a positive predictive value using a single test of only approximately 67%.

[Slide]

The CDC had conducted some additional studies looking at a combination of two rapid tests according to the World Health Organization algorithm for HIV testing in diagnostic settings.

[Slide]

The results of that test are presented on this slide, which is probably too much information in order to comprehend it. But essentially a combination of any two screening tests where there were two EIAs, an EIA and a rapid test, or two different rapid tests in the circumstance of prevalence of approximately 1.5%, which we experience as average overall in the country, would dramatically increase

the predictive value positive to these tests to approximately 100% by using those two combinations.

On the basis of this, the CDC is seeking manufacturers to make available additional rapid tests for use in the clinic settings so that we can gain both the benefit of additional individuals learning their HIV serostatus, as well as a reduction in the number of people who would be given an initial false-positive test result.

[Slide]

The summary from that meeting in October resulted in the March 27, 1998 recommendation that the need for the rapid test exists. Because there are single rapid tests with high sensitivity and specificity available, it is prudent to use these in clinic activities depending upon the specific circumstances at the clinic. We found, in addition, that the rapid test would be significantly cost effective in public health settings, and are seeking to increase their implementation in settings of publicly funded counseling and testing. Thank you.

DR. HOLLINGER: Any specific questions at this time? We are going to discuss this later on but any burning questions from the Committee right now? If not, let's go on with the next presentation. Ken Shockley, from Murex Diagnostics that produces one of the rapid tests, is going to be speaking at this point.

Murex Diagnostics Presentation

DR. SHOCKLEY: I would like to thank the Committee for giving Murex Diagnostics an opportunity to present data obtained from two recent studies of the SUDS HIV-1 and HIV-1+2 tests.

The objectives of the evaluations were to determine the performance of the existing assays for HIV-1 and HIV-2 samples. The studies were performed externally by Dr. Niel Constantine, University of Maryland, and Dr. Richard Bristow, from London.

The SUDS HIV-1 test and its counterpart, the SUDS HIV-1+2 test are manually performed, visually read 10-minute immunoassays for qualitative determination of antibodies to either HIV-1 or HIV-2 in serum and plasma. Both tests utilize a proprietary marker filtration immunoassay procedure, and with the HIV-1 test the solid phase is a mixture of marker particles which are coded with HIV-1 gag or p24 protein and a synthetic envelope peptide which represents an immunodominant region of the HIV-1. The HIV-1+2 test is similar in that it has the gag and HIV-1 peptide but we have also inserted as peptide that represents of the HIV-2 protein as well. The SUDS device is a plastic cartridge that does not contain reagents prior to adding the components.

[Slide]

Both the HIV-1 and HIV-1+2 tests are performed similarly. So, I am going to show the schematic of the HIV-1 test rather than trying to do both of them. The tests are performed by placing one or two drops of serum or plasma into the cup, adding a diluent, then putting one drop of a combined latex capture reagent, incubating that for three minutes. The liquid is allowed to absorb into the device. A wash reagent is added, followed by an enzyme antibody conjugate. That is incubated for three minutes. We follow that by a second wash; a substrate, which is a precipitating substrate, for two minutes, then we stop the reaction; flip the device over and read the reaction. Any blue color that appears in the center circle is a positive result of the test. The two outside wells are wash controls to make sure that the wash reagents are added in the correct order. If they are not, the outside wells will take on a grey to a blue color as well and it is an invalid test.

[Slide]

The data are as follows for the two studies. At the University of Maryland 55 samples were tested; 20 of those were HIV-O samples; 18 were HIV-1/2 duoreactives; and 12 of those were HIV-2 only samples; and 5 were non-reactive. As you can see, the expected reactivity on each of those was supposed to be reactive for the first 3 and then negative, and the SUDS performed well in detecting all

the reactivities in each of the samples.

We saw the same sort of pattern at Murex Biotech, in London. Of the 75 samples that were tested, 39 of those were HIV group O; 25 were HIV-2; and 11 were categorized as HIV-M. Again, both the SUDS 1 test, which is licensed for distribution in the U.S., and the 1+2 test which is being distributed outside the U.S., detected all of the samples, including the HIV Os. Although both tests performed well on the O samples and the HIV-1 test performed well on the HIV-2 samples, we are working currently with the scientists at Abbott Laboratories to evaluate and integrate into both tests a specific subgroup O capture reagent. Thank you.

DR. HOLLINGER: Thank you. The next presentation will be by Dr. Constantine, from the Institute of Human Virology, University of Maryland.

Data Presentation

DR. CONSTANTINE: Thank you. Good afternoon. I think we had better jump right into the slides.

[Slide]

Our laboratory is at the University of Maryland, the Institute of Human Virology. These three individuals are the ones that actually did the testing for the study I am going to describe.

[Slide]

The information I am going to present today is

part of a study that was published in November of '97. I have some reprints if you would like. That study looked at 7 of these 8 rapid assays, none of the confirmatory assays, and we have since expanded that. I am not going to include in today's presentation the information you just heard from Dr. Shockley on the SUDS test but, rather, other additional tests.

[Slide]

Our objective was to determine the ability of 8 internationally available rapid screening tests to detect a series of variants, but today I am going to describe just the group O variants.

[Slide]

We had 24 samples well characterized as group O. All came from Cameroon. They were characterized by Lutz Gurtler's lab in Germany, using a variety of techniques, generally an ELISA that incorporated group O. This is a commercially available ELISA in Europe, and they compared results to a competitive ELISA that does not include group O. They also used a V3-loop peptide EIA that included both the antigens of the major types of group O, subtypes I suppose. We also ourselves had the samples tested by an ANT-70 synthetic peptide ELISA here, in Rockville, at Biotech Laboratories, to confirm that they were, indeed, group O samples. Some of the samples were tested by V3-loop

sequencing but not by ourselves.

[Slide]

The assays that we used, again, are all commercially available, part of the 54 rapid assays that are available worldwide. Four of these, the HIV-Spot, the HIVCHECK, the Quix and the Multispot, are all flow through type dot blot assays that we all have been quite familiar with. The A/Q rapid assay and the Genie are the new technologies with the chromatographic movement. The Immunochrome is an ELISA actually in a dip-stick format. It is a little bit longer than rapid. Serodia is a very widely used particle agglutination assay used widely in Asia.

[Slide]

The confirmatory assays that we looked at were 3 Western Blots. We included the FDA-licensed IFA assay also.

[Slide]

A few notes on quality assurance -- we did all the testing. We followed the manufacturer's instructions. We tested each sample once but we had three technologists interpret the results. Any sample that produced discordant results following interpretation, discordant from what we expected it to be, were retested one time only, and this was because of limitations in sample volume, as you can imagine and appreciate.

Importantly, if we had a discordant result between

the initial testing and the repeat testing, we used the latter result as the final result. So, we kind of used it as if that second test was a repeat assay in duplicate. So, we used that last value.

[Slide]

Final results, positive, negative or equivocal -- we did have some we just couldn't decide if they were positive or negative and even on repeat they were repeatedly equivocal. So, that is what we left them at. We did not include equivocal results in the calculations of sensitivity because we felt that if there was any suspicion about the status of a sample, that would not be used for transfusion or whatever and another test would be done. So, we didn't want to penalize a manufacturer if the test showed something was happening.

[Slide]

Our results are as follows: There are 6 samples that produced some sort of discordant results between the 8 rapid assays. I point out here, due to time restraints, that 1 sample, 021, was actually falsely negative in 3 of the rapid assays. The sensitivity is shown over here, and 5 of the assays picked up all 24 group O samples; 3 of the assays had sensitivity a bit lower than that.

An important point here is the Quix assay is the only one that has the ability to differentiate infections

since it has three separate spots, one for HIV-1, one for 2, and one for O, and I think there is also verification that these were, indeed, group O samples. You see that 5 of these 6 samples reacted with the group O antigen specifically.

[Slide]

For the confirmatory tests -- you can't read this but I just want to show you this is the IFA and all 23/24 samples were reactive, confirming infection by the samples.

As far the Western Blots discordants, there were 7 samples that were discordant, again, this 021 being extremely problematic in the sense that all 3 blots produced indeterminate results on this sample, whereas for every other sample at least one of the Western Blots picked it up as confirmed positive.

I might also note that as far as specific reactivity to antigens, almost all samples reacted with the gag and the pol 31 and 32. There were only 2 samples, I believe, that reacted in any way with envelopes. I guess 2 samples, 3 tests that reacted just weakly with gp160, and I think this would be expected.

[Slide]

So in conclusion, most of the 8 rapid assays do have the ability to detect group O samples to different degrees. There was 1 group O positive sample that proved to

be problematic for a number of tests. I suppose we can say rapid tests, at least the ones we looked at, do vary in their ability to detect all group O samples.

[Slide]

As far as the Western Blots again, they vary in their ability to confirm infection by HIV-1 group O. The range there was 71-92% and none of the 3 Western Blot assays could confirm infection in all samples. The IFA, however, did, and this is similar to reported results from I believe Schable's study. The indeterminate results included reactivity primarily to gag and pol, with weak reactivity to the envelopes. All essentially had reactivity to the pol gene product 31, 32.

[Slide]

I might conclude by saying there are 6 published studies with the serologic reactivity to group O samples involving commercially available assays, not research ELISAs with group O and so forth. For these 6 studies, you can see the sample sizes were relatively small because these samples are quite difficult to acquire. Ours was the largest of the published studies, using 24 samples. Ours was the only one that specifically looked at rapid assays, at least the published report that I mentioned, but some other studies used a larger variety of assays.

But the important point here that I think we

should note is that in every case, all six of these studies, there seemed to be some problematic samples of group O. Most assays picked up most samples but there were a few samples that were problematic for more than one assay. I will conclude with that. Thank you.

DR. HOLLINGER: Thank you. The next presentation is by Dr. Michael Busch, from Irwin Memorial Blood Center.

Data Presentation

DR. BUSCH: Thank you. I would like to share new data on the distribution of non-B subtypes within group M within the U.S. donor setting. To put that into context, we have heard a lot of data today about group O, and everyone is well familiar with the problems in sensitivity to group O, and the surveillance activities that have been conducted to detect group O.

[Slide]

There is much less surveillance going on in terms of the subtypes within the group M, which is the major group that is then further subdivided into 9 different subgroups, and this is distinct from the group O types which have a similar diversity of subtypes within group O.

[Slide]

The concern over the non-O group, the group M subtypes with respect to serology is a little less clear but I am going to share a little bit of data that suggests that

we should be concerned about that.

This slide just illustrates that all of these different subtypes and groups are found in Central Africa and, clearly, global trafficking is the basis for the spread of the different subtypes geographically, with the early seeding of subtype B particularly in the U.S., South America and Europe and subsequent transmissions to other regions of the world, probably secondary to trafficking to North America into blood derivatives internationally. But over the last few years, particularly in Europe and Asia, there has been extensive detection and in some countries just overwhelming expansion of non-B subtypes. In the U.S., I think there are only 19 published non-B subtypes, although I think we heard earlier that there are probably twice that many that have been identified by CDC.

[Slide]

The concern over non-B subtypes in the donor population is illustrated by two studies I want to quickly share, both published. This study, French group, Courecet and colleagues, monitored for subtype prevalence in their donor pool, going back to samples collected from '85 and then through '96. They serotyped these samples, which is relatively accurate but does have problems both with inappropriate classification and sensitivity. So, overall of the 508 samples, 466 could be serotyped.

What they observed was that 11.5 % of those samples were determined to be non-B based on serotyping, with type A and type C predominant but a few Ds and a few would appear to be recombinant viruses. Interestingly, 80% of the samples that were from African-born donors who were donating in France were non-B. Also, almost 10% of samples from European-born donors were non-B. So, they were clearly detecting transmissions of non-B infections within European-born individuals.

[Slide]

When they looked at the prevalence by period from the period of '85 through '89, little less than 5% of the donations were non-B. This really increased dramatically over the decade with over 20% of donations in the more recent period, '94 to '96, being non-B group M infections.

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The importance of this is illustrated by what is probably the only study looking at sensitivity to window period of the B versus non-B group M infections. In this paper, published a year or so ago again by a French group, they were able to detect a number of seroconversion cases for both B and non-B in a study that was focused on detecting people with primary HIV infection, people presenting with symptomatic primary HIV syndrome.

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They were screening this population with p24 antigen. In the screening period they picked up a total of 19 persons who were antigen positive and antibody negative, negative Western Blots. Then these people were followed and they collected samples downstream after the people seroconverted to antibody positivity, and then subtyped them. They detected 10 cases that were subtype B early seroconverters and 9 that were non-B. What they then did was to compare the sensitivity of second-generation viral lysate test versus 3 different new third-generation assays, the Abbott combi test and then 2 European assays that are third-generation antigen sandwich format assays using recombinant envelope and gag antigens.

What they documented was that in the B subtype infections the change from the second-generation to third-generation formats dramatically increased the ability to pick up the early seroconversion antigen positive samples. So, whereas only 40% of the samples that were antigenemic could be detected by the viral lysate EIA, 70% to 90% were now detected the antigenemic prebleed by the improved format third-generation assays, which were built and designed and have been known to have enhanced sensitivity to early seroconversion.

In contrast to that, when they looked at the non-B seroconverters the rate of pick up for the prebleeds was no

different, 22%, 22.11% and 33% with the third-generation versus the second-generation assays.

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This is illustrated here sort of graphically, just looking at the single to cutoff of the different assays, the Abbott second generation, on the prebleeds. So, you can see that the prebleed from the B and the non-B on the viral lysate test were all low reactivity, mostly negative, whereas with the third-generation assays their sensitivity to the group B early infections were dramatically increased, dramatically higher compared to the non-B where there was no improvement.

So, the point of this paper was that these new third-generation format assays that have reduced the window period from probably about 40 to less than 20 days, have done so for group B seroconversions but do not appear to have increased sensitivity for the non-B group infections which are potentially being transmitted in some regions of the world.

[Slide]

So, the question that we have been interested in is understanding the distributions of these non-B subtypes in the U.S. donor setting. In a study that has been going on for about four or five years, we have been monitoring the prevalence of non-B infections in whole blood seropositive

donors. We have included in this analysis actually studies retrospectively to understand the distribution of subtypes and the diversity within subtypes dating back to the earliest epidemic in the U.S. This is a collaborative study, as you can see, from a number of people, particularly some Brazilian colleagues, Fogarty fellows, who did most of the subtyping work but also a lot of collaboration from Red Cross colleagues, and particularly support and collaboration from CDC.

[Slide]

So, what we did was to subtype infections beginning with 3 different groups. The bulk of the people were contemporary seropositive donors, collected and identified as seropositive, enrolled in the CDC donor study over the last 3 to 4 years. For comparison, we went back in time and we selected donors who were identified from the Transfusion Safety Study. These donors were found to be seropositive from a repository of samples that were stored during the 6 months before the HIV test became licensed. So, these are seropositive donors identified just when the test became available, in '84, '85. To get an even earlier picture on diversity, we went back and identified samples from 49 hemophiliacs who were known to be seropositive at their first sampling between '82 and '84. We reasoned that in order for these people to have acquired infections and

been seropositive by that point, that the donors who those people acquired the infection from probably were plasma donors back in the period of 1980 or earlier in order for the plasma to have been given and processed into derivatives and then have been transmitted in turn to these hemophiliacs. So, this is kind of the earliest picture of viral diversity within the U.S. population.

[Slide]

Then, these subjects were all enrolled in either the Transfusion Safety Study or the CDC study and cells of plasma were processed and then DNA or RNA was extracted. The bulk of the work was done using DNA extracted from cryopreserved buffy-coated PBMCs. If those samples were not available or were negative, then we went to plasma and reverse-transcribed the plasma. The subtyping was predominantly based on a method called heteroduplex mobility where you amplify the envelope gene and then you admix the envelope amplified product from each of the donor samples with a battery of separate subtypes in separate reactions, and I will illustrate that in a second. Basically, the principle of this is that if the sample is homologous to a particular subtype it will form homologous heteroduplexes, or closely related heteroduplexes that will migrate rapidly through a gel. It is the relative ability of the heteroduplexes between the different subtype prototypes that

allow you to discriminate which of the 8 major HIV subtypes the sample is represented as.

[Slide]

This just illustrates this. So, each of the donation samples are envelope regions amplified up. Then, that is mixed separately with amplified products from 8 different known prototypes. In some cases there are actually 3 or 4 different strains from different types. Then, those samples are denatured together in a tube, then reannealed by cooling. What happens when they reanneal, you both form homoduplexes where the sample amplified product reanneals with itself and the prototype reanneals with itself, but you also form heteroduplexes, which is the annealing of the prototype with the complementary strand from the sample.

It is these heteroduplexes which determine the relatedness of these heteroduplex sequences that have hybridized, determine how rapidly these migrate to a gel. So, if the sample is type B the heteroduplexes will migrate rapidly when they are formed with type B prototypes, but much more slowly up above the single stranded region with the non-B prototypes. This is a fairly standard and widely used method for subtype assignment.

[Slide]

If there was a problem with being able to get a

subtype for the non-B samples, they were verified with sequence analysis, and if we couldn't amplify up the product then they were further studied in terms of methods to understand why they didn't yield single. But also we serotyped them in collaboration with CDC to both rule out group O and HIV-2, and also serotyped them to the extent that serotype assays were possible.

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Now, to make a long story short, all of the samples from the hemophiliacs and the '85, '86, early blood donors, were typed as group B. Whereas among the 405 subjects who were from the current donor population, we could type 95% of them by HMA typing, and by HMA typing we detected the vast majority as B, there were 2 type A detected and 1 type C detected. And, 22 of the samples could not be typed by HMA and were subjected to peptide serotyping. Ten of those could be typed and were B; 1 was a C, and 1 was an HIV-2 infected donor.

The other samples all had seroreactivity from group M but could not be further subtyped. So, the samples that could not be subtyped here were not group O. So, we didn't detect in this study any group O infections, but we did detect actually 2 As and 2 Cs.

[Slide]

All of these non-B subtype infections were

confirmed by sequence analysis. This is a phylogenetic tree and it shows that the samples that we detected as group C clustered with prototype group A sequences. So, the As groups with A, the Cs grouped with C. And, all of the samples that were somewhat problematic or had slower migration were questioned from the study that were classified as B, confirmed out as B based on sequencing.

[Slide]

The four non-B subtypes are interesting case studies. Two of them were persons who before the newest African deferral criteria were placed donated. One was an A, a 40-year old male who was born in the Ivory Coast, which is a subtype A endemic country. This person's exposure within Africa was heterosexual contact. Another was a recent immigrant, a 34-year old male from Botswana whose only risk in Africa was also heterosexual contact. So, these two were imported cases of non-B subtype. Virtually all the reports to date of non-B in the U.S. have been imported. Either people have immigrated or military personnel, for example, who were infected while in Thailand and then went on to seroconvert, and then were subtyped and were determined to be infected there with an endemic strain there.

But in contrast to that, there is actually only one published report from the CDC from a study in New York,

in the Bronx, of a transmission in the U.S. of group A, where a person was found in a high endemic population, high immigrant cluster of people within the Bronx, to harbor a group A infection and that person had not been in Africa and, in fact, didn't have a discrete unequivocal exposure to a group A-infected person. So, that is in the non-donor setting.

Two of the four cases that we detected appeared to be similar U.S. soil transmissions. One is a 28-year old black female, born in the U.S.; had never traveled outside the U.S., and the only exposure was heterosexual contact with U.S. born persons. So, it is unclear who she acquired the infection from.

The second case was a subtype C, a black male, again, born in the U.S., with no travel or exposures to known non-U.S. born people. So, these two appear to be two of the known three U.S. soil transmissions of non-B infections.

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If we look at this by demographics overall, of the total group studied 4/534 subtyped individuals were determined to be non-B. By male/female, interestingly, 3 of the non-Bs or 2% of the females typed hybrid non-B infections. So, it appears as if, you know, heterosexual transmission is probably the route we will predominantly

see, especially now that we have reimposed the exclusion of sub-Saharan African immigrants. Race ethnicity -- all 4 of the non-B subtypes were found among black individuals. So, 2% of that group are seropositives.

[Slide]

A third of the samples from African born persons were non-B, which is no surprise because B is actually relatively unusual in Africa, whereas there were 2, or 0.5% of U.S. born persons non-B.

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In terms of region in the country, 3 of these individuals gave their seropositive donations in the North Atlantic region. This is actually an error. This case is a north central region case. So, a single case was outside of the sort of northeast cluster.

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In terms of risk factors, 2 of these cases, as I have described, or 12% of those born in non-B clade countries harbored -- either born or had heterosexual contact with persons were non-B subtypes. And, 2/178 cases from persons who denied classic risk factors were non-B.

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Beyond the ability to look at the subtype, we were also able to look at the diversity within the group B infections over time, comparing the heteroduplex mobility

distance among the hemophiliacs from the very early '80s, the donors identified in the mid-1980s, with the donors identified in the 1990s.

What you can see here is the relative mobility distribution plots. The bottom line here is that within group B the virus in the U.S. is evolving over time and becoming more divergent from the early prototypes. It is probably not important for the purposes of blood screening, but is important for purposes of vaccination that the virus that is, for example, in the current prototype vaccines is predominantly based on very early isolates, and as virus is continuing to grow and expand in the population within group B it is becoming more and more divergent.

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So in conclusion, HIV clade B is still by far the predominant subtype in the U.S., but within clade B we are seeing evolution. But there is a need for continued surveillance for non-B because we are now documenting a low percentage overall, about 1%, of U.S. blood donors who are infected harbor non-B group M infections. Thank you.

DR. HOLLINGER: Thank you, Mike. The final presentation in this session is on the spectrum of U.S. kit sensitivity. Dr. Koch?

Spectrum of U.S. Kit Sensitivity

DR. KOCH: The data you have just heard from Dr.

Busch underscores the need to assure that tests used in the United States are able to detect HIV infections by genetic variants other then group M, B subtype that is most prevalent in the United States.

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Just to remind us of the phylogenic distribution of the major group M subtypes, they are distinguished from one another by approximately 30% intrasubtype genetic divergence in the envelope region and 14% intrasubtype differences in the gag region. The 5 major clades of group M, that is A through E, represent 95% of the HIV infections worldwide. Where multiple subtypes are prevalent intrasubtype, recombinants arising due to dual infections adds to the genetic diversity and complexity of the subtype profile of a population, thus generating clades F through I. But these are relatively minor contributors to the overall pandemic of the world. Certainly, as a reminder, group O, the numbers of total cases in the world have been discussed on the order of 100 to 400. So, it is a relatively minor contribution to the worldwide pandemic.

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Geographically, as Dr. Busch also showed, this map just shows approximate locations where persons infected with certain HIV strains have been reported, but not their actual distribution which in many cases is actually unknown.

Moreover, the distribution of HIV, one subtype within a given population, is certainly in constant flux. So, at any given point we would only have a snapshot of what is a continuously evolving situation. Thus, it is all the more important that we assess the ability of serologic tests used in the United States to detect samples from individuals infected with HIV-1 variants other than the group M, subtype B that is the most prevalent in North America.

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We have undertaken the beginnings of such a study, looking at 6 FDA licensed tests. We chose the following tests because they represent the EIAs that are predominantly used in the blood screening arena, and chose to look at the one licensed rapid test as well. We might have looked at others but we were primarily limited by sample volumes in some of these cases. So we thought, rather, to look at only the following tests here. A panel of 250 HIV-1 subtype specimens from Asia, Africa, South America and the United States were assembled for this purpose.

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On this slide you can get a sense for the global distribution of these, and the sort of numbers. To date, as best we know, this is the largest such panel ever assembled and it comes together from 3 different sources. We have collaborated with scientists at the CDC from the global

surveillance program, and the largest number of samples in fact come from this particular surveillance and collection effort. We have also worked with scientists performing domestic surveillance, specifically targeting African nationals who have come from countries where non-B subtype strains are endemic. Finally, we took advantage of a commercially available panel sold by Boston Biomedika, a worldwide panel, and included it to round out the numbers of some of the less represented subtype variants.

A key feature of this collection that I wish to note is that although all the specimens have been characterized genotypically, the most definitive method of establishing the phylogenetic subtype, in some cases they have been sequenced in several gene regions but, at a minimum, they have all been sequenced in the envelope region. So, this represents strains which were well characterized at the genetic level.

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This is work in progress, but it is almost completed. But I thought it important to share with the Committee at this time the data that we have in hand. In some cases where the full set of 250 have not been tested, this is due to lack of sufficient sample volume, but we believe the results are very encouraging since the vast majority of specimens were detected by all tests, including

the one rapid test approved for diagnostic use.

I am allowed to call these A, B, and C rather than to identify them. In EIA for HIV-1, 226/229 were detected. For test B, 247/250, and test 3, all 250. For the HIV-1/2 combi test, EIA test A detected all 235 tested, whereas test B detected 247/250, and for the rapid test, 218 were all detected.

I would like to make some comments on the samples that were missed. For the 3 tests that missed 3 samples each, in each case 1 of those specimens was the LA group O, an infection that is known to be a challenge for many of the serologic tests out there, and you have heard this at previous meetings. The other 4 specimens that were missed are samples which are within the BBI worldwide panel, and they have been variously detected by one test or another, but they have a hallmark of being weak positives in most tests or, where they are missed, they are borderline negatives.

Western Blot patterns for these specimens are incomplete, 2 of which have actually been genotyped as subtype B, the other 2 being untypable because of the failure to generate amplicon. But a hallmark of the Western Blot patterns is that they all show antibody responses to p24 but lack gp41 and, in many cases, have weak or missing bands at gp120 and 160.

Further, a third-generation sandwich assay, specifically the Abbott HIV-1/2 combi test, and this is information that is well-known because it is supplied with the panel, gives a very strong positive signal with all 4 of these samples, which suggests that it may be detecting an IgM specific response and, in fact, the 4 samples that have been giving some tests trouble are perhaps seroconversion bleeds. At least that is one reasonable explanation of the pattern that has emerged from the serology. So, for this reason we believe that the 4 specimens that are sometimes missed in these 6 tests that we have looked at are not due to genetic variation but, rather, are due to the stage of the immunological response of the HIV B infection that was being studied.

Analysis of large repositories of blood samples from persons in the U.S. has provided evidence for HIV subtypes other than the well characterized group M subtype B. I might mention that, in collaboration with Patrick Sullivan and Charlie Schable, of the African national study, we were able to look at 31 non-B group M variants, and they were all cases that were immigrated into the United States. It gives you a sense for the kinds of numbers that are confirmed when added together with the data that was just presented.

Although the vast majority of HIV infections in

the United States have been subtype B, the major group of HIV-1, occasional detection of individuals infected with HIV-1 non-B variants indicates that multiple HIV introductions to North America have occurred and are probably continuing.

Further, the global emergence of new HIV group M variants, especially the intrasubtype recombinants with mosaic genomes, will continue to pose challenges for diagnostic tests. But the data that we have generated here I think suggests that the tests currently in use in the United States will be able to meet those challenges.

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I would simply like to acknowledge a large number of people who made this collaboration possible: Tim Dondero, Dale Hu at the International Activities Branch at CDC, Charlie Schable, Tom Folks, Renu Lal at the HIV Retrovirology Branch -- Renu Lal did all the sequence analysis for these 250 samples, Patrick Sullivan of the Division of HIV AIDS, in our laboratory Chuck Roberts, Kori Francis, Jack Shawever and Melissa Benjamin did all the actual testing, and I would like to thank Steve Alexander at Ortho for supplying us generously with several group O specimens.

We can put the question up but before we actually ask the question, I would just like to underscore again the

following considerations, now shifting gears back to group O. Firstly, I would like to remind the Committee that there are only a few hundred cases at most of HIV group O infections worldwide, most of which are in Cameroon or surrounding countries. Secondly, there have only been two cases of HIV-1 group O that have been found in the United States, and none in the last two years. Finally, most of the rapid tests already exhibit a very high sensitivity for detection of group Os.

So, with these facts in mind --

DR. HOLLINGER: Why don't we hold the question right now because that comes later on anyway and we still have some presentations to go over right now.

DR. KOCH: Right.

DR. HOLLINGER: We are now moving into the open public hearing, and there are six companies that have asked to speak during this open public hearing. They have been told to try and limit their talks to ten minutes. So, we are going to start first with Abbott Laboratories.

Open Public Hearing

DR. SCHOCHETMAN: Thank you. Good afternoon. I a Dr. Gerald Schochetman, Director of AIDS Research and Retrovirus Discovery for the Abbott Diagnostic Division, Abbott Laboratories.

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Over the past 17 years, the epidemic of HIV infection has created many challenges for those working to develop serologic and genetic tests to screen for and diagnose HIV infection.

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Perhaps the greatest challenge comes from the realization that HIV is not a single virus but a group of related viruses. The remarkable genetic heterogeneity of HIV has enabled certain HIV strains to potentially elude detection by some commercially available serologic assays. The HIV variants that have caused the most concern recently are a specific subset of the HIV viruses, known as the HIV-1 group O viruses, and as you heard this morning, possibly the YBF group of viruses.

[Slide]

Two groups of HIV are known to infect humans, HIV-1 and HIV-2. Within the HIV-1 and HIV-2 species, groups of viruses referred to as subtypes have been identified. We currently know of at least 10 genetically distinct subtypes of HIV-1 within the group M or major group of viruses. These subtypes have been termed A to J. In addition to the HIV-1 group M viruses, another group of viruses that are quite genetically distinct from them were recently identified and named HIV-1 group O for outliers. As with the group M viruses, group O viruses also contain a

collection of highly divergent viruses. Within the HIV-2s at least 5 or possibly 6 subtypes have been identified.

It should be pointed out however, that although HIV-1 subtype B is the most prevalent subtype in the developed world, and is the basis of virtually all screening tests, it only represents 1/30th of the total global HIV infections. Although the genetic diversity is greatest in Africa where most subtypes are found, subtype distribution is increasing in other areas of the world as well due to population interactions and migrations. This led the FDA to coin the term "global village" referring to the fact that any variant anywhere in the world is only a plane ride away from anywhere else in the world. Therefore, it is absolutely critical to monitor for the changing dynamics of HIV infection worldwide to ensure the continued successful detection of new viral variants.

As our understanding of HIV genetic diversity increases, knowledge of newly emerging HIVs, such as the group O viruses, together with the frequency and changing geographic distribution of known HIV variants, will play an important role in the timely and effective response by manufacturers to their continued detection. Accomplishing this requires an extensive ongoing global surveillance program to monitor the dynamics of HIV evolution and, in particular, the emergence of new divergent HIV variants.

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That is why Abbott Laboratories has undertaken the development of a strong worldwide surveillance network to identify and characterize new as well as existing HIV strains. Our network has been established in collaboration with many of the leading AIDS researchers in the world and allows us to systematically sample HIV variants on a long-term basis. As you can see from the map, our current sampling sites represent diverse geographic areas of the world containing all of the major HIV variants, including the region endemic for YBF.

[Slide]

To date, we have collected and subtyped over 500 samples representing HIV-1 group M, group O, and HIV-2. As you can see, our collection also contains mixed or mosaic viruses containing genetic information from multiple HIV subtypes. Even the subtype E virus, on the left, which predominates in Thailand is actually a mosaic with subtype E in the env gene, and subtype A in the gag and pol genes. The ability of HIV to undergo recombination allows for even greater genetic diversity of the virus. I would like to point out that a large number of these 500 samples are present in sufficient volume to become members of our performance panel for evaluating Abbott's HIV assays to ensure detection of all known variants. We continue to

increase the number and geographic distribution of our collection sites, and will also continue to add additional subtyped HIVs to our existing collection.

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Genetic characterization of HIV variants can be complicated by the potential for recombination between distinct viral subtypes yielding mosaic viruses. Therefore, all the HIV specimens we collect are sequence characterized across the viral genome to address identification of mosaic or recombinant viruses. As you can see from the slide, this is accomplished by sequencing the full-length p 24 protein from the gag gene, the full-length integrase or pol I protein from the pol gene, and the immunodominant or IDR region of the gp41 protein from the env gene. When necessary, we also sequence the V3 region of the gp120 protein in the env gene.

To date, we have also sequence full-length gp160s from 13 HIV-1 group O viruses. However, because the most important viral region for HIV detection is the immunodominant region or IDR within gp41, we have sequenced the gp41 protein from a much larger number of our group O viruses.

[Slide]

Sequence analysis of the IDR from 20 group O viruses, including 3 from the Los Alamos HIV database and 17

that we sequenced, demonstrates that among these viruses there is a substantial amount of genetic variation throughout IDR region. Similar data has been generated by Dr. Lutz Gurtler, in Germany, for an additional 22 group O viruses. Interestingly, the variant HAM112, highlighted in yellow on top, possesses a consensus sequence in the IDR for all 42 of the group O viruses.

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The combination of extensive sequence variation coupled with the limited number of epitopes or antibody binding sites within the IDR, schematically represented by antibody binding sites F, G and H, raises considerable concern for the ability to detect some HIV-1 group O samples using only a peptide. This is represented schematically by the large yellow X through the IDR region. The same would hold true for the HIV-1 group M viruses. Because of this possibility we have chosen to use a large gp41 recombinant antigen containing many epitopes in addition to the IDR. This is schematically shown as epitopes A through M, including the IDR F, G and H epitopes. The use of a large gp41 recombinant antigen increases the possibility of detecting all known HIV-1 group O variants due to the presence of additional common antibody binding sites. The greater number of distinct binding sites displayed on the recombinant antigen increases the chances of detecting

antibodies to a variety of HIV variants. This was first evident to us with HIV-1 group M subtype D and E samples, which were not recognized by a competitor's assay that relies solely on peptide antigens. These antigens were, easily detected using the Abbott assay containing large recombinant antigens.

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In this slide we have summarized the genetic variation within the IDR from all 42 of the group O viruses we analyzed. As you can see, there is considerable sequence variation within the important antigenic recognition sites as shown by the regions under the arrows. Even the cysteine residue in the highly important cysteine to cysteine loop shown in the boxed area can change. This is shown by the change of a C or cysteine residue to an F or phenylalanine residue. This change would not only lead to a loss of the important loop structure but also to its antigenic activity, thus, decreasing the ability to detect such an HIV variant.

The superior performance of assays using large recombinant antigens in detecting group O viruses versus assays relying on group O IDR peptides is clearly demonstrated in the next slide.

DR. HOLLINGER: Could you bring your presentation to a close? You have about half a minute.

DR. SCHOCHETMAN: Okay.

[Slide]

This slide shows a comparison of the performance of Abbott's PRISM HIV-1/2 group O assay compared to two licensed European HIV peptide based group O assays, A and B, against six HIV-1 group O samples. PRISM is a blood bank screening system currently under review at the FDA. The PRISM assay uses large recombinant group O antigens for both the solid phase and the conjugate. In contrast, assay A uses the ANT 70 group O peptide on both sides of the assay, while assay B uses a group O IDR peptide for its conjugate. It is clear from the data that not only are the PRISM signal to cutoffs greater at each dilution, but that strong reactivity is observed for PRISM even at significant dilutions. The endpoint dilutions for 5 of the samples exceed 1:10,000. However, these samples in the peptide based assays are either weakly reactive or in many cases negative, as shown by the yellow highlighted signal to cutoffs which are less than 1 or negative. This is especially true for sample #2156 that is a low antibody titer sample. This sample is still positive in the PRISM assay at a 1:1600 dilution whereas, the peptide assays for this sample are negative even at a dilution of 1:100. The strong reactivity generated by the PRISM assay clearly provides for a greater margin of safety in detecting HIV group O variants, and low titer samples, which may not be

provided by the two European licensed peptide based assays A and B.

[Slide]

In summary then, Abbott has undertaken a three-step strategy to deal with the continuing issue of HIV genetic variation. In the first part of our strategy, we have developed the ability to pursue a rapid response for the identification of new HIV variants. This includes an extensive ongoing global surveillance program to identify new HIV variants, the evaluation of our HIV-1/2 immunoassays to ensure detection of all known viral variants, and the ability to focus our reagent modifications specifically to those reagents affected by a particular virus variation. For example, the inclusion of group O antigens to ensure complete detection of these viruses.

[Slide]

In the second part of our strategy, we have made use of large recombinant antigens that provide a larger number of common antibody binding sites to better guarantee the detection of all HIV variants.

[Slide]

In the third part of our strategy, we continue to develop a large performance panel containing all known HIV variants to ensure detection of HIV infections across all Abbott testing systems.

Scientifically, we believe that the combined effort of proactive surveillance for new variants, identifying well-characterized specimens for product evaluation, and the selection of antigens for assay development that maximize detection of HIV variants is the most effective means of staying ahead of this ever changing virus. The evidence from our PRISM HIV assay evaluations offers confirmation that with the inclusion --

DR. HOLLINGER: I am going to have to ask you --

DR. SCHOCHETMAN: I have about ten second.

DR. HOLLINGER: All right, ten seconds.

DR. SCHOCHETMAN: -- of large recombinant antigens there is strong HIV-1 group O detection. We are applying these recombinant antigens to all of its assay systems from beads to microparticles. This strategy allows us to cast the widest net so as to ensure the broadest detection of all HIV variants including the YBF viruses.

Dr. Jim Stewart will be presenting more information on our FDA submissions and our PRISM assay in the closed section later this afternoon. Thank you.

DR. HOLLINGER: Thank you. Please stay within the ten minutes because we have a lot of talks here, and I would suggest that you present what is really critical and pass over the things that are not critical or you will have to rush through these things at the end of your talk, which I

think is usually the most important thing that you have to say. The next group is Boehringer Manheim.

DR. BAYER: Ladies and gentlemen, Mr. Chairman, let me first introduce Boehringer Manheim as a company of diagnostics. So, we are now working together with our combined forces.

[Slide]

I will talk on antibody assays that were specifically designed for group O detection. My name is Hubert Bayer, and I am director in regulatory affairs in Manheim facility of Boehringer Manheim.

So, I will go briefly into the source of antigens used and go into commercial production for non-U.S. countries.

[Slide]

As a source of antigens we use synthetic peptides and recombinants derived from gp120 and gp41.

[Slide]

We tested them in an ELISA format. We looked to see gp120 and V3 peptides, the antigens derived from 2 different group O isolates on ANT 70 and the MPV isolate, and it was compared to the MM isolate which is a B subtype. Four samples were tested, two M and two O samples, and you see the best reactivities with the O samples were seen with the O isolates, with the O antigen, and vice versa, the

reactivity of the M samples was best with an MM isolate.

What you can also see here specifically is sample A37 and the diversity of reactivity even within the O group -- this sample is obviously better reactive with ANT 70 than with the MPV. For this reason, many people use this for typing of the assays, and it is best usable for screening.

[Slide]

If we go to gp41 synthetic peptides, in this experiment peptides from the M isolate and ANT 70 isolate from the O type were compared with 3 samples in a dilution experiment. You see again differences of up to 200 titer units between the reactivity of the O samples with M sequences and O sequences. In one sample, TI196, there wasn't even a positive signal reachable with the M sequence. On the other hand, you see that the M samples detected in various titers the M antigen and showed some cross-reactivity to the O sequences.

[Slide]

In this experiment we went to recombinant gp41 and tested it in a third-generation format, using the antigen on the solid phase as well as on an enzyme label in different combinations. You see at the lower line the optimal condition for group O detection where you have both sequences from group O. If you switch to only group O on the solid phase and missing it on the enzyme label, it has a

significant reduction and you lose sensitivity if you switch away from using the O sequences at the solid phase.

[Slide]

So, we realized subtype O detection in a third-generation format for our automated immunoanalyzers in a third-generation format. I do not want to go into it.

[Slide]

And, we tested at different sources available subtype O samples. So, we got the samples from Lutz Gurtler and from Francois Simon and from Cameroon it was Prof. Kaptue. In total, there were 28 samples tested. All of them tested positive. If we go into the reactivity we have a signal to cutoff ratio. You wee that 27 of these 28 samples showed higher cutoff ratios than 10, and only 1 sample was in the lower positive range. This sample was an early conversion sample from Prof. Kaptue.

[Slide]

In order to make sure that our performance characteristics of the assay were not impaired by including group O antigens, the assay was compared to a non-group O antigen-containing approved assay for submission to Paul. Ehrlich Institute in Germany, and you see the sensitivity to HIV-1 was equal in 553 samples, as well as the HIV-2 sensitivities, as well as seroconversion sensitivity tested by the commercial samples. Specificity was at about 99.8%,

which is state-of-the-art.

[Slide]

So in summary, I would state that we were able to develop group O reactive antigen. The antigens could be derived either from rDNA or chemical synthesis. We had some examples of low titers for both samples that could not be detected through cross-reaction with M group antigens, and we could show that incorporation in a third-generation format did not impair other performance characteristics. Thank you very much.

DR. HOLLINGER: Thank you, Dr. Bayer. The next presentation is by Genetics Systems Corporation. Is there someone here from Genetics Systems?

GENETICS SYSTEMS REPRESENTATIVE: I am sorry, there must be a mistake. We are going to present in closed session, not in open session.

DR. HOLLINGER: Okay, thank you. Genprobe?

[Slide]

DR. MCDONNOUGH: I would like to thank you for the opportunity to present today. I am representing Genprobe, Inc., from San Diego. We are a DNA/RNA probe company. I am Shernel McDonnough, director of research and development at Genprobe.

[Slide]

I will be speaking on detection of HIV type O RNA.

That is what we are working on. I will give you a brief introduction to Genprobe, brief introduction to our technology and then some assay performance data.

[Slide]

Genprobe was established in 1984 and has since become a world leader in RNA and DNA probe development. As we began working on viral pathogens, we became aware of a request of a proposal from NHBLI and we were awarded a contract, 67130, in September of '96, to refine an assay for detection of both HIV-1 and HCV RNA. That contract was extended three months ago to provide reagents for pooled plasma testing in the '98, '99 time frame.

[Slide]

Our strategy is to develop a cost effective, high throughput and fully automated system, the TIGRIS, initially for detection of HIV-1 and HCV RNA in a format compatible with individual unit testing.

[Slide]

We are developing a semi-automated system for interim use until the TIGRIS is commercially available in the United States.

[Slide]

The assay we are developing co-detects HIV and HCV. The assay objectives for the HIV portion of the assay are 100 copy/ml sensitivity, analytical specificity of 99.5%

and, of course, able to detect infection prior to seroconversion and, as we are speaking about today, detecting subtypes, including the outlier type O.

[Slide]

There are three technologies used in the assay, sample processing and amplification step that uses two enzymes that we refer to as transcription-mediated amplification and a detection step that we call the hybridization protection assay.

[Slide]

I will breeze through these slides. I just mentioned sample processing. It involves the processing of 500 microliters of sample.

[Slide]

Transcription-mediated amplification uses two enzymes, produces an RNA amplicon and gives greater than 10^9-fold amplification.

[Slide]

The detection uses a chemiluminescent-based probe. It is a homogeneous system so you don't have to wash at the end of amplification. It also includes an internal control. All steps are performed in one tube, and it has a high throughput.

[Slide]

These are the steps of the assay put together. It

takes about 90 minutes for an individual to process 200 specimens in the manual mode. It takes a little over an hour to do the amplification. An individual can process about 200 specimens in less than 6 hours, less than a shift.

[Slide]

This is the type of sensitivity data we see with subtype B. We have set our sensitivity at 100 copy/ml, and as we dilute a known titer virus into negative plasma, we see at 300 copies/ml 100% positivity. When we go below that titer copy level, 90 copies/ml, we also see 100% sensitivity.

[Slide]

We were designing the assay from the beginning to detect subtypes and variants. We use multiple approaches in each of the steps of the assay, including consensus, sequences, tolerance of mismatches and redundancy.

[Slide]

We can test the processes with RNA viral isolates and infected patient specimens. This is an example of looking at dilutions of an RNA that is made <u>in vitro</u>. At the bottom we show that with an <u>in vitro</u> transcript representing type O we have 100% positivity at 100 copies.

[Slide]

This is to remind me to point out that we have obtained viral isolates and infected patient specimens from

around the world.

[Slide]

And as large a number as possible. Type O is mentioned on top, 34 viral isolates and 19 different specimens we have tested to date.

[Slide]

Here is an example of testing. This is the MVO 5180, an we make dilutions of the tissue culture supernatant into negative plasma and the copies/ml are shown in the center column. Above our target level of 100 copies/ml we see 100% positivity. Also below that, at 80 copies/ml we still see 100% positivity. As you go down in copy level we begin to see not just a lower positivity rate.

[Slide]

Here are examples of group O isolates from Western Africa. We took each viral isolate, diluted it into negative plasma, determined copies/ml in an in-house assay and looked at the reactivity in the RNA assay. Very consistently, we see positive results above 100 copies/ml. We often see it below, as shown in the second panel with 90 copies/ml. In the bottom sample, even at 10 copies/ml we are seeing plus/minus results.

[Slide]

Here are viral isolates from France. Again, we are taking dilutions of the virus. Typically, we see strong

positives to 10^{-6} and occasionally even further dilutions are positive.

[Slide]

Here are infected specimens. Of course, it is very important to look at infected specimens because tissue culture virus represents a selective group. We notice a broader distribution of variants. Again, we have taken patient specimens. We have diluted them in normal plasma to above and below 100 copy/ml cutoff, and we see positivity again above the 100 copy/ml cutoff and often results positive below that, as you can see on this slide, at 50 copies, 68 copies we have positive results and plus/minus in the third case.

[Slide]

We have seen this very often today. What I wanted to point out is that these are just the type O variants using the gag sequences and what I wanted to point out is that we have looked at representatives of type O from around the phylogenetic tree or star. So, we are trying to make sure that we are looking at a diverse group of type Os.

[Slide]

This is just an example of type O specificity results we are obtaining with the RNA assay. We have looked at a number of specimens infected with other agents. We see no cross-reactivity, and we see no false-positive results.

[Slide]

We have looked at a number of normal plasma and we see very low initial and repeat reactive rates, typically zero percent. Actually, we have only seen zero percent repeat reactive rate.

[Slide]

This just shows that we do detect RNA prior to seroconversion. In this panel, at day 30 the individual was positive for antibody, one bleed before positive for antigen, and one bleed before positive in our assay.

[Slide]

This is a case where the antibody was positive on day 15. Antigen never became positive. RNA was positive three bleeds before the antibody. Another thing I would like to point out about this is that the quantitative PCR result indicated that that first bleed that was positive was only 200 copies/ml. It is important to drive the sensitivity of these assays.

[Slide]

So in conclusion, I think we have demonstrated that we have reached our target sensitivity goal for type B, 100 copies/ml, and we used the definition of 95% positivity. Analytical specificity is greater than 99.5%. We have demonstrated HIV subtype detection. I haven't gone into a lot of detail with the type M variants but we have detected

a diverse group of type Os.

[Slide]

We can detect HIV prior to antibody detection, and the format has a turnaround time and throughput appropriate for blood bank applications, and automation of this system is under way.

[Slide]

Here are our collaborators.

DR. HOLLINGER: Thank you very much. The next presentation is by Calyptebiomedical. If you could state your name too, we would appreciate it.

DR. URNOVITZ: Thank you. I am Dr. Howard Urnovitz, with Calyptebiomedical, and I thank the Committee for letting us speak.

[Slide]

This is the introduction slide. I am going to tell you about some stuff so let's move on.

[Slide]

The bottom line is that we are quite proud to be actually part of the discovery, the first group in France with Prof. Luc Montagnier of the Pasteur Institute, and we were studying two patients with idiopathic CD4 T-lymphocytopenia, mysterious AIDS cases without HIV, and it turns out one of those ended up to be the first French group O isolate VAU.

[Slide]

This is the paper that designated the type O with Montagnier's group and his collaborators.

[Slide]

What is interesting to note and the reason even to look at this is this woman did not fit the criteria of an HIV infection but she had AIDS-defining illnesses, severe leukoneutropenia, cervical carcinoma, got opportunistic infections, very low CD4 cell depletion and died. The most interesting thing to note is that her second son, in 1980, died at the age of one with a clinical history highly suggestive of neonatal AIDS. They could not get a positive serology on this until they ran the urine test.

[Slide]

Here you can see. We presented this actually in 1992 when there was quite a bit of discussion about ICL patients. This one was the group O and here they note the lack of serum antibodies to HIV envelope but, nonetheless, the recent data showed a marked reactivity to gp160 in the patient's urine.

[Slide]

This is the slide that referred to the second abstract, which I can give you after the meeting, in which the urine samples were positive. I think it is more important just to look at the data.

[Slide]

This is from patient VAU, the first French group O isolate, back in 1992. Here are the controls in this area, here. This is urine positive; urine negative; and serum positive. This is 1990. This was so confusing to the French group that here, in early November 1990, December 1990 and February 1991, and February 1992 -- the reason they did this in duplicate was did the envelop band not come up in this patient? So this was done for three years, still always showing the same indeterminate results. This is a diagnostic Pasteur's Western Blot.

The critical thing is that when Montagnier was looking our test, then experimental, he did run urine on this individual and it was quite strongly repeat reactive in the EIA. We then ran the same Western Blots and did urine in blood, and here you can clearly see that the gp160 band is present on the same day, same draw as was the serum, showing that, in fact, the antibodies are in the urine in this first case of group O. That is what then led them to bring her back in and to truly isolate group O. So, we were glad to assist in that.

[Slide]

You have heard of the two U.S. samples of group O, the Los Angeles, which has been difficult, HIV infection not detected consistently by standard HIV serology. We did not

detect her either in urine nor by the supplemental test. But the woman that is in Maryland, who is of Cameroon background, positive HIV serology, she was very reactive, over 3.0 in our EIA. Standard antigen, just gp160, down. Then we followed up with the supplemental test and we got all the bands. The good news is that even a year later we can still see the criteria, which is gp160.

[Slide]

This is the plasma of the group O that is the positive control, and this is her corresponding urine here. For those of you who were fortunate to get in early and get the good seats, you can see that there are bands here also. They have faded a year later. She was clearly and very strongly gp160, stronger than the intensity criteria.

[Slide]

So, what is the scientific basis? I know I have shown this exact slide here two years ago this month, and I must tell you that we are all mystified why antibodies would be in urine and not in blood, and I must tell you that these last six months have given us some great insight. I will talk about compartmentalization of HIV and the variation of chemokine receptor expression in different tissues.

[Slide]

We published this in 1993, seven patients from our clinical trials that were all non-reactive in blood tests,

several different blood tests; reactive in our urine screening test EIA, and then showed blot pattern that were inconsistent with the serum, discordant if you will. Often one, two, three examples had no antibodies in the serum supplemental test but had sometimes all the bands or the majority of the bands in urine. Some were unexplained cases, like this woman with Hodgkin's disease, but some were HIV at risk or HIV sexual partners.

So, it led us to believe then that the immune response in these individuals suggested that there may be a compartmentalized response from the immune system to these individuals, and we saw seven there.

[Slide]

Dr. Ann Kiessling, at Harvard, did this elegant study, just published in 1998 AIDS Research and Human Retrovirus, human HIV in semen arises from a genetically distinct reservoir. Quite an elegant study. Eight individuals were looked at, and what they found, just for brevity, was that findings confirm the distinct compartmentalization of HIV in semen. In other words, the virus that they pulled out of semen was completely different from the virus that they pulled out of blood.

[Slide]

The most interesting thing then is -- I hope you have not seen this. This will be coming out in August, and

Dr. Bruce Patterson in Northwestern was kind enough to allow me to show you the data in this forum. This should be out, as I said, in August. The title of the paper is "Repertoire of Chemokine Receptor Expression in the Female Genital Tract: Implications for HIV Transmission." It is quite interesting and, in fact, makes a lot of sense.

If you look at the peripheral blood mononuclear cells -- these are women. They go in and take vaginal biopsy. They compare the lymphocytes, the white blood cells they have in the biopsy versus the blood cells from that individual, and compared a number of individuals.

If you look in the blood cell, here you can see CXCR4, which is the T-cell trophic chemokine. If I have 100 relative units here, you can see that the CCR5 is about 1.5 less. This is T-trophic; that's macrophage-trophic. But you see a completely different result in the ectocervix. the M-trophic chemokine receptor is 10-fold more than the T-cell trophic, and 20-fold and 100-fold more than the duotrophic in the other macrophage, which suggests strongly that the mucosal tissue, with its different patterns of chemokines may, in fact, support the growth of variants more than the M strains. Those are thoughts to date. We are looking for other confirmation. We understand that Dr. Kiessling has also confirmed this finding.

[Slide]

So, how extensive is the occurrence of urine positives, serum negatives serum indeteriminates?

[Slide]

We have published this in Nature Medicine with my colleagues, Drs. Gottfried and Sturge. The bottom line is when we were given the results of the Western Blots and then decoded them for urine or blood, we found that roughly 1% of the HIV positives that we looked at were urine positive, blood negative. The actual number is about 10 urine positive, blood negatives out of 1,181 HIV positives. The blood test got 15 that the urine test missed, which led us to conclude that perhaps, while we are still trying to figure out why there are urine positives, blood negatives, we suggested that the combination of both urine and blood tests could increase the sensitivity because the blood tests are very good.

[Slide]

This is what gave us concern. Dr. Sordillo, at Roosevelt St. Luke's published this in 1997, last year. This is really what concerns us the most, the fact that if somebody was, in fact, repeatedly reactive on our EIA; urine Western Blot was positive by our criteria, supplemental test; serum was nonreactive at Quest Labs. This was done independently. We ran it at Calypte and we couldn't get a result. IDL did get a repeatedly reactive. However, IDL

did not get a positive. It was an indeterminate. Quest could not get any bands at all on their test. We had indeterminates on ours. However, this patient was p24 repeatedly reactive at Quest. The HIV DNA was detected, and this is HIV RNA quantitative, 46,000 copies/ml of virus in the viral load test. So, urine positive, blood negative and now a second example where virus can be detected, the first one being group O VAU.

[Slide]

Therefore, our concerns are, given these new insights into HIV pathobiology of HIV compartmentalized reservoirs that HIV seems to favor some tissues over others in the same individual; the tissue variability of chemokine receptors -- then my concern is have we created a detection system that favors HIV variants with limited associated serum antibodies?

[Slide]

Therefore, our strategy for detecting HIV group O is simple. We are going to screen both blood and mucosal fluid because our concern is we are finding people and working them up based on their blood reactivity, however, we feel that there are a number of variants that don't become blood positive. We will co-screen. Right now, five sites, four in New York and one in San Francisco, that will in fact look for discordant samples and then from there work up the

viruses and see if there is an American group O, and evaluate on our existing gp160 as well as other group O peptides.

[Slide]

Our other concern is that while we look to the government to give us insight in which way to develop tests, we hope that they realize that federal mandates need to address the intellectual property. If these are really public health issues, we would hope that the legislature would make it available for small, little companies like ours to be able to have access to sublicenses.

We are concerned about access to patients. We would prefer to see a central coordination for samples, private or public. We don't care. Then, where is the ceiling? What is the federal plan for addressing emerging variants? Are we just going to make these tests every time there is a variant, or are we going to address it more from the pathobiology of the disease rather than prevalence? And, I thank you.

DR. HOLLINGER: Thank you very much. The next presentation is going to be by Organon. Is someone from Organon --

ORGANON REPRESENTATIVE: There has been a mistake. We are not presenting.

DR. HOLLINGER: Not presenting? Sorry about that.

Then the last presentation is by Roche Molecular Systems. It doesn't mean because they didn't present you get 20 minutes.

[Laughter]

It is sort of like we tell our patients that are drinking and have liver disease, we tell them "you can have one beer a day." That means, you know, if you don't drink from Monday to Friday you can have six beers. It is still one beer a day. So, it is the same thing here.

[Laughter]

DR. HERMAN: Thank you, Dr. Hollinger. I won't amplify my slides. I will just keep the same number.

[Laughter]

[Slide]

My name is Steve Herman. I am from Roche Molecular Systems, and I am going to discuss recent work on the development of an RT-PCR assay for HIV-1 group O. The work I am going to present was conducted by Karen Young and her group in our research department in Alameda.

[Slide]

As everyone here is aware, the sequence diversity of HIV-1 group O isolates, both within the group and compared to group M, pose additional challenges in design of PCR assays compared to organisms with more conserved genomes.

Our design objectives for detection of HIV-1 group O are to achieve efficient amplification and detection of all group O isolates in an assay that detects both group M and group O isolates with high sensitivity.

[Slide]

Our initial efforts focused on developing a single primer-pair for both group M and group O isolates. At that time the number of pol gene sequences from the various HIV-1 subtypes was very limited, especially for group O. Nevertheless, we focused on the pol gene, believing it likely to be more highly conserved than gag.

A candidate primer-pair was developed that targeted the most conserved region in pol based on the limited sequence information available. Our initial evaluation of the primers on 5 group O isolates was promising. All were detected. However, initial evaluation on group M isolates of various subtypes was disappointing. Several African isolates were not detected, and the efficiency of quantitation was reduced.

Sequencing of the pol gene target region of additional group M isolates revealed greater sequence diversity than we had expected. We concluded that even in the pol gene the overall sequence diversity of group O and group M was too large to develop a single primer-pair for all HIV-1 isolates. So, we decided to develop separate

primer-pairs from group M and group O, and to work in the gag gene where much sequence information was available.

[Slide]

So, we have now developed several candidate group O primer-pairs in the gag gene. We selected a highly conserved region of gag, and designed primers with 3 or fewer mismatches with all of the known group O sequences. Based on primer target mismatch studies that examined the effects on PCR at various numbers and positions of mismatches, primers with 3 or 4 mismatches are expected to yield efficient and equivalent amplification.

In the next few slides I will present the results on one primer-pair from our initial evaluation of candidate group O primers.

[Slide]

These results show that the candidate group O primer-pairs amplified all group O isolates tested with a sensitivity of 10 copies per reaction, but had little or no reactivity with group M isolates. The group O primer-pair overlaps with current group M primer-pair but has no effect on amplification of group M isolates and reactions containing both the group O and group M primer-pairs. A candidate group O hybridization probe has also been designed and evaluation is in progress. However, in the studies I will describe today the amplification reactions were

evaluated by gel electrophoresis.

[Slide]

We evaluated the performance of the candidate group O primers on 10 group O isolates, including 5 newly obtained isolates whose sequences were not available when the primers were designed. From each isolate a gag gene fragment was cloned into a transcription vector, and RNA transcripts were prepared and quantified. Serial dilution of the transcripts at 1000, 110 and 1 copy per reaction where then amplified and analyzed by gel electrophoresis.

[Slide]

This slide shows the results from amplification of 1000 copies of each transcript RNA. Each isolate was analyzed in duplicate, and you can see that each isolate was detected in both reactions except for isolate TI191 where one reaction was negative. This appears to be an experimental error since both duplicates at 100 and 10 copies per reaction were positive for this isolate.

The next two slides summarize the results of all the isolates at all three RNA concentrations tested.

[Slide]

This slide shows the results on 5 of the isolates. The remainder are on the next slide. At 1000 and 100 copies per reaction both duplicate amplifications were positive for all five isolates except, as I just said, for isolate TI191.

At least 1 of the duplicate reactions was positive for all isolates at 10 copies per reaction, and 1 isolate yielded a positive result at 1 copy per reaction.

[Slide]

Here are the results on the remaining 5 isolates. Again, both duplicate reactions were positive at 1000 and 100 copies per reaction, and at least 1 of the duplicates was positive at 10 copies per reaction.

Please note that these results were generated with RT-PCR reactions that have not yet been optimized for the candidate primer-pair. With optimization of the reaction conditions and the thermocycling profile we anticipate achieving a sensitivity of 1 copy or nearly 1 copy per reaction.

[Slide]

The study shown on this slide and the next was done to evaluate the performance of RT-PCR reactions concerning both the group O and group M primer-pairs. And, 10 copies, 1000 copies and 100,000 copies of a group M subtype B RNA were amplified with the group O primers alone, the group M primers alone or both the group O and group M primers together.

The group M primer amplify the group M target RNA and yield the expected 173 base pair amplicon, indicated here by the arrows. The lower band in this gel is target

independent primer artifact occasionally observed in PCR reactions.

The group O primer did not amplify with the group M RNA, as indicated by the absence of 173 base pair band. However, the reactions containing both the group O and group M primers had an equivalent yield with reactions containing only group M primers, indicating that the group O and group M primers do not interfere with each other.

[Slide]

This slide from the same study shows the results obtained with the group O target RNA. Again, with the group O target RNA amplification with the group O primers yielded the expected band of 173 base pairs, and in a 10 copy reaction that doesn't appear too visible on this slide. Group M primers had no reactivity on the group O isolate, but the 2 primer-pairs together had equivalent efficiency to the O primers alone.

[Slide]

In summary, we are actively working to develop new RT-PCR assays that will detect all group M and group O isolates with high sensitivity. Although it was initially thought that the pol gene is more highly conserved than gag, the pol regions that we examined have not been sufficiently well conserved across group M and group O to develop a single primer-pair for all HIV-1 isolates. Therefore, we

are developing a separate primer-pair from group O and are working in the gag region where more sequence information is available.

Preliminary results with the candidate group O primer-pair in gag are very promising. All group O isolates examined were detected with a sensitivity of 10 copies per reaction, and the group O primer-pair can be combined with the group M primer-pair in the same reaction. By designing RT-PCR reactions for HIV-1 that contain 2 or more prier-pairs, we anticipate achieving high sensitivity and equivalent quantification of all HIV-1 isolates in both group M and group O.

Perhaps the biggest challenge in achieving this goal is to understand the full extent of HIV-1 diversity, which requires the identification and characterization of HIV isolates of all subtypes and groups worldwide.

[Slide]

So, I will conclude with this slide that lists the investigators with whom we are working to obtain HIV-1 isolates from around the world. Thank you.

DR. HOLLINGER: Thank you very much.

DR. SMALLWOOD: We will go into closed session. For the general public, you may return to this room at four o'clock. At this time, I would like all FDA employees who will be attending the closed session to remain seated, and

those sponsors and any of their identified guests to also remain seated. All other public participants are asked to leave the room quietly. Please take with you any briefcase or electrical recording, or any other type of electronic equipment. We will be checking.

[Closed Session]

Open Committee Discussion

DR. SMALLWOOD: Dr. Hollinger, whenever you are ready.

DR. HOLLINGER: Yes, this is now the portion of the meeting that is the open Committee discussion, but there are still two individuals that are going to provide some more information I think. Is that correct? No. That has been changed.

If we could have the presentation of the questions again at this time to the Committee, I would appreciate it, and then we will open the discussion.

DR. KOCH: To review then the question posed to the Committee, with regard to rapid tests used in diagnostic settings, should FDA relax its current policy to require as a condition of approval that all new tests for antibodies to HIV-1 have demonstrated ability to detect HIV-1 group O?

DR. HOLLINGER: Thank you. It is open now for discussion regarding the issues which are related to rapid screening tests basically. Yes, please, anyone? Yes, Dr.

Ellison?

DR. ELLISON: The phrase a "global village" was used earlier and I think it is unrealistic to expect that we are not going to see more of this, and I think to not require that be part of the test would be wrong.

DR. HOLLINGER: All right. Yes, Bill?

DR. MARTONE: I just want to review the definition of a rapid test.

DR. HOLLINGER: If there is a definitive description of a rapid test -- does the FDA have a description of what a rapid test is, or is it just quicker than a slow test?

[Laughter]

I suspect it is a test that can be completed while a person is there, in terms of minutes rather than hours, but there must be a more specific definition.

DR. EPSTEIN: We don't have a legal definition. I think operationally tests that are being performed in 15 minutes or less have been categorized that way. They also tend to have qualitative readouts, require minimal operator training, minimal sample processing, and typically they have been based on certain kinds of technologies that lend themselves to such use, such as immunoconcentrator systems, latex cards. In other words, it is really a set of technologies that involve minimal process execution by the

operator and on the spot result.

DR. HOLLINGER: Okay, thank you. Yes, Dr. Nelson?

DR. NELSON: It is a little tricky because obviously there are some public health problems involved here. One is detecting all of the genetic variants, new viruses, etc., and it is important that the test be quite sensitive to do that. On the other hand, it is also very important that it be quick or rapid. Dr. Branson presented data from STD clinics and other places where a lot of people didn't come back and, therefore, didn't get the benefit of the result of the test and might have even had an erroneous impression of what it was. Even in the blood bank setting, I can say that there are people who have to leave the blood bank who have a positive test, and in one blood bank that amounts to nearly a thousand donors a year. They can only find 70% of them. So, the benefit, even if there were diagnostic error, even if a few were group O positive and weren't detected, might be outweighed, at least for the moment, by notification and counseling of those who were detected. So, you know, I see a tension here.

Also, the other issue too is that we do need a test, and several of the manufacturers have shown data that there have been substantial developments to comply with the FDA mandate, and I think that is important, and they have been very successful, many of the data suggest that they

have. If we vote to relax this, does that mean that for group O, if it costs more money to make these tests -- you know, if one test can be licensed without that specification, does that mean all of them, or if they can be made more cheaply? Or, will this inhibit development of the best products? Those are the issues that I see.

DR. LINDEN: I agree with Dr. Nelson. I think from a public health standpoint it is really desirable to reach some of these populations that are very difficult to reach, and I think it is more important to reach people than to necessarily have all the bells, whistles and Cadillac version that may not be possible to address what are apparently very, very rare occurrences in this country. I think we want to move towards addressing the very rare variants. It seems to me that addressing the group O could, in a way, be done in counseling since most of the cases we heard about seem to be associated with travel to, or sexual contact or, you know, potentially sharing needles with people from Africa. People, you know, could be specifically counseled that there is a risk that would necessitate use of a different test, but there does seem to be cross-reactivity and I think we need to look at the big picture. So, I think this might be helpful.

DR. MCCURDY: It seems to me that one of the critical questions is whether we should have a test for

blood screening that is qualitatively different from the test that is being used diagnostically. I mean, there are a lot of situations where that may be all right. I think one has to consider very carefully, otherwise you have two levels of tests that are available in the community in one place or another and the patients or testees may make some decisions as to where they go based on what they think is the better test.

MS. KNOWLES: I agree with Dr. Linden in terms of the counseling that really needs to be addressed, and with our current system we have people return, hopefully, in person to get the test results and people don't, but the bottom line is that post-test counseling session is another educational intervention, and I think what needs to be thought about at some other point, maybe with some other committee, is how to actually improve the counseling piece.

DR. DUBIN: I am going to wear two hats in this one because the other hat that I wear is as one of the co-chairs of California's Community Planning Working Group. We wrote the State's HIV prevention plan under the CDC cooperative grant. We have what CDC calls the best counseling and testing program. I think this particular question creates a bit of a dilemma. As Dr. McCurdy just said I think is important, setting almost a class stratification in testing.

At the same time, with all our success in California, a rapid test would be a big step forward in populations we are having trouble with, that we are not getting the return visit to get the result, period. We have been wrestling with this question over the last three meetings of a group of 50 people from all the communities, doing interventions on the ground.

The counseling is another intervention, but the question of whether or not you are going to get answers that would indicate risk for O, I am not so sure given our experience. I think ideally we want the same test, whether it is in the environment of a blood bank or in the environment of an STD or community clinic. However, as Dr. Linden said and I think Dr. Nelson was saying the same thing, there are serious gains to be considered from a rapid test.

My concern is if we lower the standard, the manufacturers have a cheaper way to get to the marketplace that may not be the most efficient in terms of an equal test that gets O, and if we want to move them towards a rapid test that also is sensitive, I am not sure this decision can do that. I mean, I am quite torn between these two roles because I see the benefit but I think Dr. McCurdy hit it on the head. And, then you look at this week's U.S. News & World Report where a doctor allegedly is quoted as saying,

in the hepatitis C article, if you want to get a cheap hep. C test go to a blood bank, which is beyond belief that that would be said. My guess is no doctor said that, that came out of some reporter's drawer. But the point being that is an example. This is a tough one. I mean, I would lean towards taking the benefit but after voting that way I would go home thinking for many days whether or not I made the right choice.

DR. HOLLINGER: It is interesting, we have heard a lot of talks here today but really only one from a rapid test and, yet, that is the question that we are asking to be dealt with here.

MR. DUBIN: Right.

DR. HOLLINGER: Although Dr. Constantine did show that there are a lot of rapid tests at least in Europe or other places. It is something that one has to deal with and find out. Dr. Boyle?

DR. BOYLE: In looking at the numbers that were presented, the rapid test strategy probably will improve detection of about 8000 positive cases who, having been told they are positive, hopefully, will not be coming in to donate blood, and I am looking at this from the standpoint of blood supply. Without the requirement of O testing, there will be a group -- we are talking about a handful but it will grow over time -- who will not be detected there,

may come in to give blood but then will be tested with the current blood bank tests which, in fact, do require the O.

From the standpoint of improving the protection of the blood supply, it seems to me the rapid test works in that direction. What I am not clear on is why, if we do have one licensed rapid test, it isn't in place and that 8000 difference requires a change in the licensing strategy. So, I like the rapid test but what I am not clear on is if there is a licensed test and it does deal with O, why is it necessary to relax the strategy to get more? It seems to me it is more important to get that out and whatever other ones that follow it. That is my question.

DR. MITCHELL: I have also performed counseling and testing in a number of urban communities -- people of color, injection drug users, gay men -- and I think that it is very, very important that we provide some information at that time. It is difficult to get people back, particularly those that are at risk.

Since there is one test out there, then I think that that should be promoted. I mean, it does cover a lot of O groups. It looks like they are saying that in Europe there are many other tests that also cover most O groups, and it sounded like there is a question about even the samples that it doesn't cover, as to whether those are in the seroconversion phase and whether they would have been

detected hours, days, months later.

On the other hand, if we don't keep the same standards, then you are going to be missing a lot of O and we are going to selectively promote the spread of O diseases, and I think we can't afford to do that. So, I think that the FDA should keep the standard that it has. I think that we need to make sure that the samples that are tested for O are, in fact, positive for O, and we need to maintain the current standards so that we can prevent the spread of variations in the U.S.

DR. HOLLINGER: Are you concerned at all about -- or do you think it may be an advantage or a disadvantage, the fact that there are a lot of false positives so you would be counseling people -- and I would like you deal with that because you talk with these people -- that you would be giving somebody a response and, of course, then you could only say that it is positive, but it does trigger a lot. I mean, I have been in that situation where you are talking about somebody who has a positive and it takes a lot of undoing to get around it because they don't understand the concept.

DR. MITCHELL: Yes, I think that where the expertise has to be, in how to tell people. But I think that it is actually essential that you say that this test came up positive; we are going to have to reconfirm this

test. If it is negative, then you say it is negative. If it is positive, you say that, you know, there is a 50% or 80% chance that you may be positive. We will be confirming that and getting back to you. They are much, much more likely to come back if you say that to them. So, I think that that makes a big, big difference and that is how it should be addressed.

DR. HOLLINGER: Come up and join us.

DR. CHAMBERLAND: Do I get to eat a cookie?

[Laughter]

DR. HOLLINGER: No, you can't have a cookie. We won't go that far. Mary Chamberland is from the CDC and is a guest of the Committee.

DR. CHAMBERLAND: Just a couple of thoughts based on some of the comments, although I wasn't privy to sitting in on the closed session as a guest of the Committee, my understanding from the data that were presented in the public session and just general knowledge is that the concerns about the two-tier testing system -- my understanding is that the rapid tests that are out there are actually very good. It is not as if there is a big chasm between what is used in a blood screening and what might be used in a diagnostic clinical setting. So, the rapid tests that might be out there are actually good.

I think the idea of trying to relax standards with

respect to group O in the diagnostic clinical setting is that it actually would enable these tests, as you mentioned, from Europe to come to the FDA and give us the opportunity to have more than one test potentially out there in the market. If we have more than one rapid assay on the market, then wouldn't we be able to take advantage of, like, a two-test strategy, have two rapid assays, the algorithm that is used in developing countries.

I guess the final thought is we are dealing, as I think Jeanne Linden mentioned, with a very rare occurrence. Yes, it is evolving and changing but, I mean, in more than 15 years 2 group O isolates. So, I mean, we need to keep that in mind too.

DR. HOLLINGER: All right. Mike, I won't forget you but I want to go through the Committee right now. Is it something that is being dealt with here?

DR. BUSCH: Well, the discussion has avoided discussion of HIV-2. The fact is that virtually all the diagnostic tests that are used out there is, quote, because they are much less costly and because you don't have to do the confirmatory for 2, almost all diagnostic testing currently is done with HIV-1 lysate type assays, and we have probably at least 50 or 60 HIV-2 infections found in this country. So, all the discussion about missing Os is sort of trivial compared to the fact that the current tests that are

being used in diagnostic settings are missing HIV-2s, and the discussion is specifically on HIV-1 assays. If the debate is on this, then why isn't the CDC and the country as a whole moving towards exclusive use of combi tests? And those same tests that are used out there also lack the window phase sensitivity because they are not third-generation assays. So, in the diagnostic setting we are missing 2s, we are missing window period in general. The O issue is trivial.

DR. STRONCEK: I was struck by the discussion this afternoon by how much progress has been made in HIV testing that is used for donors. I can't argue that rapid tests aren't important, but I would think exactly the group of patients that we are testing with the rapid test are where we would expect to see the variants in the HIV first, and I think that would be an important public health question, to see if different strains are coming into the country.

I think, yes, one solution would be to loosen the standards and that would make more tests available, but I don't think that is the right solution. I think it is important that we maintain integrity of testing, both diagnostic and for blood donors, and maybe there is some other way to entice manufacturers to improve the availability of good tests for the rapid tests.

DR. HOLLINGER: I would like to ask the FDA,

somebody at the FDA to respond to what Dr. Busch asked because you have required that of the licensed tests which are currently out there, the EIA tests, that they detect not only HIV-1 and HIV-2 but now group O. Are we to interpret that you are making an exception here with the rapid test, that it not only do well with HIV-1 but that you want to add group O as a possibility since that is what you are requiring for these other tests? You really haven't said anything about HIV-2. Could you respond to that so that we can see if we have to deal with that as far as the question?

DR. EPSTEIN: Well, that debate occurred in 1992 when we first approved HIV-1/2 combi tests, although at that time it was not a public health policy position to encourage the use of rapid tests and the advocated paradigm was still to have the test subject come back after performance of confirmatory testing to be notified.

The issue did arise whether public health testing should include HIV-2 screening as a routine. The posture that was taken, based on the very low prevalence of HIV-2 and the very low rate of rise of HIV-2 infections in the U.S., was that that was not necessary. Instead, what should be done was HIV-2 testing based on whether the individual had risk factors for HIV-2. That is still the current policy position of the CDC.

Mike Busch is absolutely correct in his

description of what is done for public health diagnostic testing. FDA's role in that has been to allow claims for HIV-1 only tests and to continue to improve them for diagnostic indications but not donor screening indications. So, yes, we are simply dealing with a second case of a variant at low prevalence in the population, and we are asking whether to go down the same pathway. The difference is that in the wake of the discussions that we had in 1996 about HIV-1 group O, there was a recommendation that all new tests approved should have group O sensitivity because of the increased concern about the rapidity with which new variants might be introduced in the United States, and FDA took the action of sending letters to the IND holders and the current holders of approved tests, advising them to include group O antigens for any tests that might be approved in the future by the FDA. There was no effort to remove tests from the market because that would, of course, be doing some harm.

So, the difference here is that for HIV-2, our policy for diagnostics, not indicated for blood screening, has not been to require HIV-2 sensitivity but to monitor it, to ask the companies to test HIV-2 sera and to report the cross-reactivity of their tests and allow the marketplace to choose. But that was within the confines of the umbrella PHS policy, which was to test for HIV-2 in the public health

arena only based on risk factors.

DR. HOLLINGER: Yes, but I think from what even Dr. Boyle has said, I can understand the problem here. As I think you indicated, one could test for HIV-1 then and the small amount of group Os that are there are not going to be a problem -- may be a problem but should not be a problem for the donor screening. That will be picked up in the donor screening anyway.

DR. EPSTEIN: Well, I think it is important to distinguish the blood safety issue from the public health testing issue. Part of the purview of the Committee is dealing with retroviral diagnostics and, although the name of the Committee is Blood Products Advisory Committee, the fact is that our group at FDA is responsible for retroviral diagnostics generally. So, we are here asking a public health question. I would tend to agree with Dr. Boyle that as long as donor screens are kept sensitive for the viral variants we are not compromising blood safety. It does trouble me to have different standards for public health testing and donor screening, but if there are any differences to be tolerated at least there has been a general sense that we want the highest standard possible to apply to donor screening. And, that is not on the table to be compromised. That question is not being asked, and there is no intention by FDA to relax the expectation that new

tests shall be sensitive to group O.

DR. BOYLE: Could I just ask a pragmatic question about the two-test scenario? You have two tests on the market now. Is the second test to be used in the same setting only for positives so you don't have to come back for confirmation? Or, is it two tests of everybody to eliminate false negatives? What is the intent? Because it is going to impact upon cost and a number of other things.

DR. HOLLINGER: Mary, did you want to respond to that?

DR. CHAMBERLAND: I was actually going to ask Bernie Branson because he is more familiar with what is done.

DR. BRANSON: Our expectation for the two-test scenario would be to use the second test to improve the predictive value of positives, which is to reduce the number of people who would be given a false positive. We have not advocated eliminating a confirmatory strategy. The issue is that in many settings there has been a reluctance or a delay of implementing the rapid test is available because of the concern in some settings of a 50% or 60% predictive value that too many people would receive a positive result. So, we were not advocating using two tests on everybody in order to reduce negatives.

DR. BOYLE: Then let me ask a follow-up question.

The first test is going to be used using these numbers on two million people. If you are using the second test only on positives, it is only going to be used on 36,000. If you are bringing on a new test kit, if you will, or test and its market is only 36,000, is this something that people realistically are going to want to do, or are you going to find yourself in a position where for cost purposes potentially you can reverse the roles, and the O that is out there already if it is more expensive, and I don't know if it is, but if it is do you end up substituting a test for cost purposes?

DR. HOLLINGER: If I understand, I mean, basically these two tests would compete in the market for anything else. So, a person would choose those tests either way. It is not just to say we are going to market this so we can confirm or validate, if you will, previously positive tests. They will be competing for each other, and you will say if we get this positive then we will use the other test to try to validate, if you will a false positive. There are some issues with that validation because they may be detecting the same thing but there are some benefits to that. Yes, go ahead, Dr. Buchholz.

DR. BUCHHOLZ: I am getting a little confused. As I have understood and listened to the conversations, it seems like there are two issues here. It is clearly

desirable to have a rapid test and we have some issues with false positives. But, I mean, the implication that I have picked up a couple of times is that the false positives are due to the fact that the test has group O detection specificity, and I don't think that is the case. If that is not the case, why is the false-positive issue an issue at all in the discussion of whether a test should have O specificity or not. It seems we are taking some facts and kind of commingling them and then saying, gee, because of this there is a problem, which seems to me to be a separate issue. So, if I am in error can somebody correct me?

DR. EPSTEIN: You are correct that the issue of specificity is not linked to the issue of group O sensitivity. The link in these issues is whether FDA should relax the approval standard for rapid tests so as to foster the development of additional rapid tests which, if they entered the marketplace, would permit a dual testing strategy. In other words, currently using U.S. approved tests, there is no second test to run.

DR. BUCHHOLZ: I understand that.

DR. EPSTEIN: So, the question is if we lower the bar on the approval standard will we get in more applications and, therefore, more rapidly make available commercially a second or a third rapid test which would then facilitate the public health objectives of testing at STD

clinics and the like.

DR. BUCHHOLZ: Would you not think the seven other tests that are available outside the U.S. would be a stimulus for those manufacturers to get those tests approved by FDA?

DR. EPSTEIN: We don't know what they will do but presumably they are listening to this discussion, and if they are hearing that there is an incentive they may react.

DR. HOLLINGER: Dr. Constantine?

DR. CONSTANTINE: Yes, I agree. We are kind of dancing around the issue of the group O many times. I would like to ask a question about the question. That is, what is the impetus for the FDA asking whether they should relax the requirement? The technology is clearly there to be able to detect group Os. Is the impetus that you are worried that the test will become more expensive?

I also know, and I think it is public knowledge, that one rapid assay before the FDA right now has group O antigens. So, clearly the tests are there. Clearly, they are being brought to the FDA. I am not sure there is a cost issue. In fact, if there is more than one rapid assay available competition is going to bring the cost down. What is the reason for relaxing it?

As far as the prevalence of two group Os, it might be a little strange to realize that those group Os were

found when we weren't looking for them. If we should look for group Os, if we did widespread surveillance in the States, I think we would find more than two. And, HIV-2 now is up to 100 cases in the States. Is that right? They started off as two cases. So, the technology is there. Why not use it? I don't understand why relax; why not move forward?

DR. HOLLINGER: Is there someone here from Murex still? Could you tell us how this test does with HIV-@?

DR. SHOCKLEY: All the ones that we have tested so far, it picks up the HIV-2s. Again, it is purely cross-reactive. We don't have HIV-2 capture in the one that is licensed. We have the same version of that test outside the U.S. and we have HIV-2 capture.

DR. HOLLINGER: You have a version outside the United States which has HIV-2 antigen?

DR. SHOCKLEY: That is correct.

DR. HOLLINGER: But the one that is here still has picked up most of the HIV-2?

DR. SHOCKLEY: That is correct.

DR. HOLLINGER: And how many have there been?

DR. SHOCKLEY: I would say we have probably tested on the order of 30.

DR. HOLLINGER: Okay, thank you very much. Yes, Dr. Verter?

DR. VERTER: I think the issue for me is that there are two public health issues. One, my understanding is that we are supposed to make sure that the blood supply is as safe as possible. And, it seems to me that there are techniques, methods, assays in place now which, from what I have heard over the last couple of years sitting on this Committee, show that the blood supply is very safe, and with the methods we are using it picks up all the HIV-1, 2 and even the O now, as it exists. I don't see a reason to lower the bar then.

The reason I see lowering the bar, the United States is an instant society. We like it instantly, from breakfast to replays. If the manufacturers of these kits can come up with an instant kit that has the same attributes as the current system, great. I mean, I think it would be great because you would get a higher return; the people who are supposedly positive, they could be counseled more efficiently; they are less likely to go back and you would have less worry about the getting into the blood supply by accident. It is a wonderful attribute. I don't think the bar should be lowered.

DR. KOERPER: I agree. I don't think the bar should be lowered. The reason that those individuals were not given their test results right away was not because we don't have a rapid test; it is because the rapid test wasn't

being used at that clinic where they were seen. I think we need to remember that. We do have a test. And, if people are concerned that the testees are not getting their results right away, then people need to use the test. So, lowering the bar is not going to change that strategy of whether the test is used.

I also agree with someone who said, you know, that we had 2 HIV-2s and now we are up to 100. So, we have 2 group Os. In a few years we are going to be up to 100. I remember the days when we had 3 hemophiliacs and now we are up to 6000. So, you know, it starts slow and it picks up, and I don't think we should lower the standard.

DR. KAGAN: My only comment would be that I think we need to keep watching and raising the standards.

DR. VERTER: I am sorry, there is one other thought I had. I am also concerned about the false positivity. I agree that in certain hands the counseling would be outstanding but you are not at every clinic, and I worry that not everyone would educate as well as you would. I think we do have to be sensitive to the second public health issue in the testing, and that is those who are told they are positive but may not be positive -- how they are told and how quickly that is corrected.

DR. HOLLINGER: Yes, and perhaps even to emphasize the low prevalence areas, in terms of the number of

positives that will be false positive. That might not be a place for rapid tests for that very reason. It was in that group anyway that had very good return, I think it was 96% or 98% -- so, that is not the group that this possibly would be directed to but that is what the market will determine anyway. Yes, Dr. Mitchell?

DR. MITCHELL: I also have a question of CDC. Since we do have one test out, you know, when you repeat testing it should improve the specificity and I wanted to find out if they had looked at repeating the current testing and how it improves specificity.

DR. HOLLINGER: Yes, Dr. Branson?

DR. BRANSON: These figures that were presented were based on repeatedly reactive SUDS screening test. So, all those figures were based on already repeating the test.

DR. HOLLINGER: So, are you saying that in the rapid test if you get a positive result -- if a person is there because that is going to increase the time obviously, but if you get a positive result, rather than talking to the person right at that time, the test is repeated again, even just a single test. Is that correct? Before that person is talked to, which means it increases it to maybe 30 minutes?

DR. BRANSON: You would get a repeatedly reactive test before you would give a result at the current time, and part of the reason that CDC is interested in seeing the

availability of other tests is to improve the predictive value further using a different test. So, if a person is positive, we would prefer that they would have repeatedly reactive tests, tested with an additional test, to minimize the number of people who receive false positives. Much of the reluctance in using what is available now is the reluctance to give people a potentially false-positive result.

DR. HOLLINGER: And that wouldn't impinge upon its public health benefits of reporting this -- people would stay around for that period of time. Yes, Dr. Nelson.

DR. NELSON: Mike Busch raised another question. With the combi test and the HIV-2 antigen etc., the third generation, not only has it become very sensitive but also the period that a person is infected or infectious negative on the serology has decreased substantially. What about the rapid tests? Do they still have the window period of the first generation or the earlier tests, or are they also very sensitive in the window period?

DR. BRANSON: The only rapid test I can address is the one that is currently on the market, which is whole viral lysate, and I think it is the same as the older window, not the newer recombinants.

DR. NELSON: So, potentially we could not only tell somebody he is positive when he is not, but we might

also tell somebody they are negative when, with another test that is licensed, they would be told they are positive because of the short window, and if they were at high risk in some populations it could be a significant number of people.

But, again, there are two words that I think need defining, "screening" and "diagnostic." For the blood donors we do need the best diagnostic test available, but I still can see a strong reason for screening tests even if they are not perfect because you have the person there and you can communicate a message, and you can use the word "screening" in the message in some fashion that the person understands. Whereas, if nothing is done you may lose them, and that is not an insignificant problem. In fact, you know, right now how are we going to control this epidemic? We have to find people as early as possible; get them on therapy; counsel them, all this kind of thing. That should be a high priority.

DR. HOLLINGER: I am going to call for the question now if there are no other comments. Let's vote on the question as it is stated, and that is, with regard to rapid tests used in diagnostic settings should FDA relax its current policy, that is, the current policy which requires as a condition of approval that all new tests for antibodies to HIV-1 have demonstrated ability to detect HIV-1 group O?

All those that agree with that question, please raise your hand.

[Show of hands]

All those opposed?

[Show of hands]

Any abstaining?

[No response]

Ms. Knowles, your comments?

MS. KNOWLES: I don't want to relax the policy.

DR. HOLLINGER: Pardon?

MS. KNOWLES: I do not want to relax it. I don't want the FDA to relax the policy. It is a no.

DR. HOLLINGER: Actually, I misread the thing myself.

[Laughter]

I am sorry about that. Let's vote again. That is my prerogative; I can do that. I really apologize for that. That is not what I mean to vote. So, should FDA relax its current policy to require that all these tests have antibody to detect HIV-1 group O?

All those in favor of that, raise your hands, that it should relax its policy? All those in favor, voting yes, raise your hand.

[Show of hands]

All those that feel that it should not relax the

policy, raise your hand.

[Show of hands]

And abstaining?

[No response]

MS. KNOWLES: No.

DR. BUCHHOLZ: No.

DR. HOLLINGER: Jeanne, a comment, if you wish. You don't have to.

DR. LINDEN: Well, I certainly see both sides of the argument, and in a sense it is something I feel strongly about and clearly it is something that we want to work towards. Consistent with the existing public health policy, as Dr. Busch pointed out in terms of HIV-2, I think rare events can be treated consistently in terms of doing specialized tests when indicated. That is what we are doing already.

DR. HOLLINGER: Also, I think there was a sentiment here, and if I am wrong, please correct me, but a sentiment that there also ought to be the same kind of policy here for the HIV-2 as well. It is not an issue here. This is an HIV-1 test. But there seems to be, if I can put this message across to the FDA, that we feel it also should include HIV-2 as well.

DR. SMALLWOOD: The results of the vote are as follows. There was one yes vote; 12 no votes; no

abstentions. Both the consumer and industry rep. agree with the no vote. There are 13 members of the Committee present that are eligible to vote.

DR. HOLLINGER: Tomorrow is a very heavy day, particularly because we want to be sure we have enough time in the afternoon in a closed session to discussion the issues about the research at the FDA, and so on, as has been sent to you. We are slated to be out at three o'clock. See you at eight o'clock.

[Whereupon, at 4:50 p.m., the proceedings were recessed to be resumed at 8:00 a.m., Friday, June 19, 1998.]

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CERTIFICATE

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

Alice Toigo

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