TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

62ND MEETING

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Pages 1 thru 303

Bethesda, Maryland
March 25, 1999

MILLER REPORTING COMPANY, INC.
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at

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

62ND MEETING

Thursday, March 25, 1999

8:15 a.m.

Bethesda Ramada Inn
8400 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
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CONSULTANT

Michael G. Fitzpatrick, Ph.D.

at

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1 P R O C E E D I N G S

2 **Statement of Conflict of Interest**

3 DR. SMALLWOOD: Good morning. Welcome to the 62nd
4 Meeting of the Drug Products Advisory Committee. I am Linda
5 Smallwood, the Executive Secretary. At this time, I will
6 read the conflict of interest statement that applies to this
7 meeting.

8 This announcement is made a part of the record at
9 this meeting of the Blood Products Advisory Committee on
10 March 25 and 26, 1999. Pursuant to the authority granted
11 under the Committee charter, the Director of the FDA Center
12 for Biologics Evaluation and Research has appointed the
13 following consultants as temporary voting members: Dr.
14 McCurdy for all committee discussion and Dr. Jane Piliavin
15 for the discussions on validation of donor history
16 questions.

17 Based on the agenda made available and on relevant
18 data reported by participating members and consultants, it
19 has been determined that all financial interest in firms
20 regulated by the Center for Biologics Evaluation and
21 Research that may be affected by the committee's discussions
22 have been considered.

23 No waivers under Section 208 were necessary. In
24 regard to FDA's invited guests, the agency has determined
25 that the service of these guests is essential. There are

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1 reported interests which are being made public to allow
2 meeting participants to objectively evaluate any
3 presentation and/or comments made by the participants.
4 The interests are as follows: Dr. Michael Busch
5 reported that he has a grant from the National Heart Lung
6 and Blood Institute to study nucleic-acid testing in which
7 Roche and Gen-Probe are collaborators. He also has a grant
8 reported by Roche to develop PCR assays. In addition, Dr.
9 Busch is a member of the Gen-Probe Scientific Advisory
10 Group.
11 Dr. Christina Giachetti is employed by Gen-Probe.
12 Ms. Sue Preston is employed by Alpha Therapeutics
13 Corporation. Alpha has contacted firms that could be
14 affected by the discussions of p24 antigen test kits. Dr.
15 Susan Stramer has a financial interest in Abbott
16 Laboratories.
17 The topics that Drs. Celso Bianco and Jane
18 Piliavin and Alan Williams are commenting on are not subject
19 to conflict of interest. In the event that the discussion
20 involves specific products or firms not on the agenda for
21 which FDA participants have a financial interest, the
22 participants are aware of the need to exclude themselves
23 from such involvement and their exclusion will be noted for
24 the public record.
25 Screenings were conducted to prevent any

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1 appearance, real or apparent, of conflict of interest in the
2 committee discussion. With respect to all other meeting
3 participants, we ask, in the interest of fairness, that they
4 address any current or previous financial involvement with
5 any firm whose products they wish to comment upon.
6 At this time, are there any further declarations
7 to be made by any of the advisory committee members or the
8 participants?
9 Hearing none, I would just like to announce to all
10 assembled here that the environment in which we are having
11 this meeting is obviously a little different than what we
12 have had in the past.
13 We are trying to be accommodating in terms of
14 making it as comfortable as possible and we are working on
15 the audio system. I hope that you will be patient with us.
16 We do have a full agenda and we would like to proceed. But,
17 just to let you know, we are trying to do the best that we
18 can and, if there are any inconveniences, please let me know
19 very gently.
20 At this time, I would like to introduce to you the
21 members of the Blood Products Advisory Committee. We also
22 have two new individuals that are serving on the committee
23 with us today.
24 First, I would like to introduce Dr. Blaine
25 Hollinger, who is our Chairperson. Dr. Gail Macik. Dr.

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1 Macik is new to the Blood Products Advisory Committee. She
2 is a hematologist and she is with the University of
3 Virginia. Dr. Mark Mitchell. Dr. David Stroncek. Dr.
4 Michael Fitzpatrick is from the Department of Defense. He
5 is new with us now.

6 Dr. Kenrad Nelson. Dr. Donald Buchholz. Dr.
7 Marion Koerper. Dr. Norig Ellison. Mr. Corey Dubin. Dr.
8 Rima Khabbaz. Dr. John Boyle. Dr. Paul McCurdy. Dr.
9 Jeanne Linden.

10 Our members absent today are Dr. Richard Kagan,
11 Dr. Kwaku Ohene-Frempong and Dr. Joel Verter. Dr. Jane
12 Piliavin will join us later this afternoon.

13 Also, if Dr. Epstein would like to come forward
14 and introduce our new members on our staff, our new Deputy
15 Director.

16 DR. EPSTEIN: If I could just ask Richard Lewis to
17 stand and to, perhaps, come a little bit forward so you are
18 visible. Richard was appointed new Deputy for the Office of
19 Blood Research and Review. We welcome him aboard in this
20 new role. Let me not delay our meeting, but let me also
21 send a personal welcome to our new members on the committee.
22 As always, we have a very full agenda and look forward to
23 full participation of the group.

24 DR. SMALLWOOD: Thank you. At this time, we will
25 proceed with the agenda and I will turn the proceedings of

1 this meeting over to our chairman, Dr. Blaine Hollinger.

2 **Welcome and Opening Remarks**

3 DR. HOLLINGER: Thank you, Linda. While Linda was
4 saying this, I remember a few years ago standing up at a
5 conference giving a talk and I asked the same thing Linda
6 did. I said, "Can you hear me in the back?" And some
7 people said, "No; I don't think so, not very much." And two
8 or three people in the front row got up and went to the
9 back. So I don't do that anymore.

10 Just so that the committee members know, these
11 mikes have a push button on and off. So when you see this
12 little red thing here on top, that means your mike is on and
13 live.

14 The last time we met in December, there were
15 impeachment trials going on. This time, there is a NATO
16 operation. So I am not sure we should have another one in
17 June. But this is an interesting meeting today. I saw
18 somebody from the Pentagon today say something like, "There
19 is nothing such as a risk-free military operation." I
20 think, obviously, we can say the same thing. There is
21 nothing such as a risk-free blood transfusion.

22 But I will tell you, it is getting to the point
23 where we are getting extremely good, safe blood. A lot of
24 the things that we are doing now are looking for ways in
25 which we can reduce the number of operations that need to

1 take place such as in donor histories, such as looking for
2 ways to reduce, perhaps, some of the testing that was done
3 in the past. All of these things are going to go on over
4 the next, I think, several months to a year to try and find
5 out if we can reduce those operations, make the blood even
6 safer.

7 Most of the operations that are being introduced
8 are actually not going to change the safety of the blood
9 except to make it safer. It is not going to make it less
10 safe. I think that is a real plus.

11 So, today, we do have several items and I think we
12 need to get started. The first thing we start on is
13 committee updates, not so much for discussion but more to
14 give us an idea of some of the issues that are before us.
15 The first one is on the HCV lookback guidance. Paul Mied is
16 going to talk about this.

17 **Committee Updates**

18 **HCV Lookback Guidance**

19 DR. MIED: Good morning. Thank you, Dr.
20 Hollinger.

21 [Slide.]

22 This morning, I will provide the committee with an
23 update on HCV lookback. Specifically, I will summarize the
24 actions of the Public Health Service and the blood industry
25 to implement HCV lookback and the current status of the

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1 lookback effort. I will review the resolutions on HCV
2 lookback approved by the Advisory Committee on Blood Safety
3 and availability on January 28, 1999 and I will conclude by
4 discussing the upcoming draft FDA revised guidance for
5 industry document with a review of the recommended time
6 frames for implementation of HCV lookback by the industry.
7 The current PHS initiative and industry effort for
8 identifying transfusion recipients at risk for HCV infection
9 includes direct notification of recipients of blood from
10 donors who had subsequently tested repeatedly reactive on a
11 multiantigen screening test--that is, the EIA 2.0 or 3.0--
12 with a reactive supplemental test result and general
13 notification of all persons transfused before July, 1992.
14 [Slide.]
15 The current status of the implementation of HCV
16 lookback may be summarized as follows. The blood
17 organizations report that blood establishments have
18 implemented HCV lookback programs prospectively, or based on
19 current donor testing and retrospectively, or based on
20 review of records of historical donations tested using EIA
21 2.0 or EIA 3.0.
22 They have established written SOPs for lookback
23 based on current and historical donations. They have
24 diligently conducted record searches to identify prior
25 collections from donors who were reactive on multiantigen

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1 screening and supplemental tests and they have been
2 performing additional tests on stored samples or, in some
3 cases, on fresh donor samples.
4 As I reported in my December update to this
5 committee, some blood banks have already begun doing
6 lookback based on EIA 1.0. The Chiron RIBA 3.0 supplement
7 test was licensed in February and it is useful for
8 resolution of donor-infectivity status to minimize false
9 notifications of recipients.
10 Blood establishments have begun to notify
11 consignees. The deadline for this consigning notification
12 was specified as March 23, 1999 in the FDA guidance document
13 issued last September 23. Blood establishments will need to
14 complete consignee notifications by March 23, 2000. In
15 coordination with the public education and physician efforts
16 of the CDC, transfusion services have begun to notify
17 recipients.
18 The Advisory Committee on Blood Safety and
19 Availability met on January 28, 1999 in Washington, D.C. to
20 consider options for implementing the November 24, 1998
21 recommendation of the advisory committee to expand the
22 current targeted HCV lookback program to include recipients
23 of blood from donors subsequently identified as repeatedly
24 reactive by the single-antigen enzyme immunoassay, EIA 1.0,
25 screening test of HCV infection that was licensed in 1990.

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1 Now, it would be necessary for lookback based on
2 EIA 1.0 to include unconfirmed as well as confirmed EIA 1.0
3 tests because about 80 percent of the EIA 1.0 repeatedly
4 reactive donations had been culled by EIA 1.0 screening
5 before the first confirmatory test became available.
6 The committee considered that it might be
7 reasonable to limit the lookback for EIA 1.0 based on the
8 signal-to-cutoff ratio of the screening test in cases where
9 supplemental testing had not been done. In other words, it
10 may be optimal to perform lookback on a subset of the EIA
11 1.0 repeat reactives to capture the vast majority of the
12 true positives and minimize the unnecessary false-recipient
13 notifications.
14 Data were presented at that meeting to support the
15 use of the signal-to-cutoff ratio as an estimate of what the
16 result of a RIBA 2.0 test would have been if the RIBA 2.0
17 test had been available and performed on the donor sample.
18 [Slide.]
19 In a study of HCV EIA 1.0 data from four
20 regionally diverse blood centers, Tobler and Busch and
21 several other colleagues found a highly significant
22 correlation between the signal-to-cutoff ratio and RIBA 2.0
23 positive or negative results.
24 Dr. Busch discussed the choice of a signal-to-
25 cutoff ratio that would optimally distinguish an uninfected

1 from an infected donor using the expected results of a RIBA
2 2.0 test as the gold standard. A signal-to-cutoff value of
3 greater than 2.5 yielded an 89 percent sensitivity for RIBA
4 2.0 positives.

5 In other words, if a signal-to-cutoff value of 2.5
6 is taken as the trigger for lookback, 89 percent of
7 recipients from repeatedly reactive donors who would be RIBA
8 2.0 positive would be notified. For a signal-to-cutoff
9 value of greater than 2.0, 91 percent of recipients from
10 donors who would be RIBA 2.0 positive would be notified.

11 For a signal-to-cutoff of greater than or equal to
12 1.5, 95 percent of recipients from donors who would be RIBA
13 2.0 positive would be notified. However, for a signal-to-
14 cutoff value of greater than 2.5, of the 11 percent of
15 repeatedly reactive donors who would be RIBA 2.0 positive
16 for whom recipients would not be notified, only 48 percent
17 of those donors would have been HCV RNA positive.

18 So, in effect, of 100 people who would have been
19 notified simply on the basis of EIA 1.0 repeatedly reactive
20 results, if the signal-to-cutoff value of greater than 2.5
21 is taken as the trigger to lookback, there would be only
22 five at-risk individuals who would not be notified since
23 their donors had signal-to-cutoff values of less than 2.5 or
24 an EIA of 1.0.

25 The flip side of this is that as you approach a

1 signal-to-cutoff value of 1.0, the specificity drops off
2 rapidly. However, for a signal-to-cutoff value of greater
3 than 2.5, 87 percent of recipients from donors who would be
4 RIBA 2.0 negative would not be notified.
5 In other words, if the signal-to-cutoff value of
6 greater than 2.0 is taken as the trigger to lookback, we
7 would not be notifying 87 percent of those individuals who
8 are not at risk who would have been notified on the basis of
9 their donor being EIA 1.0 repeatedly reactive.
10 [Slide.]
11 Now, Dr. Busch estimated that if direct
12 notification was to be based on a signal-to-cutoff ratio of
13 2.5 or above, about 100,000 notifications would be
14 triggered. About 10 percent of these individuals would be
15 alive and be traced by the notification effort; that is,
16 10,000 of those individuals.
17 About half of those, or 5,000 individuals, would
18 have been previously unaware of their potential HCV
19 infection. Dr. Busch estimated that using a signal-to-
20 cutoff ratio of 2.5 to trigger direct notification as
21 opposed to simply using an EIA 1.0 repeatedly reactive test
22 to trigger direct notification would prevent about 452
23 false-positive notifications. For every true-positive
24 notification that would not occur.
25 [Slide.]

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1 Having taken the signal-to-cutoff value of 2.5 as
2 being the optimal ratio for triggering lookback for EIA 1.0,
3 the Advisory Committee on Blood Safety and Availability
4 unanimously approved the following recommendations at its
5 January 28, 1999 meeting.
6 One, the advisory committee recommends that
7 targeted lookback should be initiated based on the
8 repeatedly reactive EIA 1.0 test result on a repeat donor
9 unless a supplemental test result was performed and did not
10 indicate significant risk of HCV infection, no supplement
11 test result is available, but the signal-to-cutoff ratio of
12 the repeatedly reactive EIA 1.0 test was less than 2.5 or
13 follow-up testing from the same blood donor is negative.
14 [Slide.]
15 Two, the advisory committee believes that, in
16 light of the scope of the hepatitis-C epidemic, current
17 funding is inadequate for notification, testing, counseling,
18 education and therapy. We urge the secretary to take
19 immediate measures to increase funding to meet this major
20 public-health challenge.
21 We further urge the Public Health Service to work
22 with professional and private organizations to promulgate
23 appropriate recommendations for testing, counseling and
24 therapy and to secure additional resources for these
25 purposes.

1 [Slide.]

2 Three, the advisory committee urges the Secretary
3 to consider providing appropriate support and resources for
4 blood centers and hospitals, both public and private, to
5 conduct HCV lookback activities.

6 In accordance with these recommendations, FDA
7 intends to issue a revised guidance for industry document
8 that will replace the guidance issued on September 23, 1998.
9 This revised guidance, which will be issued for
10 implementation and comment, will include recommendations for
11 implementation of targeted lookback based on a repeatedly
12 reactive EIA 1.0 test result on a repeat donor except in the
13 cases listed in recommendation 1 of the advisory committee.

14 [Slide.]

15 With respect to the time frames for implementation
16 of the retrospective HCV lookback by industry, the current
17 September 23, 1998 guidance document recommended that blood
18 establishments should begin notification of consignees--that
19 is for EIA 2.0 and 3.0--within six months of the date of
20 issuance of the September 23 guidance--that is, by March 23,
21 1999.

22 As I mentioned earlier, this deadline has passed
23 and blood establishments have begun this notification of
24 consignees. In addition, blood establishments should
25 complete all notifications of consignees within eighteen

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1 months of the date of issuance of the September 23 guidance-
2 -that is, by March 23, 2000.
3 FDA anticipates that the new revised guidance will
4 issue in May, 1999. In this revised guidance, due to
5 concerns raised by the blood organizations with respect to
6 having adequate time for implementation of retrospective HCV
7 lookback pertaining to EIA 1.0, FDA is considering
8 recommending that blood establishments should begin
9 notification of consignees for EIA 1.0 as soon as feasible
10 and within six months of the date of issuance of the
11 upcoming revised guidance expected in May--that is, by
12 November of 1999.
13 However, blood establishments should complete all
14 notifications of consignees for EIA 1.0 by the same date as
15 that for completing all consignee notifications for EIA 2.0
16 and 3.0--that is, by March 23, 2000.
17 Thus, FDA intends to recommend that this date for
18 completion of all consignee notifications be unchanged from
19 that in the current September 23 guidance document.
20 [Slide.]
21 The other target dates will remain the same. A
22 transfusion service should begin notification of the
23 recipient when notified by the blood establishment and
24 should complete all notifications of recipients within one
25 year following receipt of notification from the blood

1 establishment--that is, by March 23, 2001 for the last of
2 the notifications received.
3 Thank you.
4 DR. HOLLINGER: Thank you, Paul. Any burning
5 questions for Paul from the committee on this issue?
6 MR. DUBIN: It is a question, but I need to
7 precede with some comments so we know where we are. The
8 Committee of Ten Thousand, which has been involved in
9 calling for this lookback for a number of years supports the
10 targeting lookback as was designed and the recommendations
11 at the Blood Safety and Availability Committee.
12 We have raised the issue of pre-1989-88, because
13 if we are going back in terms of donor and donor records
14 that are in pretty good shape until 1990, we will get to
15 recipients in the 1988-89 range. Our concern is that the
16 majority of potential exposures identified by the
17 Subcommittee on Human Resources, the Sherman Chase
18 Committee, the figure he gave is $1 million.
19 Two-thirds of that $1 million will fall outside of
20 this targeted lookback. We are concerned if they are left
21 as part of the overall CDC general campaign on the hepatitis
22 C epidemic that two things will happen. The connection
23 between that campaign, their transfusion or usage of blood
24 products or blood components, that hepatitis C will not be
25 very direct and the unique relationship between consumer and

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1 manufacturer of plasma derivative or consumer and blood bank
2 will be lost.
3 What we suggested at the advisory committee and
4 what we continue to suggest, and when I asked FDA staff
5 about--we believe that what should occur is the "Dear
6 Resident" letter a la what Surgeon General Koop did in the
7 1980s a la HIV and that that should go to every home in
8 America, something to the effect that, "If you were
9 transfused or received blood, blood components, blood
10 products, you should be antibody tested for hepatitis C."
11 This, we believe, is the only way to reach the
12 entire potential exposed population. So I wonder how FDA
13 has looked at that and if FDA supports, at a staff level,
14 the issuance of a "Dear Resident" letter.
15 Thanks.
16 DR. MIED: Corey, I don't know. We were both at
17 the same meeting. That concern was raised. That point was
18 made. Frankly, I don't know if any action will be taken to
19 that end regarding a letter.
20 DR. EPSTEIN: You highlight an important issue.
21 There are really two different points here. With respect to
22 a mailer to all households, that is under discussion at the
23 CDC. There is an issue of finding the funds to do it, but,
24 generally, the concept is well endorsed and we are looking
25 at feasibility. That lies with CDC.

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1 As far as whether the records search for the
2 targeted lookback could be extended prior to 1988, the key
3 issue there is a practical one which is the state of the
4 records. Many transfusion services, and, indeed, blood-
5 collection centers, were not computerized at that point in
6 time. Some of them were, but, in many cases, the records
7 are paper records, index-card records.
8 They are sitting in boxes. They are deep-sinked
9 in warehouses. It becomes impractical to think that they
10 can be searched. What FDA is doing is considering where we
11 can draw the line. We will come forward with some practical
12 recommendation based on a feasible search of records as far
13 back as can be done.
14 But there is a practical constraint and we are
15 just going to have to live with it.
16 DR. HOLLINGER: Who is paying for the--people who
17 are notified and they come in, are they supposed to come
18 into blood banks primarily, and the blood banks are taking
19 care of the testing?
20 DR. EPSTEIN: For the most part, the answer is
21 yes. And it is my understanding that there is a statement
22 recently out of HCFA that Medicare will reimburse recipient
23 testing based on targeted lookback. Now, that, of course,
24 will not affect all recipients, but the majority of blood
25 recipients living today are over age 65 and are Medicare-

1 eligible so it will go a long way toward providing funding
2 for lookback testing.
3 DR. HOLLINGER: But increased funding was not
4 provided, or has not been provided through the Health
5 Department.
6 DR. EPSTEIN: I don't believe it has. Perhaps,
7 Rima knows the answer. But I don't think that there have
8 been any earmarked funds for this; no.
9 DR. MIED: HCFA Memo 804 talks about funding a
10 little bit. It was just released over the past week.
11 DR. HOLLINGER: I think we will move forward,
12 then, to the next update. Dr. Mary Jacobs is going to give
13 us an update on the Transmissible Spongiform
14 Encephalopathies Advisory Committee meeting. I guess this
15 was the one in December.
16 DR. JACOBS: Yes; that's correct.
17 **Transmissible Spongiform Encephalopathies Advisory**
18 **Committee Meeting Summary**
19 DR. JACOBS: Thank you, Dr. Hollinger.
20 [Slide.]
21 My presentation is a brief summary of the December
22 18, 1998 meeting of the Transmissible Spongiform
23 Encephalopathies Advisory Committee which we usually call
24 TSEAC which was asked to make recommendations to FDA
25 concerning new deferral criteria for blood donors to attempt

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1 to reduce the theoretical risk of new-variant CJD from
2 possible food-borne exposure to the agent of bovine
3 spongiform encephalopathy, or BSE.
4 [Slide.]
5 First, what is the current status. There have
6 been no cases of BSE or of new-variant CJD in the U.S. As
7 an aside, the March 20 paper in Lancet by Dr. Robert Will
8 reported that, as of the first quarter of 1999 with
9 incomplete data for that quarter, there have been 39 deaths
10 from new-variant CJD.
11 Although there have been no cases in the U.S., we
12 are well aware of precautionary measures taken in the U.K.
13 including implementation of universal leukoreduction and
14 also not using U.K. source plasma.
15 We brought the question of potential deferral to
16 the TSE Advisory Committee and asked them to consider the
17 questions in the light of potential shortages. In order to
18 have continuity with BPAC, Drs. Hollinger and Nelson were
19 temporary voting members of the committee as was Dr.
20 Lightman of NIH.
21 In addition, Dr. Gilcher of the PHS Blood Safety
22 and Availability Committee served as a guest. Drs. Katz and
23 Sayers, former chairs of this committee, were guests as well
24 bringing blood-banking experience and took part in the
25 deliberations.

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1 The complete transcript is available on FDA's
2 website as shown on the overhead. I think you might find it
3 interesting to read.
4 [Slide.]
5 The agenda addressed the issues which are relevant
6 to the questions of the safety of blood, blood products and
7 plasma derivatives. First, the scientific presentations
8 included Dr. Robert Will who had first described new-variant
9 CJD in U.K. patients, who described the characteristics of
10 the disease and its demographics.
11 Dr. Robert Rohwer discussed experimental studies
12 in animals using infected blood.
13 [Slide.]
14 Dr. Adriano Aguzzi discussed the role of
15 circulating lymphocytes. Next we turned to the time course
16 of the BSE epidemic which was discussed by Dr. Ferguson of
17 the U.S. Department of Agriculture.
18 [Slide.]
19 Because we had asked the committee to talk about
20 shortages, we then went first to the topics of donor-
21 deferral policies. Captain Gustafson, who is Division
22 Director for Blood Applications in our office, talked about
23 U.S. donor deferral policies. Dr. Alan Williams, who is
24 here today, of the Red Cross, talked about results from the
25 REDS study, Retrovirus Epidemiology Donor Study, which were

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1 relevant to this question. Dr. Mark Weinstein, Director of
2 our Division of Hematology, talked about withdrawal and
3 recall policies and their relationship to the supply of
4 plasma derivatives in the U.S.
5 To talk about policies, we had Dr. Jeremy Metters
6 who is Deputy Chief Medical Office of the U.K. and is their
7 senior spokesperson on this issue, and Dr. Douglas Kennedy
8 of Canada.
9 [Slide.]
10 Turning to their recommendations; first, we asked
11 them should FDA recommend new deferral criteria for blood
12 donors to attempt to reduce the theoretical risk for
13 transmitting new-variant Creutzfeldt-Jacov disease by
14 excluding donors potentially exposed to the agent of BSE.
15 The committee voted nine yes, six no.
16 [Slide.]
17 In the next question, they were asked whether this
18 recommendation should apply to those who had resided in the
19 U.K. or other BSE countries. As you can see, they decided
20 to restrict the considerations to the U.K. Secondly,
21 because of the results from the REDS donor survey, we showed
22 that 11 percent of U.S. donors had to travel in the U.K or
23 resided there between 1984 and 1990.
24 They decided that, before they went to the more
25 detailed questions which we will come to in a minute, that

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1 they would like to see the results of a survey giving them
2 more specific data about times of residence. The committee
3 voted 12 to 1 in favor of a survey.
4 [Slide.]
5 Before we go to the remaining questions, let's
6 look at the planned survey. It is a joint survey by the
7 American Red Cross, the American Association of Blood Banks,
8 America's Blood Centers and the National Heart, Lung and
9 Blood Institute. The principle investigator is Dr. Williams
10 who also has head the REDS study.
11 It is going to be an anonymous mail survey using
12 eight blood centers from the 1998 REDS survey and four
13 ARCNET sites which are part of the Red Cross system for
14 collecting data. It will include questions on BSE countries
15 which could be useful in the future.
16 [Slide.]
17 These survey results can be used for the other
18 questions which we had asked the committee to address which
19 they are going to address at a later date. Those include,
20 should FDA recommend distinguishing between donors who were
21 resident in BSE countries during periods of higher or lower
22 risk of exposure because of the time course of the BSE
23 epidemic and, secondly, should we recommend exclusion of
24 donors who had less intense exposure to beef products based
25 on limited travel to the BSE country.

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1 That time period will be addressed in the survey.
2 [Slide.]
3 The committee did go on to address, based on the
4 information presented to them in their deliberations,
5 additional questions, however. In the case of
6 recommendation of withdrawal for blood components, based on
7 donor-deferral criteria, they have voted 7 yes and 5 no. In
8 the case of withdrawal for plasma derivatives based on these
9 criteria, they voted 11 no, 1 yes.
10 [Slide.]
11 We also discussed with them that we plan to refer
12 possible cases of new-variant CJD to the CDC for
13 investigation. Considering precautionary withdrawal for
14 possible new-variant CJD, we asked, "Should we recommend
15 precautionary quarantine or withdrawal for plasma
16 derivatives to which a possible new-variant CJD donor
17 contributed, pending confirmation?"
18 They voted 8 yes, 1 no, 1 abstaining and asked to
19 have the question of definitions of possible brought back to
20 them at the next meeting.
21 [Slide.]
22 We also asked whether or not a tonsil biopsy
23 negative for PRP would be sufficient to make product
24 withdrawals unnecessary. They voted 3 abstaining, 6 no.
25 [Slide.]

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1 What is the planned follow up? We expect that the
2 survey results will be ready for the next meeting of the
3 advisory committee which is scheduled for June 2, 1999. We
4 will then consider their recommendations within FDA. We
5 will consult with other PHS agencies in the Department. We
6 may discuss it at the PHS Advisory Committee on Blood Safety
7 and Availability and then there will be an announcement of
8 policy through revised guidance.
9 DR. HOLLINGER: Thank you, Dr. Jacobs.
10 Any questions for Dr. Jacobs from the committee?
11 If not, then we will go to the next update on current policy
12 regarding CJD and blood donors by Dr. Dorothy Scott.
13 **Current Policy Regarding CJD and Blood Donors**
14 DR. SCOTT: Good morning.
15 [Slide.]
16 I am going to provide you with a summary of recent
17 events and current considerations regarding CJD and blood
18 donors. First, I want to refamiliarize the audience with
19 the previous recommendations regarding CJD and blood
20 products.
21 These recommendations were formalized in a
22 guidance in August of 1995 and this guidance was revised on
23 December 11, 1996. Basically, the recommendations were to
24 defer all donors who had CJD risk factors, of course, or CJD
25 and the CJD risk factors included a family history,

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1 pituitary-growth-hormone recipients and dura-mater-graft
2 recipients.
3 In addition, it was recommended to withdraw all
4 plasma derivatives, all products, if a donor developed CJD,
5 had a strongly positive family history, was a pituitary-
6 growth-hormone receipient or a dura-mater recipient.
7 [Slide.]
8 These recommendations were revised. This revision
9 was announced on the Internet on September 9, 1998. These
10 revisions were based upon an extensive review of old and new
11 epidemiologic and scientific evidence about the possible
12 transmission of CJD through blood and blood products and
13 also there were many discussions with advisory committees
14 and the CDC.
15 So the revised recommendations are not to retrieve
16 quarantine or destroy plasma derivatives if a donor has CJD
17 risks, as outlined previously, or CJD. However, it is still
18 recommended to defer donors who have CJD risks or CJD. In
19 addition--and of course, this is completely new because of
20 the concern about possible new-variant CJD--it was
21 recommended to retrieve quarantine and destroy any materials
22 if the donor develops or is reported to have new-variant
23 CJD.
24 Obviously, new-variant CJD is of particular
25 concern because there is a lack of experimental data about

1 blood infectivity with new-variant CJD. We don't know
2 anything, really, about blood infectivity at this point and
3 we don't know anything about partitioning of this new-
4 variant agent during the manufacturing of plasma
5 derivatives.
6 In addition, we do know that new-variant CJD is
7 biologically different from classical CJD. For example, in
8 new-variant CJD--and there is a paper that came out in The
9 Lancet in January of 1999--it is clear that the patients
10 have tonsillar expression of the prion protein, which is not
11 seen in classical CJD cases.
12 Of course, this raised concerns that there might
13 be more expression of the agent, or some expression of the
14 agent, in blood. Furthermore, we don't really know whether
15 the new-variant agent is more virulent or infective.
16 Finally, because it is an emerging agent and has only been
17 around since the early '90's, or has only been identified
18 since the early '90's, we lack the kind of epidemiologic
19 data that might reassure us.
20 [Slide.]
21 How is new-variant CJD diagnosed? I will mention
22 some of the biological features of new-variant CJD, just
23 very briefly. These patients have what are called florid
24 plaques. They have spongiform changes that are common in
25 certain parts of the brain but are not common in the

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1 cerebral cortex. They tend to have a very high density of
2 prion protein accumulation, especially in the cerebrum and
3 cerebellum.
4 There may be a role now for tonsillar biopsy in
5 the diagnosis of these patients. In addition, they have
6 been reported to have a unique glycoform of the prion
7 protein.
8 [Slide.]
9 As you have seen from Dr. Jacobs' presentation
10 just now, the TSE Advisory Committee has recommended
11 quarantine and withdrawal of materials that come from a
12 suspected new-variant CJD patient. And so we have been
13 working with the CDC on a case definition for suspected new-
14 variant CJD. The reason this can come about, obviously, is
15 because there may be a patient who has characteristics of
16 new-variant CJD for which we do not have a brain biopsy or
17 an autopsy.
18 Suspected cases, of course, would be patients with
19 some form of dementia and some or all of the following
20 characteristics; a young age of onset--that is, age less
21 than 55 years. All the new-variant patients have had
22 sensory or psychiatric presentations so this would be a
23 characteristics that would raise suspicion.
24 In addition, overt movement disorders such as
25 chorea and myofungus are often delayed after the initial

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1 presentation of systems. New-variant patients tend to have
2 a prolonged duration of illness, an average of fourteen
3 months as compared with classical CJD patients. Of course,
4 if such as suspected patient arose, the index of suspicion
5 would be greatly increased if they had been exposed to the
6 BSE agent, obviously by travel and residence in the BSE
7 country.

8 Again, suspected new-variant case would be
9 somebody who did not have another explanation for having a
10 CJD-like illness such as iatrogenic exposure and the other
11 things that I have outlined here.

12 So this is a working definition. It hasn't been
13 finalized.

14 [Slide.]

15 I should mention that the CDC is investigating all
16 such cases that are reported to it. I think, to date, they
17 have investigated about forty suspected cases and have not
18 come up with a new-variant case yet.

19 After September, 1998, we were almost immediately
20 challenged with an unusual case of CJD which initially
21 raised concerns about the possibility of new-variant CJD in
22 a plasma donor. This person actually does have CJD. The
23 patient was a regular plasma donor since 1996 and made
24 donations through August of 1998 and had obvious signs of
25 mental decline as of May, 1998.

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1 So there were a couple of unusual and unexpected
2 aspects of this case as compared with other kinds of CJD-
3 donor reports that we have had in the past. First of all,
4 the donor was very young, 29 years of age, when its symptoms
5 were first exhibited. In addition, there were donations
6 made during the symptomatic period.
7 So the initial manufacturer action, when they
8 heard about this case, was one with which the FDA concurred
9 and that was to place all products and intermediates under
10 their control on hold.
11 [Slide.]
12 Further investigation occurred. There was a brain
13 biopsy and this patient actually had a biopsy that was
14 consistent with classical CJD. Prion glycoforms were also
15 done and the glycoform was consistent with classical and not
16 new-variant CJD. However, the manufacturer voluntarily did
17 withdraw factor VIII and factor IX.
18 The FDA further recommended, along with advice
19 from the Blood Safety Committee, that the manufacturer could
20 distribute medically necessary products such as immune
21 globulins, antithrombin III and alpha 1 protease inhibitors.
22 They were asked to limit albumin distribution to documented
23 medical requests and also to notify vaccine manufacturers to
24 avoid use of this albumin.
25 This was not really a safety issue, but this was

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1 to address concerns about public confidence in vaccines.
2 Finally, they were asked to find out whether any of the
3 affected product lots were used to make non-medically
4 necessary products and, if so, to let us know.
5 [Slide.]
6 So, finally, this is just a summary of the ongoing
7 CJD regulatory issues and FDA actions. Of course, FDA
8 continues to review epidemiologic and scientific studies of
9 CJD transmissibility by blood and, naturally, this will
10 include new-variant CJD.
11 If there are other suspected new-variant CJD
12 cases, we will--currently, at least, we are treating any
13 products from such a donor on a case-by-case basis with CDC
14 investigation. So we are actually working through the CDC
15 to investigate cases like that.
16 Labeling issues are planned to be addressed in
17 terms of labeling plasma derivatives with a generic
18 statement indicating that there is a theoretical risk of
19 transmission of the CJD agent by blood. As you have already
20 heard, deferral of United Kingdom donors is under discussion
21 and will be addressed at the June 2 TSE Advisory Committee
22 meeting.
23 Finally, we are in the process of drafting new
24 recommendations of formal guidance which will include
25 criteria for suspected and new-variant CJD and, obviously,

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1 will incorporate, in much greater detail, the
2 recommendations made in September, 1998.
3 That's all.
4 DR. BOYLE: On your list of regulatory issues, why
5 isn't mandatory reporting on that list of issues being
6 discussed?
7 DR. SCOTT: The mandatory reporting of--
8 DR. BOYLE: Of CJD cases, new-variant CJD cases.
9 DR. SCOTT: I think that is a CDC issue. In other
10 words, that has to be--that is not under our control.
11 DR. BOYLE: I just noticed that your list of
12 things included things of your work with CDC, in terms of
13 the whole blood-product safety issue. I was wondering where
14 that stands.
15 DR. KHABBAZ: The authority for mandatory
16 reporting lies with states and a number of states actually
17 have made CJD a notifiable disease. But some have not.
18 DR. BOYLE: Does CDC recommend to the states
19 things that should be under mandatory reporting?
20 DR. KHABBAZ: We work with the Counsel of States
21 and they are the ones making the recommendation.
22 MR. DUBIN: Just a couple of issues. Obviously,
23 we would support the mandatory reporting question. And the
24 landscape seems to be changing out there with classical CJD
25 over the last six or seven months, year, year and a half.

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1 We have seen cases of classical CJD confirmed in people in
2 the 27- to 31-year-old range.
3 We are aware of two confirmed. We believe there
4 are three. And that would mean that something had changed
5 in that equation. And we are absolutely concerned about
6 that. We are concerned about the slowness in which the
7 government is responding to the British donor question.
8 Obviously, action in Canada, Europe and the UK has been at a
9 different pace.
10 I think all of these things indicate we still have
11 a lot to learn about this and need to put the resources on
12 the table in both the private sector and government to get
13 answers at the most rapid pace possible. In lieu of those
14 answers, I think we need to be responding faster to
15 questions like British donors.
16 DR. HOLLINGER: Thank you, Dr. Scott. Oh; Dr.
17 Mitchell?
18 DR. MITCHELL: I had a comment and then a question
19 about your presentation. First of all, I think that it is
20 important that we get information about blood products that
21 are under the jurisdiction of other committees. So I am
22 very happy to be able to receive the information on the
23 deliberations and the recommendations of the SE committee
24 and the other Blood Product Safety and Availability
25 Committee.

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1 The question that I had is that you said that the
2 recommendation was changed to not retrieve or quarantine
3 people who are known to have CJD. Could you talk about why
4 that was done?
5 DR. SCOTT: That is actually a talk in itself, but
6 I think that I can summarize for you that there was a lot of
7 reassuring epidemiologic data. Quite a bit of that has been
8 new since 1995 which suggested, for example, through case-
9 control studies, that transfusion did not infer a risk of
10 CJD.
11 In addition to that, we have access to lookback
12 studies. The largest one, I think, is by Marian Sullivan
13 where people did receive blood components from donors who
14 came down with CJD or, I think even, in a few cases,
15 actually had some symptoms of CJD. These people have been
16 followed, now, for up to, I think, it is twelve to fifteen
17 years and have not come down with CJD.
18 There is experimental evidence which also
19 suggests, in animals, that the titer of the CJD agent in
20 endogenous infection is very low and that transmissibility
21 through blood is extremely difficult unless you do a blood-
22 to-brain injection.
23 In addition, in the last several years, we have
24 had a lot more information about partitioning of the CJD
25 agent in plasma derivatives and so I would refer you to Paul

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1 Brown's article in Transfusion in 1998 where he did spiking
2 and endogenous experiments and showed that the processing of
3 plasma derivatives just to--the early fractions diminish the
4 titer of the CJD agent.
5 In addition, we have access to unpublished
6 information from manufacturers. Some of these experiments
7 are extremely well done which also show that the
8 manufacturing procedures, many of them cause log reductions
9 in titers of the CJD agent in spiking experiments.
10 We also, of course, have not heard of any case
11 reports of transmissions through blood. There is a
12 cryoprecipitate study in Seattle where people also receive a
13 great deal of cryoprecipitate and are now being followed,
14 and haven't come down with CJD.
15 There is also some surveillance of the hemophilia
16 community, both active now and also there was a brain-
17 autopsy study of hemophilia people who had died of
18 neurologic disease. None of those have shown evidence of
19 CJD-like illness.
20 In addition, the CDC went back and searched death
21 records for the concurrence diagnosis of CJD and other
22 diagnoses which would cause people to receive a lot of blood
23 products such as hemophilia A, hemophilia B, thallasemia,
24 and sickle-cell anemia.
25 They also found now CJD cases, and there were more

1 than 4,000 for the period that they had studied. They had
2 found no cases where the person also had that co-diagnosis
3 of one of those blood disorders. So there was sort of a
4 massive accumulating reassuring epidemiologic data. In
5 addition, there was the laboratory data.

6 It is the scientific weight of that. Also, in the
7 context of shortage of many products that has caused or
8 precipitated this change. I think the Blood Safety and
9 Availability Committee also recommended that we relax our
10 CJD criteria because of shortage but, really, it was the
11 scientific and epidemiologic evidence that has been pushing
12 this.

13 DR. HOLLINGER: I think the problem is, though--
14 and just a comment--that there is a massive and overwhelming
15 group of scientific evidence that CJD, not the NV CJD data
16 right now, but the CJD, does appear to be--that the safety
17 issue seems to be clear.

18 On the other hand, when one has a recommendation
19 and then you remove or quarantine products under these
20 things, I don't think that allays public fear. I think it
21 just, perhaps, points out to the public that you may not
22 have the convictions that you do of this scientific data.
23 So I think there is a real problem here when manufacturers
24 then remove products when the recommendations are made that
25 it seems to be safe.

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1 DR. EPSTEIN: I just wanted to comment, in follow
2 up to Mr. Dubin's remark. Everyone, of course, is concerned
3 about the question whether cases at a young age are
4 increasing in frequency. But, to the best of my knowledge,
5 they are not. About 95 percent of cases have always been
6 over age 55.
7 There is more attention being paid to these very
8 young cases for two reasons. One is because of the known
9 association of new-variant CJD at a young age and,
10 therefore, the need to make sure that young cases in the
11 U.S. do not represent the appearance of new-variant in this
12 country.
13 The second is because it is known that, of the
14 young cases that have been reported, the majority are
15 associated with exogenous exposure. So when you have young
16 cases, you want to be sure you are not dealing with some
17 form of novel, exogenous exposure. But it is well known
18 that, among sporadic CJD cases, 95 percent are over age 55.
19 That has not changed, to my knowledge.
20 The second point about how quickly one can proceed
21 about considering deferral of donors with potential BSE
22 exposure due to food consumption in endemic countries,
23 particular of the U.K., the problem that we face is that we
24 can't ignore the impact on the blood supply.
25 What we learned, to our astonishment and, as Dr.

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1 Jacobs pointed out, 11 percent of U.S. donors have resided
2 in or traveled in the U.K. We simply can't dispense with
3 11 percent of the blood supply. So it is going to take us
4 some time to find out what the impact of a deferral
5 criterion would be and how to craft it sensibly.
6 I believe that is the responsible course.
7 MR. DUBIN: Jay, we, of all people, wouldn't
8 suggest for a moment that you dispense with 11 percent of
9 your potential donors. That has not been suggested. We
10 still believe, within the context of responsible action, we
11 are not moving fast enough. There are questions about
12 youth. I don't have the numbers with me. I will get them
13 to you. They are in our office. I don't have them with me.
14 But there has been no concept, on our part, of
15 dumping 11 percent in an irresponsible way. We could begin
16 to talk about other issues as well, about the way we
17 conceptualize the donor pool in this country, the smallness
18 of our conceptualization. There are a lot of issues that
19 relate to this that have come up, and to narrow it in like
20 that and suggest that we would make a suggestion like that,
21 doesn't work for us, Jay. Not at all.
22 DR. HOLLINGER: Thank you, Corey.
23 We will move on, then, to the last committee
24 update. It is on Group O sensitivity in rapid test.
25 **Group O Sensitivity in Rapid Test**

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1 DR. MIED: We will hear from Dr. Bernard Branson
2 of CDC who will present a CDC recommendation on this issue.
3 Then I will return to give the update.
4 DR. BRANSON: When the first case of HIV-1 Group O
5 infection was detected in 1996, when CBER, on the
6 recommendation from the Blood Products Advisory Committee,
7 asked manufacturers of approved HIV tests to revise their
8 currently approved products to include a consensus antigen
9 for Group O.
10 CBER also instituted a requirement which specified
11 that any new HIV-1 test must demonstrate the ability to
12 detect Group O in order to be considered for approval.
13 Several developments since that time have led CDC to
14 conclude that, in posing this requirement, on rapid HIV
15 tests intended for diagnostic use only, represents a major
16 missed opportunity for public health because this
17 requirement presents a barrier to manufacturers seeking
18 licensure for such tests.
19 First, CDC's system for sentinel surveillance has
20 allayed initial concerns about the extent and spread of
21 Group O infection in the United States. Only one additional
22 case of Group O has been identified in the three years since
23 the first case was detected in 1996. Thus, the requirement
24 for Group O sensitivity appears unnecessary.
25 HIV-2 has been detected more frequently than

1 Group O but, because it is still rare, CDC does not
2 recommend routine diagnostic testing for HIV-2 unless it is
3 warranted by epidemiologic circumstances. Although HIV-2
4 and HIV-2 combination tests are FDA approved, a recent
5 survey indicates that 88 percent of public-health
6 laboratories use HIV-1-only tests when testing for purposes
7 other than blood donation.
8 Second, the need for rapid HIV tests that detect
9 Group M infection, the strain observed in almost all HIV-
10 infected persons in the United States, has become
11 increasingly acute. CDC's data from clinics at publicly
12 funded testing sites consistently demonstrate that persons
13 do not return to receive about a quarter of positive test
14 results.
15 This problem could be virtually eliminated by the
16 use of rapid tests from which results could be provided
17 immediately. Thus, the use of rapid test would, each year,
18 allow approximately 8,000 more positive test results to be
19 provided to persons at publicly funded testing sites at the
20 time they are tested.
21 Numerous studies have demonstrated that many HIV
22 infections go undetected in persons seeking health services
23 in emergency rooms, clinics and hospitals because they are
24 not tested. Since 1993, CDC has recommended that testing be
25 routinely offered to persons in areas with high HIV

1 prevalence when they access healthcare.

2 This recommendation has rarely been implemented
3 because the logistics of testing with the convention EIA
4 Western Blot makes this impractical. Studies have shown
5 that when HIV testing is offered in these venues, many
6 tested persons do not make the routine visit required to
7 learn their results.

8 Many institutions do not conduct the recommended
9 testing because they lack the resources necessary to locate
10 and notify the infected persons who do not return. Using
11 rapid tests for screening in such settings would solve many
12 of these logistical problems and could help to identify a
13 substantial number of HIV-infected person who are unaware of
14 their infection.

15 A study published in the February, 1999 issue of
16 Annals of Emergency Medicine by researchers at Johns Hopkins
17 compared standard and rapid tests among emergency department
18 patients and found that the use of a rapid test for
19 emergency departments was well accepted and detected a
20 number of new HIV infections.

21 Even when the standard EIA test was performed
22 immediately, persons who received the rapid test were less
23 likely to leave before receiving their test results and more
24 likely to keep their follow-up appointments.

25 Rapid test also promises to substantially boost

1 efforts to eliminate perinatal HIV transmission. Data from
2 New York State described in the November 1998 New England
3 Journal of Medicine revealed that initiating antiretroviral
4 therapy for infants born to HIV-infected mothers who were
5 not identified during pregnancy reduced transmission by 50
6 percent.

7 This prompted the State of New York to require
8 that HIV test results for infants be available within
9 48 hours of birth and also led New York to formally request
10 FDA to expedite the approval of rapid HIV tests.

11 The only FDA-approved rapid test currently
12 available for use in the United States, SUDS, the single-use
13 diagnostic system for HIV-1, is insufficient to address
14 these needs. Although relatively rapid, the SUDS test poses
15 its own logistical problems in that it is cumbersome to
16 perform and somewhat difficult to interpret.

17 More importantly, two recent evaluations using
18 stored sera found a low specificity for SUDS, 75 percent in
19 the WHO performance evaluation and 77 percent in the study
20 by the neurology lab of the Walter Reed Army Institute of
21 Research.

22 Even if SUDS specificity approached the
23 99.6 percent observed in the clinical trial submitted with
24 the PMA application, there remains the problem of the low
25 predictive value when using a single screening test in a low

1 prevalence population. This is of particular concern for
2 the screening of intrapartum mothers and neonates. A two
3 rapid-test algorithm will provide a much better predictive
4 value in such populations.
5 Since CDC's March, 1998 recommendation for the
6 expanded use of rapid HIV tests, several manufacturers of
7 tests in use outside this country have indicated intentions
8 to commercialize these tests for use in the United States.
9 CDC and Walter Reed have evaluated several of these tests
10 and found their sensitivity and specificity to be excellent
11 and a clinical trial evaluating for such tests under field
12 conditions is currently under way in Los Angeles.
13 Although several of these tests, marketed outside
14 the U.S., detect both HIV-2 and Group O, rights for the use
15 of these antigens are subject to complicated cross-licensing
16 agreements. The requirement for Group-O sensitivity
17 threatens to impede or preclude their availability in this
18 country.
19 Based on these observations, and in view of the
20 urgent public-health needs for additional rapid tests in the
21 United States, CDC considers it prudent for CBER to suspend
22 the requirement for inclusion of a specific Group-O antigen
23 in HIV tests not intended for blood screening.
24 CDC will maintain active surveillance for HIV
25 subtypes and will advise CBER and the Blood Products

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1 Advisory Committee immediately of any increase in Group-O
2 infection that might warrant such a requirement in the
3 future.
4 Thank you.
5 DR. MIED: Thank you.
6 [Slide.]
7 In 1996, following the discovery of the first HIV-
8 1 Group-O case in the United States, FDA sent letters to kit
9 manufacturers alerting them to the need to move rapidly to
10 develop new tests or to modify existing tests to detect
11 individuals infected with HIV-1 Group O. This request
12 applied to both screening and supplemental assays.
13 Specifically, a letter to IND holders notified
14 them of the requirement that all new tests be able to detect
15 Group O in order to obtain licensure for their test.
16 Manufacturers who had a product-license application under
17 review at CBER for a test which was close to licensure were
18 requested to modify the test as soon as possible after
19 licensure. Manufacturers of licensed tests were requested
20 to modify their tests as soon as possible.
21 [Slide.]
22 In the letters to kit manufacturers, FDA indicated
23 that the modified kits should contain some portion of an
24 HIV-1 Group O virus. It was stipulated that a claim of
25 sensitivity for Group O will be permitted if the

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1 modifications to their test include the incorporation of
2 either a Group O consensus antigen in the test--that is, a
3 published Los Alamos-type consensus antigen--or the
4 manufacturer's own composite consensus antigen derived from
5 reactivity data for various sequences or, a sequence from a
6 prototype isolate that is highly representative of Group O
7 as a whole.

8 Secondly, it was necessary for manufacturers to
9 show best effort in obtaining Group-O sera and to
10 demonstrate reactivity of all Group-O sera they run on their
11 modified test.

12 Thirdly, it was essential for them to demonstrate
13 that sensitivity of the test for antibodies to the Group-M
14 viruses had not been compromised; that is, they would need
15 to perform an equivalency study to demonstrate that their
16 modified kit retains its previous sensitivity for HIV-1
17 Group M.

18 Although manufacturers have been diligently
19 addressing this issue and making the necessary modifications
20 to their kits, at the present time, there are no licensed
21 tests that are labeled with a specific claim of sensitivity
22 for Group O. FDA is aware that the policy of requiring all
23 new tests for HIV to be sensitive for Group O by meeting
24 these criteria, especially the inclusion of a Group-O
25 antigen in the kit may be a barrier for manufacturers who

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1 wish to submit new rapid tests to FDA for approval and
2 introduction into the U.S. marketplace.
3 In June of 1998, FDA brought to the Blood Products
4 Advisory Committee the question of whether to retain the
5 requirement of sensitivity for Group O in rapid tests for
6 use in diagnostic settings. The committee voted 12 to 1
7 that FDA should continue to require Group-O sensitivity in
8 all new HIV tests to be used in a diagnostic setting.
9 [Slide.]
10 However, FDA had reconsidered this issue for
11 several reasons. As Dr. Branson had indicated, there have
12 been only two HIV-1 Group-O cases identified in the United
13 States. These two cases, which were discovered by CDC's
14 ongoing surveillance for HIV variance represent an extremely
15 low incidence of Group O infection.
16 A CDC study showed that the currently licensed
17 blood-screening or diagnostic kits, including the licensed
18 rapid test, detect most Group-O sera due to cross reactivity
19 with the Group M antigens in the kits.
20 In recent studies conducted by Dr. Neil
21 Constantine using a panel of 24 Group-O sera, five out of
22 eight unlicensed internationally available rapid tests
23 detected 100 percent of the samples while three of the tests
24 detected 89 percent to 96 percent of the Group-O samples.
25 It is of note that four of the five tests that detected all

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1 24 samples did not contain a Group-O antigen.

2 [Slide.]

3 The major reason for the FDA reconsidering its
4 policy on Group-O sensitivity in rapid tests is that of the
5 public-health benefit that would result from the approval of
6 additional rapid tests. In the March, 1998 MMWR on expanded
7 use of rapid tests, CDC estimated that, in 1995, over 8,000
8 more infected individuals would have learned of their
9 infection if a rapid test were used.

10 In the MMWR, the Public Health Service advocated
11 providing preliminary positive results from a rapid test to
12 the patient at the time of their first visit to the clinic.
13 In settings with a high prevalence of HIV infection where
14 the rate of patient return for test results is low, this
15 would be a clear public-health benefit.

16 However, of the two rapid tests which have been
17 licensed by FDA, only one remains commercially available,
18 the Murex SUDS test. Use of the Murex test alone carries
19 the disadvantage of having more than 8,000 additional
20 preliminary false positives per year.

21 When FDA approves another rapid test, that test
22 could be used concurrently with the Murex test to minimize
23 preliminary false-positive notifications. It is for this
24 reason that the World Health Organization currently
25 recommends that combinations of rapid tests be run.

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1 With the approval of another rapid test, the
2 Public Health Service could recommend a diagnostic algorithm
3 governing the concurrent use of two rapid tests to improve
4 the predictive value of a positive test result. So, to help
5 achieve this public-health benefit, FDA would like to
6 facilitate the submission and approval of applications for
7 rapid diagnostic tests.
8 Inclusion of Group-O sensitivity is a clear
9 barrier to market for manufacturers of rapid tests so, in
10 accordance with CDC's position statement on this issue as
11 presented by Dr. Branson, FDA, therefore, has suspended the
12 requirement of inclusion of a specific Group-O antigen in
13 rapid tests for HIV-1 antibody for use in a diagnostic
14 setting.
15 [Slide.]
16 For approval, the manufacturer of a rapid test
17 that does not include a specific Group-O antigen will be
18 required to demonstrate a level of sensitivity for Group-O
19 sera based on cross-reactivity with the current Group-M
20 antigens in the test that is comparable to that of the
21 currently licensed non-rapid EIA tests for HIV antibodies.
22 In addition, FDA may require labeling for Group-O
23 cross-reactivity based on a panel of sera. This approach
24 was useful in the past to address cross-reactivity for HIV-2
25 and HTLV-2 without creating a false claim for kits that

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1 lacked the specific antigens.

2 In addition, for approval of a rapid test, the

3 manufacturer will be required to make an explicit commitment

4 to file a PMA amendment within two years of initial approval

5 to modify the test to obtain a specific claim for

6 sensitivity for Group O. This amendment would include the

7 incorporation of the Group-O antigen in the test an

8 clinical-trial results that demonstrate Group-O

9 detectability as well as retention of sensitivity for HIV-1

10 Group M.

11 I should emphasize that this policy does not

12 affect the current requirement that new tests licensed for

13 use in blood screening include a Group-O antigen in the test

14 and be labeled with a claim for sensitivity for HIV-1

15 Group O.

16 We welcome feedback from the committee on FDA's

17 current policy which suspends the requirement for inclusion

18 of a specific Group-O antigen in rapid diagnostic tests.

19 DR. HOLLINGER: Any comments? Any questions?

20 DR. LINDEN: I have two questions. One; when is,

21 or was, this effective?

22 DR. MIED: We are making it effective now. The

23 suspension of the requirement for inclusion of a Group-O

24 antigen in a rapid test.

25 DR. LINDEN: Do you have any feedback from any

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1 potential sponsors as for how many this might make a change
2 that will cause them to apply?
3 DR. MIED: We think it will help most of the
4 manufacturers because there are difficulties with obtaining
5 patent positions and licensure of the rights to using
6 specific Group-O sequences in the United States. It is a
7 very difficult matter for them and that alone, is a major
8 part of the reason why it represents a barrier to inclusion
9 of such antigens in a rapid test.
10 DR. LINDEN: My last question is I assume that
11 there is no change in terms of the product that is currently
12 on the market; right? I mean, they are approved and there
13 is not a necessity for them to move to group O?
14 DR. MIED: Are you referring to the Murex subtest?
15 DR. LINDEN: Yes.
16 DR. MIED: In the CDC study that I talked about a
17 little earlier, I believe the Murex subtest, although the
18 numbers are low, did detect seven of eight Group-O sera in
19 that evaluation. So it does well with Group-O sensitivity
20 as it is.
21 DR. LINDEN: Thank you.
22 DR. HOLLINGER: Thank you, Dr. Meid. This
23 concludes the committee updates. We are now going to move
24 into the first open session. The session, at this point, is
25 on nucleic acid testing of whole blood. It is

1 informational, primarily. The committee does not have any
2 questions to respond to. It is mostly for discussion later
3 on.
4 I want to remind the speakers that the time
5 allotment that is given to you is ten minutes. We will hold
6 you to that.
7 So the first person to discuss this is Dr. Hewlett
8 who will give an introduction and background to the session.
9 Dr. Hewlett?
10 **I. NUCLEIC ACID TESTING OF WHOLE BLOOD--INFORMATIONAL**
11 **Introduction and Background**
12 DR. HEWLETT: Thank you, Dr. Hollinger and good
13 morning, everyone.
14 [Slide.]
15 This morning, we are going to discuss the status
16 of nucleic-acid testing, or NAT, of whole-blood donations by
17 testing minipools of plasma. I would like to also mention
18 that this is an information session intended to provide the
19 committee with an understanding of how NAT is being
20 implemented and some of the issues surrounding this
21 implementation.
22 [Slide.]
23 By way of background, the key measures in place to
24 insure viral safety of blood and blood products are the
25 screening of donations for the presence of viral antigens

1 and antibodies and the use of viral inactivation methods to
2 eliminate virus from products.
3 However, a small number of transmissions continue
4 to occur, primarily from whole blood and transfusable
5 components collected during the seronegative phase of
6 infection.
7 [Slide.]
8 In September, 1994, FDA held a conference on the
9 feasibility of genetic technology to close the HIV window in
10 donor screening. Data presented at this conference
11 indicated that nucleic-acid testing could reduce the
12 infectious window period, particularly of HIV and HCV from
13 several days to several weeks.
14 However, the techniques in development did not
15 lend themselves to application for mass screening at that
16 time. As an interim measure, to further reduce the low risk
17 in HIV transmission, p24-antigen screening of blood and
18 plasma was implemented. The former Commissioner of our
19 administration, Dr. David Kessler, had urged the plasma-
20 derivatives industry and the blood-banking community at the
21 time to purse the development and implementation of new
22 technology that would improve the safety of the blood
23 supply.
24 [Slide.]
25 Since then, industry, in collaboration with

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1 government, has been actively engaged in developing NAT for
2 donor screening. Due to the complex and labor-intensive
3 nature of this type of testing, there was considerable
4 interest in screening small pools, or minipools, rather than
5 single donations.

6 Also, testing minipools is a concept in process
7 control to assure viral safety of fractionation pools. By
8 1997, some countries in Europe had initiated voluntary
9 screening of donations by testing pooled donations of plasma
10 using a nucleic-acid-based method.

11 Also, a directive was issued by the European Union
12 that HCV RNA testing would be required in Europe for all
13 plasma for fractionation by July 1, 1999 and that HIV-1
14 testing of such plasma would be required at some unspecified
15 later date.

16 [Slide.]

17 This move on the part of the Europeans created an
18 impetus in the U.S. to implement such testing for blood and
19 plasma. FDA discussed its position that pool testing would
20 be considered a form of donor screening at the Blood
21 Products Advisory Committee meeting in September, 1997.

22 FDA also developed guidance outlining regulatory
23 approaches for implementing pool testing and discussed them
24 at this meeting. Briefly, FDA described possible approaches
25 to implementing testing under the IND involving three

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1 potential scenarios for pool testing; one, a commercially
2 provided test kit; two, a testing service; and, three, an
3 in-house test.
4 In addition, FDA developed and published draft
5 guidance to industry for validation of nucleic-acid tests.
6 At this time, virtually all source plasma--that is, at the
7 present time--in the U.S. is being screened for HCV RNA by a
8 nucleic-acid-based test and some source plasma is being
9 tested in a similar manner for HIV-1. A significant portion
10 of this testing is performed by a central testing laboratory
11 or a testing service.
12 [Slide.]
13 The primary regulatory concerns for FDA in regard
14 to pool testing by NAT include, but are not limited to, the
15 manufacturing consistency of the test, pool size and its
16 impact on test sensitivity, clinical and analytical
17 sensitivity and specificity, reproducibility, validation of
18 methods for tracing positive results back to the unit and
19 the donor, and validation of instrument and software as well
20 as lot-release requirements for the test.
21 FDA also defined a proposed sensitivity limit of
22 100 copies per ml which is the analytic sensitivity of the
23 pool test and is currently considering establishing a
24 sensitivity limit of 5,000 copies per ml for the original
25 donation. Compliance with these limits will be monitored

1 using reference materials and lot-release panels developed
2 by FDA in addition to clinical trials.
3 [Slide.]
4 The European directive spurred the development and
5 implementation of pool testing for whole blood donations at
6 a rapid pace. Establishments involved in the collection of
7 whole blood and transfusible components are currently
8 implementing plasma pool testing nationwide under the IND.
9 Again, testing is being accomplished by the use of test kits
10 or by centralized testing laboratories.
11 Due to the current technology limitations, NAT
12 requires several days more than conventional tests and,
13 consequently, some blood products--example, platelets and
14 some red cells--are expected to be released on the basis of
15 serology, basically. This is necessary to prevent product
16 shortages and harm caused due to lack of products.
17 This phase, which is expected to be of short
18 duration, will be followed by a phase where all components
19 are released on the basis of both NAT and serology.
20 [Slide.]
21 Other implementation issues are that donor testing
22 in all cases is subject to informed consent and the
23 necessary IRB approvals. Issues such as donor notification
24 and counseling, deferral and lookback, are consistent with
25 the practice that has been developed for other viral marker

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1 tests. Donors whose blood is confirmed as being NAT-
2 reactive are notified and counseled regarding their
3 investigational test result.
4 Such donors are deferred until their status is
5 resolved and are indefinitely deferred from donating after
6 they have undergone seroconversion. During the phase where
7 products are released on the basis of serology only, a small
8 number of recipients of labile components may be informed
9 that they had received a product that was potentially at
10 risk for HCV or HIV based on an experimental test on the
11 donor.
12 Such recipients would be appropriately counseled
13 and referred for follow up and medical care as well as
14 follow-up testing. FDA allows local hospitals to decide
15 whether the risk of such notification necessitates any
16 special notice to patients prior to transfusion. In the
17 subsequent phase, when products are released on the basis of
18 both serology and NAT, it is anticipated that this number
19 will be reduced.
20 [Slide.]
21 In conclusion, NAT is being implement for whole
22 blood via the IND mechanism. NAT testing is expected to
23 further reduce the low risk of viral transmission of HIV and
24 HCV during the window period and the introduction of NAT is
25 considered a major public-health advancement in viral safety

1 of blood and blood products.

2 So, with that, I will conclude my presentation. I

3 would just like to say that in the presentations that will

4 follow, you will hear from various blood organizations and

5 manufacturers of test kits about the strategies and

6 approaches to implementing NAT in the blood-bank setting.

7 Thank you.

8 DR. HOLLINGER: Thank you, Dr. Hewlett.

9 The next speaker is from Gen-Probe, Dr. Christina

10 Giachetti.

11 **High-Throughput Assay for the Simultaneous**

12 **Detection of HIV-1 and HCV RNAs**

13 DR. GIACHETTI: Thank you.

14 [Slide.]

15 I would like to thank the organizers for inviting

16 me to give this talk. I will present the Gen-Probe high-

17 throughput assay for the simultaneous detection of HIV and

18 HCV RNA.

19 Gen-Probe's strategy is to develop a cost-

20 effective high-throughput automated system named TIGRIS for

21 the detection of HIV and HCV RNA for individual donor

22 testing and, as an interim measure until TIGRIS is

23 commercially available, to develop a semi-automatic system,

24 the TMA component system for plasma pool testing.

25 This test is currently used at the American Red Cross.

1 [Slide.]

2 Our assay objectives are shown here. It is an
3 analytical sensitivity of 100 copies per ml, detection of
4 HCV and HIV subtypes, detection of infection before
5 seroconversion, a specificity higher than 99.5 percent,
6 incorporation of internal control. The same reagent
7 formulations will be applicable to both systems, the semi-
8 automatic and the fully-automatic. And we provide
9 discriminatory assays for resolution of multiplex assays
10 repetitive reactives.

11 [Slide.]

12 The assay protocol consists of three steps. They
13 are all hybridization based and they are all fully
14 integrated. The steps are sample processing followed by
15 amplification and then detection.

16 [Slide.]

17 For the sample preparation, we use target capture
18 and magnetic microparticle separation. During these, the
19 RNA target is hybridized to a capture probe with
20 hybridization through a poly-A-tail to a poly-DT-tail which
21 is present in magnetic microparticles. Once hybridization
22 occurs, the use of magnetic rods allows separation our or
23 input target from all the rest of the specimens.

24 The system is very efficient and allows for batch
25 processing of the samples and allows us to eliminate all

1 potential inhibitory substances.

2 [Slide.]

3 Following sample processing, we do transcription-

4 mediated amplification to amplify our target. The reaction

5 uses two enzymes, reverse transcriptase and T7 polymerase.

6 It can be used to RNA or DNA targets. It produces a RNA

7 amplicon. The system is very efficient. In our reactions,

8 we generate around 10^{12} molecules of HIV and HCV per copy

9 input of target and the reaction is isothermal.

10 [Slide.]

11 Detection occurs with the hybridization protection

12 assay. During this assay, what you do is you utilize

13 acridinium ester-labeled probes which will hybridize to our

14 target amplicon RNA.

15 [Slide.]

16 Hybridization of the probe to the RNA allows for

17 protection of the A level so that addition of a selection

18 reagent will only destroy the level on the non-hybridized

19 probe, and then the hybridized probe is passed to a

20 detection step where chemiluminescence allows detective of

21 our protected probe.

22 [Slide.]

23 Incorporation of the internal control requires the

24 use of the dual kinetic analysis. They use different

25 acridinium ester labels with different kinetics. We label

1 our internal control with a probe with rapid kinetics which
2 called a flasher probe and our target molecules are labeled
3 with a glower probe with slow kinetics. We use the
4 exponential tail-fit algorithm to be able to deconvolute the
5 mixed signal and calculate the amount of internal control or
6 target that we have in each sample.
7 [Slide.]
8 I will switch here to show some data for assay
9 performance. We tested analytical sensitivity, clinical
10 sensitivity, subtype detection and specificity. First, HIV
11 sensitivity. Here, I am showing this table which is
12 analytical sensitivity for four different lots of reagents
13 and manufacturers.
14 As you can see, in all the cases, we were able to
15 obtain 100 percent detection at the 100 copies per ml level.
16 Also, sensitivity is still very good at 30 copies per ml
17 where our lots have between 88 and 98 percent detection at
18 30 copies per ml.
19 To confirm these, we have tested different panels.
20 In this case, I am showing results from the CBER panel
21 distributed in 1997. As you can see, we can detect as
22 positive signals all the positive panel members including
23 the one which has just 25 copies per ml.
24 [Slide.]
25 We make it big effort to demonstrate detection of

1 different subtypes. Here is a summary in which I show which
2 are the different subtypes which we have tested, subtypes
3 from A to H belongs to Group M and also we tested subtypes
4 that belonged to the new Group N as well as type Os.
5 As you can see, for type O, we tested a total of
6 39 different viral isolates and 19 different specimens. In
7 all the cases, are test is able to detect it even after very
8 serial dilution of the viral isolates down to 10^{-6} or 10^{-8}
9 dilution.
10 [Slide.]
11 We tested clinical sensitivity in seroconversion
12 panels. On an average, our test is able to detect
13 infections 3.6 days before seroconversion and we are able to
14 detect infection 7.5 days before the detection with p24
15 antigen. If these samples are pool-diluted, we still were
16 able to have early detection with this test.
17 [Slide.]
18 Now to HCV sensitivity.
19 [Slide.]
20 Here, again, I am showing results from four
21 different clinical lots. In all the cases, we were able to
22 have 100 percent detection in 100 copies per ml.
23 Sensitivity, at 30 copies per ml, is between 100 and
24 90 percent for our lot, showing very good sensitivity.
25 Again, we tested different panels. Here is the

1 HCV panel distributed lots here and we were able to detect
2 HCV in all the panel members including the one that had just
3 5 genomic equivalents per ml. In many cases, we were able
4 to detect it after further dilution.

5 [Slide.]

6 Again, here we detect subtype from Group 1 to 5.
7 And, in all the cases, our test is positive for all the HCV
8 subtypes. Clinical sensitivity was tested with these
9 seroconversion panels. On average, we were able to detect
10 HCV infections 83.8 days before seroconversion for undiluted
11 samples. For pool-diluted samples, still we were able to
12 detect 31.7 days before seroconversion.

13 [Slide.]

14 Specificity was tested in normal plasma as well as
15 a variety of problematic samples. I am just going to show
16 the results from normal plasma. Here we show specificity
17 studies with four different lots of reagents that we have
18 manufactured so far. Overall, specificity, in terms of
19 repetitive reactive rate is 0 percent. This test has very
20 good specificity.

21 Also, we monitor internal control as a measure of
22 assay inhibition and our repetitive internal-control failure
23 rate is 0 percent confirming that our method removes all
24 potential inhibitors.

25 [Slide.]

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1 Conclusions regarding specificity; we haven't
2 found any cross-reactivity with other infectious agents or
3 conditions of liver diseases. No interfering substances
4 have been found so far. Our sample processing removes all
5 interfering substances and we have an internal control that
6 is very useful for confirmation of amplification
7 performance.
8 Regarding sensitivity, we have 95 percent
9 detection of 100 copies per ml and 50 percent detection at
10 the 8 copies per ml letter. For HCV, 95 percent detection
11 at 100 genomic equivalents per ml and 50 percent detection
12 at the 5 genomic equivalents per ml level.
13 We were able to detect virus before seroconversion
14 on an average 16.3 days before antibody and 7.5 days before
15 p24 antigen for HIV.
16 [Slide.]
17 For HCV, we were able to detect 32.8 days before
18 seroconversion. We were able to detect all different
19 subtypes including type O and N as well as HCV subtypes.
20 [Slide.]
21 Finally, this process has been funded in part by
22 federal funds from the National Institute of Heart, Lung and
23 Blood.
24 Thank you very much.
25 DR. HOLLINGER: Thank you.

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1 The next speaker is from the American Red Cross,
2 Dr. Susan Stramer.

3 **American Red Cross**

4 DR. STRAMER: Thank you. I am going to update the
5 committee and others present on the progress that the
6 American Red Cross has made for NAT testing for HIV and HCV.
7 [Slide.]
8 First, I need to go through a little bit of the
9 history that the Red Cross has had with NAT. In December of
10 1996, the Red Cross submitted an amendment to National
11 Genetic Institute's IND using pool using sizes of 512 for
12 HCV and HIV PCR testing. That pooling and testing would
13 have occurred at NGI.
14 Following that, myself and Roger Dodd met with
15 members of NHLBI to solicit increased support for Gen-Probe
16 to pursue pool testing. That occurred during September of
17 '97. That would allow pooling and testing within the blood
18 center control.
19 Following that, the Red Cross submitted a two-part
20 IND with Gen-Probe and that included using pool sizes of 128
21 on the test you just heard described, the multiplex HIV-1
22 HCV transcription-mediated amplification assay including
23 discriminatory-probe reagents; that is, when you get a
24 multiplex reactivity, you then have the ability to
25 distinguish HIV from HCV reactivity. The Gen-Probe

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1 submission went in on December 14.

2 [Slide.]

3 The Red Cross submission went in on 12-23. We

4 received IND approval on January 21 and we initiated linked

5 testing on March 3 of this year with collection starting

6 from March 1. This corresponded with AABB releases of the

7 Association bulletins on NAT, 99.3 and 99.6.

8 [Slide.]

9 Our program objectives include to evaluate the

10 feasibility, efficacy and performance characteristics of the

11 Gen-Probe test. Regarding performance, what we are going to

12 evaluate is sensitivity, specificity and reproducibility of

13 both the multiplex and discriminatory reagents. Under that,

14 we must meet all international regulatory standards

15 including those from Europe--that is the CPMP requirement,

16 which is a test requirement--and, as you have heard from Dr.

17 Hewlett, an FDA requirement per test and an FDA requirement

18 per donation of 5,000 copies per ml.

19 As part of the feasibility and efficacy, we must

20 implement NAT to testing to meet the European plasma

21 requirements promulgated for July 1, 1999 with the eventual

22 release of all products based on NAT.

23 [Slide.]

24 Other IND objectives are to define the meaning of

25 the NAT-reactive seronegative result; that is, to determine

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1 the yield and time-to-seroconversion for both HIV and HCV
2 and through resolution by follow-up testing which I will
3 describe in more detail.
4 Also, as one goal which you will hear more about
5 this afternoon, is to evaluate the replacement of p24
6 antigen testing.
7 [Slide.]
8 To go through our IND program in a little more
9 detail, all 37 Red Cross regions collect samples in a
10 dedicated tube which is a plasma preparation tube which is a
11 plastic gel-sep tube spray-coated with EDTA which we find to
12 be the anticoagulant of choice for the stability of RNA.
13 All regions will ship their tubes to a one centralized
14 facility within the Red Cross referred to as the National
15 Genome Testing Laboratory, NGTL.
16 At the NGTL, during our phase I, which I said has
17 started on March 3, we will construct pools of 128 donations
18 using the Tecan robot. Anti-HIV and anti-HCV seroreactives
19 will be removed prior to pooling. In this program,
20 management of donors and products will be based on a
21 reactive single donor. All products, except for plasma--
22 that is cellular products--will be released during phase I
23 based on serology.
24 Results will be available on it is actually days 3
25 to 4 following collection and we anticipate, even with this

1 turnaround, that 70 to 80 percent of red cells will still be
2 in our control and available to quarantine if we get a NAT-
3 reactive result.

4 [Slide.]

5 The pooling scheme looks something like this. We
6 take 128 individual donations, put them into primary pools
7 of 16--and this is important because I will be focusing on
8 primary pools. All eight primary pools, then, are pooled by
9 the robot into a 128-member pool.

10 If a reactive pool occurs at the 128 level, the
11 resolution scheme involves testing all eight primary pools
12 containing sixteen donations each. One reactive primary
13 pool is identified and then the individual donations are
14 tested. We have one individual donation in our program
15 donor and product management.

16 [Slide.]

17 Our phase II, which is projected to begin on July
18 of '99, will involve pools of 16. As I just showed you, we
19 are already creating those pools by the Tecan. They will
20 include all seroreactives. That is so we have simultaneous
21 release of all products based on NAT and serology. All
22 donors that have a NAT test result in this case--any
23 seroreactive will have a NAT result as well which will aid
24 in donor counseling.

25 The main part of this program is that all products

1 then will be released based on NAT. We will then add NAT
2 testing to one or two of our national testing laboratories
3 so we can really expedite turnaround time and, finally, we
4 will pursue FDA licensure.

5 [Slide.]

6 Phase I program donor notification is based on the
7 reactive donation, as I said, following the discriminatory
8 results so we know if the donor is HIV or HCV reactive. We
9 will then follow up the TMA test by a confirmatory NAT test
10 of a different type and that will be PCR testing at NGI.

11 Product withdrawal and recovery, as I said, will
12 be based on the reactive donation. Consignees then will be
13 further notified as we find out the discriminatory test
14 result that is HIV or HCV. Previous collections from NAT-
15 reactive donations will be recovered for three months for
16 HIV and twelve months for HCV--that is, following the
17 established FDA guidelines.

18 Lookback of previous donations--that is, recipient
19 tracing of previous donations--will be performed only if a
20 discriminatory test result is confirmed by a supplemental
21 NAT test.

22 [Slide.]

23 Regarding our IRB issues for donor management, our
24 study involves donors as the study subjects of the IND under
25 informed consent. HIV and HCV NAT-reactive subjects

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1 following discriminatory testing will be enrolled in a
2 follow-up study to resolve the meaning of the NAT result.
3 HIV follow up will be for three months or until
4 seroconversion occurs with weekly sampling.
5 Testing will include p24 antigen, HIV-1,-2
6 antibody and Western Blot if applicable; supplemental NAT
7 test, again, at NGI which will include a quantitative test
8 and genotyping. For HCV, we will do twelve months or until
9 seroconversion occurs with monthly sampling. Testing for
10 ALT, HCV antibody, RIBA is appropriate, supplemental NAT
11 which will then include NGI PCR quantitative and genotyping.
12 [Slide.]
13 Recipient management; you heard a little bit about
14 this from Indira. Let me elaborate. Recipients are outcome
15 of this research. However, they are not classified as
16 research subjects of this IND. During phase I, what our Red
17 Cross IRB, has required us to do is notify hospitals of the
18 program such that modification of transfusion consent can be
19 determined by each hospital individually.
20 Recipients receiving NAT-reactive units--we hope
21 them to be very few, if at all--will be notified when the
22 individual donation is identified followed by letting them
23 know the discriminatory results--that is HIV or HCV--
24 followed by any other supplemental testing information that
25 we have on NAT and follow-up information.

1 Let me just comment that these units would be
2 transfused if we were not doing NAT testing so this does not
3 decrease the safety of the blood supply. This also enables
4 early treatment as an option and knowledge regarding
5 secondary transmission, if we inform these recipients.
6 It will be up to the primary-care physician and
7 the transfusion-service medical director to determine if
8 there is post-exposure treatment.
9 [Slide.]
10 Our time line; phase I, I said, initiated on 3-3-
11 99. We are now up to 14 regions who are doing testing with
12 all 37 blood-collection regions testing by June 7. Our
13 phase-I modifications, which are actually occurring now but
14 will take full swing in the middle of April, will be shipped
15 as we collect. So, as we collect samples, they will be
16 immediately shipped for testing.
17 Discriminatory testing will be moved up to the
18 primary pool level so that as soon as we find a reactive
19 donation, we also know, presumptively, if it is HIV or HCV.
20 We will base product quarantine on the reactive master pool-
21 -that is, on the pool of 128--and you will see that the
22 specificity of this test is so good that it will allow that.
23 This will enable us to immediately take control of product
24 either within Red Cross control or consignee control.
25 As I mentioned, our phase II project is targeted

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1 for July 1 and this, again, will involve all product-release
2 based on NAT and then we will file a PLA.
3 [Slide.]
4 Just to show you some data, before I get
5 terminated, our sample storage-requirement studies have been
6 divided into two sections; whole blood and plasma. This
7 gives you these three bullets here. We collected EDTA. We
8 will store for up to three days as whole blood at
9 temperatures less than 10 degrees, less than or equal to
10 10 degrees.
11 EDTA plasma, the same temperature requirement.
12 But we have a prolonged storage time as plasma--this was the
13 time period, seven days, we did our studies at--with no
14 greater than 24 hours at room temperature. Room temperature
15 and time sitting on the cells is what destroys RNA from the
16 studies that we have done.
17 [Slide.]
18 Look at specificity, the specificity of this test
19 is, again, excellent. We looked at three different master
20 lots denoted by three different colors. The population mean
21 is all less than 0.3 which is really excellent for the test.
22 We have no reactive samples in our pre-clinical feasibility
23 study including almost 200,000 donations.
24 [Slide.]
25 Looking at sensitivity, briefly, this is a plasma

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1 seroconversion series. You can see frequent sampling here.
2 Blue indicates for HCV when the donor became EIA reactive.
3 You can see a 46-day window period if you look against
4 quantitative PCR. These were the data we generated with the
5 National Genetics Institute under that IND.
6 [Slide.]
7 Then, adding the data from the TMA IND, the Gen-
8 Probe IND, you can see that if we do the testing either at a
9 neat, undiluted or multiplex of 128 pool size, there is no
10 difference. So there is no difference between the dilution
11 and undiluted sample.
12 [Slide.]
13 Looking at another seroconversion series for HCV,
14 because this one is a little different, here you see a 32-
15 day window period reduction from the EIA--that's serology
16 anti-HCV 3.0--to the first reactive on the NAT test that is
17 PCR, quantitative PCR.
18 [Slide.]
19 If you add the TMA data to that, interestingly
20 enough, the multiplex test here, tested neat, was a little
21 bit more sensitive, three days more sensitive than
22 quantitative PCR but we lost seven days here based on the
23 pooling of 128 dilution.
24 Interestingly enough, the sample that was not
25 detected at a pool had 100,000 copies. What we have seen

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1 reproducibly in our hands is HCV does aggregate and it does
2 influence the efficacy of pooling if you are doing large
3 pool sizes. But it is really not an issue with pool sizes
4 of 128 or lower, as I will show you.
5 [Slide.]
6 Looking at the reactivity of a neat--that is,
7 undiluted--sample relative to a pool dilution of 128, and
8 these are only the seronegative donations on this X-Y plot--
9 shows you only those critical samples. There are only two
10 samples in this study of 117 total, actually from 22
11 individuals, that were not detected when diluted.
12 [Slide.]
13 These samples had this viral load, 100,000 and
14 90,000. Here you can see the diluted S to CO and undiluted
15 S to CO.
16 [Slide.]
17 So if we look at the analytical sensitivity
18 studies that we did under IND, these were now not control
19 samples as Indira talked about, but real seroconversion
20 samples that we diluted to endpoint in which we did see
21 aggregation. We saw a mean endpoint titer of these samples
22 at 95 percent confidence using Spearman-Karber analysis of
23 4,395 copies per test. That was the limit of detection.
24 If you multiply this by a pool size of 16, that
25 would give us a theoretical cutoff of 70,000 copies and the

1 two samples I showed you, those two of 117, had 90,000 and
2 100,000 copies per ml. So, even under worst-case conditions
3 predicted by aggregation, we would detect those two samples
4 at a 1 to 16 dilution.
5 So, in this case, HCV testing in a pool size of 16
6 is equivalent to single-donation testing.
7 [Slide.]
8 Doing the same analysis for HIV, you see here the
9 neat assay plotted on the X axis and the 128 dilution
10 plotted on the Y axis. There were eight such samples that
11 fell below the cutoff at a pool dilution of 128.
12 [Slide.]
13 Looking at the viral load in these samples--
14 firstly, let me say they were all p24-antigen negative.
15 This is the multiplex S to CO undilute. This is the diluted
16 S to CO at pools sizes of 128. This is viral load.
17 [Slide.]
18 Doing the same type of analysis by Spearman-Karber
19 on seroconversion samples gave us a 95 percent endpoint
20 detection by the test at 66 copies per ml. Multiplied by 16
21 would give us a final copy number of 1,056. So all eight
22 samples that I showed you on the previous slide would not be
23 detected at a pool size of 16.
24 So, interestingly enough, in this study for HIV, a
25 pool size of 128 was equivalent to that of a pool size of

1 16. However, if we use the p24 antigen yield to project how
2 frequently we would see such individuals, they would occur
3 once--that is, one of these sample from seven different
4 donors--in every 2.68 years.

5 [Slide.]

6 So, in conclusion, we believe there is earlier
7 detection for HIV and HCV. By our pooled NAT program, we
8 will decrease the possibility of a viremic window-period
9 donation. I didn't go through all the means of this, but
10 based on a viremic window period for HIV of six to ten days,
11 pool testing, even in pools, in this case, as large as 500
12 would have cut the window period down by 30 to 50 percent.

13 For HCV, similarly, the viremic window period as
14 defined in our studies at 41 to 57 days, would be cut by 50
15 to 98 percent doing pooled NAT testing. All the unlinked
16 studies we have done, including, now, linked studies of
17 86,016 donations, revealed no false-positive results. And,
18 as an update, we have also had no true positives, either.

19 Thank you.

20 DR. HOLLINGER: Thank you, Susan.

21 The next speaker, Dr. Michael Busch, is going to
22 be talking for the America's Blood Centers.

23 **Blood Centers of the Pacific, Irwin Center**

24 DR. BUSCH: I will presenting a summary of one of
25 the two America's Blood Centers' NAT implementation programs.

1 [Slide.]

2 America's Blood Centers represents a consortium of

3 the majority of the non-Red-Cross blood centers in the

4 country representing approximately half the blood-collection

5 program.

6 America's Blood Centers have developed two

7 relationships and is submitting two INDs. One of these

8 relationships is with Gen-Probe Chiron and I will be

9 presenting that program. Then later we will hear the

10 program that is a collaboration with Roche.

11 I will be summarizing each of these points with

12 the exception of skipping a number of slides on test

13 methodology because you have already seen a summary of that

14 from the folks from Gen-Probe.

15 [Slide.]

16 The program will consist of three testing

17 laboratories. The IND will actually has been submitted

18 under the overall sponsorship of ADC with collaborators, a

19 coordinating center, NCGS, and Gen-Probe Chiron, the test

20 manufacturer. There will actually be a cross-reference to

21 the IND submitted by Gen-Probe in the context of the Red

22 Cross program.

23 So much of what we will be presenting in this talk

24 will be built on the prior two presentations, the Chiron-

25 Gen-Probe test system and the Red Cross strategy for many of

1 the implementation processes.

2 There will be three testing laboratories; the

3 Blood Centers of Southeast Wisconsin, Blood Systems in

4 Scottsdale and the Florida Blood Services. Overall, there

5 will be approximately 60 different collection centers

6 contributing specimens to these three laboratories and,

7 overall, there are approximately 2.5 million donations which

8 will tested annually by these three laboratories.

9 [Slide.]

10 We have gone through the appropriate process in

11 terms of institutional review. We have already obtained IRB

12 approval using a central IRB. The donors, like the Red

13 Cross program, are considered the research subjects, not the

14 recipients, and the donors will be required to consent.

15 Actually, the consent is built in to the routine donor

16 informed consent with an extra information sheet apprising

17 the donors of the full context of the NAT testing and

18 potential follow-up activities.

19 If the donors are found to be reactive, they then

20 proceed through a more complete informed consent for follow

21 up activities. The participation in the study is a required

22 event. So, in other words, a donor cannot give blood, an

23 allogeneic donor, without agreeing to participate in the NAT

24 activities.

25 [Slide.]

1 The study, in terms of the IND formal study
2 component, will really take place during the very brief
3 period following implementation of NAT testing with
4 continued testing after the initial phase under IND. But, in
5 terms of generating the critical data to submit the FDA,
6 that will be generated rather quickly and is really focused
7 on a quick validation of the specificity of the test system,
8 the reproducibility and sensitivity in the context of
9 external standards, and then the logistical issues; can this
10 program operate without significantly impacting blood
11 availability.
12 [Slide.]
13 In terms of this initial phase specificity study,
14 per FDA expectations, the initial phase will represent
15 approximately 270,000 donations that will distributed in
16 11,000 pools. This will actually be accomplished in the
17 course of only about several months of initial phase
18 testing. We feel this will be an adequate period to define
19 the specificity of the assay and to demonstrate the
20 performance characteristics in the context of the
21 sensitivity and logistical issues.
22 The committee handout can skip through the next
23 about eight slides because they are really a repetition of
24 the Gen-Probe test platform.
25 [Slide.]

1 Some of the details in terms of samples and then a
2 little bit of logistics. We will be using EDTA
3 anticoagulated specimens like the Red Cross although we will
4 not be using the PPT special tubes. We believe that the
5 logistics and turnaround time we are able to accomplish will
6 allow us to process the pooled specimens in time to meet the
7 storage requirements.

8 The stability data that Gen-Probe has generated,
9 much of which is in collaboration with the Red Cross, we
10 believe documents the current package-insert stipulation
11 that the samples need to be tested within 72 hours of
12 holding at a reduced, below room-temperature hold, of which
13 no more than 24 hours would actually be at full-fledged room
14 temperature.

15 And then the residual period, up to five days
16 after separation, complete separation off of the spun
17 packed-cell red-cell pellet could be held--the plasma could
18 be held a further period of 2 to 10 degrees. The samples
19 will be transported from the point of collection through to
20 the central laboratory and all subsequent downstream periods
21 under validated shipping and storage conditions.

22 An important component of the ABC Gen-Probe
23 strategy is actually to try to demonstrate the potential to
24 do a sorting strategy. This involves sorting the donations
25 into those that come from first-time versus repeat donors.

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1 Actually, within this single IND, two of the three testing
2 sites will test all comers in parallel; in other words,
3 seroreactive donations will be admixed with unscreened
4 products.
5 Basically all products will go through NAT testing
6 in parallel with serology whereas the larger testing site
7 will sort donations into the 20 percent of donations that
8 come from first-time donors versus the 80 percent that come
9 from repeat donors.
10 The strategy here is to take the 80 percent from
11 repeat donors straight through the NAT testing in parallel
12 with serology with results out almost at the same time as
13 results are out currently releasing product hopefully within
14 four to eight hours of current release, whereas the first-
15 time donors in which the vast majority of your seropositive
16 specimens are represented will be held back.
17 Those donations will not be processed through for
18 NAT testing until the serology is available and the
19 seroreactive units removed. The advantage of this is that
20 dramatic reduction in the number of projected NAT-positive
21 pools by culling out what would be approximately 98 percent
22 of seropositive specimens through this sort of the first-
23 time donors.
24 This will dramatically reduce, by about 50
25 percent, the number of repeat resolution tests performed, a

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1 substantial reduction of cost and labor and, most important,
2 the potential for contamination of laboratories due to the
3 representation of seroreactive units in the overall process.

4 [Slide.]

5 Our pooling strategy will consist of predominantly
6 pooling donations into pools of 24. Basically, at the end
7 of runs, if there are less than 24 donations left that
8 require testing, those specimens will be tested singly. So
9 we will either be testing pools of 24 or individual
10 donations.

11 Like the Red Cross, we will be using a Tecan
12 pipetting system to generate the pools, and all of the
13 software has been established to link the pooled process
14 with the final resolution in testing output data. We are
15 validating that every pool has been generated appropriately
16 through weighing of the intermediate pools and the final
17 pools to validate that all specimens were introduced as
18 appropriate.

19 [Slide.]

20 Samples will be screened using the Gen-Probe
21 system with the initial pool tested by the multiplex HIV-HCV
22 assay. The individual donations from reactive pools with be
23 then tested again in singlicate by the multiplex assay and
24 then further testing using the discriminatory HIV-1 and HCV
25 assays.

1 Product interdiction and donor deferral will be
2 based on the individual reactive multiplex result. In other
3 words, at the point where an individual donation is
4 determined to be reactive on the multiplex assay, it is at
5 that point that we will defer the donors and trigger recall
6 of products from that donation and any prior donations from
7 that donor.
8 In terms of notification of the recipients,
9 however, we will wait until we have determined which virus
10 is responsible. So we will wait until that next run-through
11 where we have discriminated is it HIV-1 or HCV before we
12 would notify recipients of the current donation, were they
13 in phase I released.
14 In contrast further, prior recipients--so lookback
15 notification to prior recipients, we feel, should be further
16 justified by even additional data confirming infection
17 either by a supplemental NAT procedure or follow-up testing
18 on an alternative sample.
19 [Slide.]
20 In terms of the phasing of the activity, like the
21 Red Cross and, as indicated by Indira at the beginning,
22 during the very early implementation phase, we do not want
23 to jeopardize blood availability. Were there some problems,
24 our program is actually phased to try to implement on-line
25 testing as soon as possible, hopefully within weeks to

1 months of implementation of initial testing.

2 But during this initial trial and implementation
3 phase, we recognize that it may be necessary to release
4 blood based on serology and we are planning to implement the
5 phase-I testing on April 15. During this period, all frozen
6 products will be released strictly based on NAT results plus
7 serology.

8 And then we hope to rapidly transition to phase
9 II. The pool sizes are small enough and the centers testing
10 distributed enough that we anticipate being able to do this
11 in the first several months of primary testing. This will
12 be actually site-specific and really based on the ability to
13 work out the logistical issues that require availability of
14 NAT data to release product.

15 [Slide.]

16 This is just an illustration. There are actually
17 about fifteen of these resolution algorithms. I don't have
18 time to walk through them, obviously, but just to give you a
19 sense of the complexity of sorting through combining the
20 serology with the NAT data and, depending on the results,
21 various discriminatory processes kick in.

22 It is an extraordinarily process and I should
23 comment, particularly, that Sally Cagliotti of Blood Systems
24 has really been the drive of this ABC program and has done
25 an outstanding job of pulling this whole process together.

1 [Slide.]

2 Finally, a few of the donor follow-up issues.
3 Much of this activity has been modeled on the Red Cross'
4 program. I really compliment the Red Cross on being
5 extraordinarily forthcoming and sharing with a number of
6 procedures and policies that have been well thought out and
7 have been adopted by the ABC programs.

8 We will be following, actually, at FDA's request,
9 up to 100 persons who are found to be antibody-confirmed
10 positive and NAT negative. This is something that is just
11 sort of peripheral to the critical issues here. We will
12 follow all donors who are found to be NAT positive and
13 serology negative. This is the critical question yield of
14 the program including HCV, NAT reactives monthly for one
15 year or through seroconversion and HIV weekly for three
16 months, then at six months and twelve months or until
17 seroconversion.

18 The donors will be followed both using an
19 alternative NAT procedure as well as standard follow-up
20 serology and the NAT test of record here.

21 That completes the presentation. Thank you.

22 DR. HOLLINGER: Thank you very much.

23 The next presentation will be by Mr. John Flynn of
24 the Association of Independent Blood Centers.

25 **Association of Independent Blood Centers**

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1 DR. GAMMON: Actually, I am Dr. Richard Gammon,
2 the principal investigator. I am going to be presenting the
3 presentation for the Association of Independent Blood
4 Centers. I want to start the talk off by giving a little
5 bit of background of the Association of Independent Blood
6 Centers and then I want to move to our testing strategies.
7 The Association of Independent Blood Centers is a
8 501(c)(3) non-profit Florida corporation. The IBC was
9 founded in 1983 by two independent blood centers.
10 Membership in AIBC can be in two forms; it can be an owner
11 member and it can be a user member. Presently, there are
12 three owner members and 30 user members representing
13 approximately 980,000 volunteer blood donations throughout
14 the eastern United States.
15 In order to be a member, an organization must be
16 an independent blood-collection center with the 501(c)(3)
17 non-profit status. The basic philosophy of AIBC was founded
18 to provide services that will allow stability for small to
19 moderate-sized blood-collection organizations in the future.
20 In the early 1980s, the AIBC services were
21 concentrated on providing group purchasing. This has
22 allowed the membership to have a stable cost base and thus
23 assure a stable, safe and local blood supply to many regions
24 of the United States. After the establishment of group
25 purchasing, user membership requested that the AIBC expand

1 its services. Today, it provides reference services in red
2 cells, HLA and viral testing as an AABB-accredited, FDA-
3 registered, Florida-licensed and Medicare-approved
4 laboratory.
5 AIBC also has an active bone-marrow program and is
6 a member of the National Bone Marrow registry. In 1998,
7 nucleic-acid testing began to be discussed as a serious
8 possibility. In the past, AIBC has always looked at
9 contracts that allowed each of its members to test its own
10 blood donations. However, with NAT, individual testing
11 became less likely. The reason was the limited availability
12 of tests and high costs.
13 It became clear to AIBC members interested in NAT
14 testing that the only reason for its early introduction was
15 to further increase the safety of the blood supply.
16 Although the European April 1, 1999 deadline mandating NAT
17 testing was a catalyst to move forward, the economics did
18 not make it attractive since the cost of this testing would
19 easily exceed the value of the plasma.
20 If the question of blood safety was not part of
21 this equation, blood banks may have been better off
22 financially by not providing plasma for remanufacture in
23 Europe.
24 NAT choices. In 1998, AIBC became committed to
25 the provision of this service through some method that had,

1 as its key feature, the issue of blood-component
2 availability while maximizing the safety of those blood
3 components. AIBC's research into NAT resulted in several
4 conclusions that were evaluated and acted upon.
5 Number one; blood-component availability was
6 dependent on the test-pool size and pool size did affect
7 cost. Number two; testing for two viruses, HIV-1 as well as
8 HCV, when NAT commenced was better for the blood supply than
9 for testing by HCV alone. It was clear to AIBC that no
10 pooling would provide the most rapid turnaround time of
11 blood to assure its availability.
12 However, at this time, it would be cost
13 prohibitive. On the other end of that spectrum, large pools
14 would reduce the availability of fully tested blood
15 components due to the lengthy turnaround time, greater than
16 24 hours. But costs would be lower.
17 It was determined that, in order to assure the
18 continuity of fully tested blood components, including those
19 tested by NAT to the hospitalized patient, testing would
20 need to occur within 24 hours of collection. Based on the
21 estimate of 500,000 donations tested annually and the time
22 constraints wanting to complete NAT testing within 24 hours,
23 pools of 8, 16 and 24 were considered.
24 The potential high costs associated with smaller
25 pools resulted in AIBC's determination that the pool of 24

1 would allow for a 24-hour turnaround time while holding cost
2 recovery to a minimum. The pool of 24 will allow for
3 standardization, also for some of the other Chiron-Gen-Probe
4 users.

5 Once it was established that AIBC would offer its
6 members the Chiron-Gen-Probe NAT test in a pool of 24
7 donations, other issues had to be considered. Laboratory;
8 since AIBC members are primarily across the Eastern United
9 States, we needed a lab where the delivery of specimens
10 would be least likely affected by inclement weather and
11 access to multiple major airports.

12 We chose Citrus Regional Blood Center, an FDA-
13 licensed blood center located in Lakeland, Florida. Its
14 location in the center of Florida with two international
15 airports less than 60 minutes away made it idea.

16 Personnel; although Citrus Regional Blood Center
17 has a full complement of Florida-licensed technologists, it
18 was determined that a separate staff would be developed for
19 the NAT laboratory and, in order to assure continuity of
20 supervision, Citrus supervisory staff are also chosen to be
21 trained in the NAT process.

22 All positions for the NAT lab have been filled
23 and, by this presentation, will have been trained by Chiron-
24 Gen-Probe facilities. In order to meet the tight time
25 constraints for the introduction of NAT testing, it was

1 determined that part of the existing Citrus Regional Blood
2 Center facility would be converted into a NAT lab.
3 This has three labs of pooling, preamplification
4 and postamplification areas. The laboratories are completed
5 and functioning in the validation test mode presently.
6 Equipment; we have backup for all major equipment
7 including the Tecan and luminometer. Our IND was submitted
8 on February 17, 1998 and the FDA received the IND on
9 February 19, 1999 and we have received FDA approval on our
10 IND on March 19, 1999. Our IRB will be meeting in late
11 March to deal with issues concerning the consent.
12 Membership in IRB has been sought throughout the community.
13 The nucleic-acid testing; regarding that, the AIBC
14 will begin to offer its member participants NAT testing
15 using the Chiron process on April 1, 1999. Since this
16 testing is being done under an IND, it is understood that
17 clinical objectives are the primary focus. This will be
18 accomplished by the collection of clinical data while
19 assuring that all donations submitted will be tested with a
20 24-hour turnaround time.
21 The rapid turnaround time will be more costly but
22 will assure that all blood components, including platelets,
23 will be fully tested.
24 Participant profile; all the participants in AIBC-
25 -the collection centers range from a minimum of 5,000 to a

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1 maximum of 150,000-plus donations annually. All donors will
2 have to meet the standard FDA and AABB requirements and
3 routine serology infectious-disease testing will be done by
4 the individual participating collection centers concurrently
5 with NAT testing.

6 Informed consent and specimen collection. Since
7 the NAT process is being accomplished under an IND, it ill
8 not fit the standard blood donation consent. So, as part of
9 AIBC's IND, an informed consent was included. This is a
10 single paragraph that would need to be used by the
11 collection center either as part of the standard donation
12 consent or as a stand-alone consent.

13 The informed consent must be obtained prior to
14 specimen collection. Refusal to agree to NAT testing will
15 result in the donor being deferred. The NAT specimen will
16 be collected in a PPT tube or a dipotassium EDTA tube. No
17 other anticoagulant will be acceptable. We have a 24-hour
18 window available for the collection process and
19 transportation of NAT samples to each collection center
20 provided the temperature does not exceed 30 degrees celsius.

21 Samples store at less than 24 degrees celsius are
22 acceptable for up to 70 hours as whole blood. Samples may
23 be stored for an additional five days a 2 degrees celsius to
24 10 degrees celsius as plasma following centrifugation to
25 separate plasma from cellular components.

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1 Shipping; prior to shipment to the NAT laboratory,
2 the collecting facility will use a donor number replicator,
3 DNR, Computype, that will produce a NAT sample number that
4 combines the collection site ID and the unique donor-
5 collection number. This label will be applied at the NAT
6 sample tube and used for tracking the specimen throughout
7 the process.

8 This method was chosen to prevent problems with
9 duplicate donor numbers from different blood-collection
10 sites. All shipments will be made on wet ice at 2 to
11 10 degrees celsius. Late arrival, 3:00 to 4:00 a.m., is
12 designated to assure that all late apheresis platelet
13 collections will be part of the first NAT run of the day.

14 Testing; on arrival, all specimen samples will be
15 unpacked and checked for temperature. All pools will be
16 composed of 24 samples. AIBC does not intend for NAT
17 testing to be delayed while EIA testing is completed since
18 this would extend the turnaround time. Again, we will be
19 using the pools of 24. We will be using the Chiron-Gen-
20 Probe process so I won't go into too much detail here other
21 than to say we will be having the pools of 24, we will be
22 having the target-capture phase, the transcription-mediated
23 amplification process and the detection phase using the
24 hybridization-protection assay.

25 The results will be either reactive or non-

1 reactive and will be available by mid-afternoon the day of
2 specimen arrival.
3 All breakouts of reactive pools will occur on a
4 next-test shift or late evening the day of specimen arrival
5 in order to minimize turnaround time. In the breakout, each
6 of the 24 pooled samples will be treated as a separate
7 sample and tested by the multiplex assay. The results of
8 the breakout will define which of the pool samples is or are
9 reactive
10 All non-reactive samples will be reported as such
11 to the submitting blood-collection center for a turnaround
12 time of less than 24 hours. The reactive samples will be
13 fully defined as to which of the two viruses or both were
14 reactive, the HCV or the HIV-1. This identification process
15 will be performed at least once per week.
16 Reporting will be done by computer modum, E-mail
17 or fax hard copy. Follow up; a reactive donation will start
18 the NAT donor testing profile which is a single form that
19 will track the status of the donor in the follow-up process.
20 This form is composed of collection data, NAT test data,
21 serologic test data, follow-up donor counseling, follow-up
22 data and comments.
23 HIV-1 reactive donors will be followed monthly for
24 a period of six months. HCV reactive donors will be
25 followed monthly for twelve months. All NAT-positive donors

1 will be followed until the donor seroconverts. Retesting
2 will include both NAT and ELISA testing and appropriate
3 confirmations. The NAT donor-testing profile form will
4 allow the AIBC IND to meet its clinical objectives.
5 Wrapping it up, our primarily objectives are to
6 determine whether the addition of NAT testing to blood pools
7 eliminates more potentially infectious blood units than FDA-
8 licensed and recommended tests. Two, to evaluate the
9 evolution of serologic tests in NAT-positive individuals.
10 Our secondary objectives were to evaluate the NAT blood-pool
11 testing process and to refer an NAT-reactive donor for
12 further medical evaluation and follow up.
13 In summary, the AIBC has determined that there is
14 a need to provide NAT testing for its members in a timely
15 and cost-effective manner. Again, on March 19, 1999 AIBC's
16 IND using the Chiron-Gen-Probe TMA process was accepted by
17 the FDA. This testing is anticipated to begin April 1 and
18 will continue for at least the next twelve months or as
19 necessary until discrete NAT donor test is available.
20 As always, AIBC is committed to providing the
21 safest and highest quality blood products to the communities
22 it services.
23 Thank you.
24 DR. HOLLINGER: Thank you, Dr. Gammon.
25 The final talk in this session on nucleic-acid

1 testing is from Roche Molecular Systems, Mr. Alex Weslowski.

2 **Roche Molecular Systems**

3 MR. WESLOWSKI: Good morning, everybody.

4 [Slide.]

5 Over the next ten minutes or so, I would like to
6 describe to you the COBAS AmpliScreen HCV test system,
7 specifically the system description in clinical study
8 design.

9 [Slide.]

10 This table summarizes the test-kit components
11 which comprise the COBAS AmpliScreen HCV test. The
12 components in the top box are those which are packaged
13 together. You will see that there are seven different
14 components. Actually, this test includes an internal
15 control which is coamplified with the HCV target, although
16 detection is done separately for the target and the internal
17 control.

18 A wash buffer which is a high-volume component of
19 the kit is packaged separately.

20 [Slide.]

21 In regards to performance characteristics, I would
22 first like to note that the test uses two different
23 specimen-processing procedures. The first is called the
24 multiprep procedure which is used for primary and secondary
25 pools. We will cover that in a little bit. The other

1 procedure is called the standard-specimen processing
2 procedure and that is used for individual donor testing.
3 In terms of analytical sensitivity, our in-house
4 data indicate that the multiprep specimen-processing
5 procedure gives us an analytical sensitivity, or a limit of
6 detection, of 15 international units per ml and the standard
7 specimen-processing procedure gives us 25 to 50
8 international units per ml.
9 These levels meet the criteria provided by the
10 agency here in the U.S. as well as the international
11 agencies. In terms of genotype inclusivity, testing was
12 done with donor specimens. Actually, I think these are HCV-
13 infected patient specimens that have been typed and actually
14 sequenced. All of the available genotypes were found to be
15 detected by the COBAS AmpliScreen test.
16 In terms of analytical specificity, 21 different
17 viral isolates tested including HIV-1, HIV-2, HTL-1 and 2,
18 hepatitis B, hepatitis A, various other viral isolates that
19 may be found in human blood samples. The levels that were
20 tested were 10^4 and higher and we obtained negative test
21 results for all of the viral isolates.
22 In terms of clinical specificity, 502 HCV
23 seronegative blood donors--we obtained specimens for these
24 donors. They were tested by both the multiprep and standard
25 specimen processing procedures and negative test results

1 were obtained for all.

2 [Slide.]

3 Just briefly about the COBAS AmpliCor analyzer.
4 This analyzer is 519(k) cleared by the Device Center and is
5 currently in use in the United States for diagnostic
6 testing. This will be the first time it will be used in a
7 blood-screening operation.

8 This slide simply summarizes the five different
9 units integrated into the COBAS AmpliCor analyzer. Specimen
10 processing is done off-line.

11 [Slide.]

12 This slide summarizes the COBAS AmpliScreen
13 system, itself. You can see it is comprised of a few
14 different analyzer components linked together by a File
15 Server computer. The Hamilton AT/Plus2 diluter pipetter is
16 used for preparation of the pools. Testing is performed on
17 the COBAS AmpliCor analyzer.

18 The AmpliLink system is a Roche molecular systems
19 computer interface which acts as the data input and brains
20 for the COBAS AmpliCor analyzer. Three COBAS AmpliCor
21 analyzers can be linked to a single AmpliLink instrument and
22 the File Server has the capacity for handling three
23 AmpliLink systems and, therefore, nine COBAS AmpliCor
24 analyzers.

25 Specimen identity and integrity is carried on

1 through the entire system through the use of bar coding.
2 The Hamilton can read primary bar codes, translates that
3 into bar coding that is assigned to the pools. The COBAS
4 Amplicor also has the capability of reading bar codes and
5 the specimen integrity and identification of donors in a
6 pool is performed that way.

7 The File Server serves to link together the
8 Hamilton diluter pipetter as well as the COBAS test system
9 and identification of negative or positive donor units are
10 performed that way. Finally, the File Server is linked to
11 the blood center laboratory information system for reporting
12 out test results.

13 [Slide.]

14 In terms of the clinical-study objectives, the
15 first two bullets summarize the primary objectives of the
16 study and, as I am sure is no surprise to anybody in the
17 room, the primary objective is really to assess the ability
18 of HCV RNA, a test for HCV RNA, to identify positive or
19 infected blood donors. We are using 24 plasma-specimen
20 pools for this testing.

21 The second or related clinical-study objective is
22 to specifically determine if the COBAS AmpliScreen test can
23 be used to detect the presence of HCV RNA in donor units
24 that are negative by the licensed antibody test for HCV.
25 The secondary objectives, but important nonetheless, of

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1 course, is to evaluate the development of serological
2 markers--i.e., the seroconversion patterns and HCV antibody-
3 negative PCR-positive or HCV-RNA-positive donors and, last
4 but not least, to evaluate the clinical sensitivity,
5 specificity and reproducibility of the COBAS AmpliScreen
6 test system for HCV.
7 [Slide.]
8 The clinical study will be performed in
9 collaboration with America's Blood Centers and the Stanford
10 Medical School Blood Center. There are 13 sites involved
11 with the study. There is a single protocol so everybody is
12 essentially working under a single protocol.
13 The primary sites--there are four in this study--
14 are responsible for developing the data that will be used to
15 establish the clinical performance characteristics of the
16 product. All HCV serological and PCR test results from
17 these sites will be reported to the agency in the product
18 license application.
19 Of course, clinical follow up will be performed on
20 all HCV-positive antibody-negative donors. For the nine
21 secondary sites, donor follow-up, of course, will be
22 performed for the HCV-RNA-positive antibody-negative donors
23 and that information will be reported to the agency.
24 All other study-related data will be collected and
25 kept on site. The importance of the need for two sites

1 really is brought out by the ability to find a sufficient
2 number of HCV-RNA-positive antibody-negative donors. Having
3 a large number of sites, as we are looking at here, vastly
4 increases our ability to do so.

5 The important message here is that everybody is
6 using the same singular clinical protocol.

7 [Slide.]

8 Actually, one of the bullets missing from and
9 which just came to mind a few minutes ago is concurrent
10 testing is being performed in this study. So antibody
11 testing and PCR testing is being performed at the same time.
12 We are not culling out antibody-positive units or separating
13 out first-time donors from repeat donors.

14 The pools are comprised of 24 donors in this test
15 procedure. We are going to look at a minimum of 10,000
16 pools representing 240,000 individual donations from the
17 primary clinical-study sites and those will be tested. We
18 have used the rare-event theory from Poisson distribution
19 that only three PCR-positive antibody-negative donors are
20 needed to establish the significance of the utility of
21 nucleic-acid testing for volunteer blood donors in addition
22 to the licensed antibody test.

23 Donor deferral, of course, will be included for
24 all PCR-positive antibody-negative donors and, for the
25 follow-up period, consistent with the other studies

1 underway, a monthly follow up will be performed for up to
2 twelve months for the PCR-positive antibody-negative donors.
3 And, also consistent with the other studies in progress or
4 proposed, during the initial phase of the clinical-study
5 release of the cellular components will be based upon the
6 licensed serological test results only.
7 [Slide.]
8 This table just summarizes the clinical sites
9 involved with the study. I would like to note that the four
10 primary clinical sites are Gulf Coast Regional Blood Center,
11 New York Blood Center, Oklahoma Blood Institute and the
12 Sacramento Medical Foundation Blood Center.
13 For the thirteen sites, there are numerous
14 collection sites that will be providing blood to these sites
15 for testing and I believe the last number I had on the
16 number of collection sites was approximately 118.
17 [Slide.]
18 As I have said already, the primary pools are
19 comprised of 24 donor specimens. Secondary pools are
20 comprised of six donor specimens and it could be looked upon
21 as four secondary pools comprise a primary pool. All
22 initial testing is performed in single on the primary pool
23 specimens. If the primary pool specimen result is negative,
24 no further testing is required and all donors are considered
25 NAT negative.

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1 When a primary pool is positive, then the four
2 six-specimen secondary pools will be tested. We would
3 identify the positive secondary pool or pools and then, from
4 there, test each individual donor specimen in the secondary
5 pools. In that manner, we can identify the positive donor
6 or donors in each pool.
7 [Slide.]
8 This is an eye test for everybody in the back of
9 the room. Actually, similar to what Mike said, we are not
10 going to go through this. This just represents the test
11 algorithm that will be used for the clinical study. We have
12 taken into account all possible test results and this will
13 be the basic guide that will be used by the blood centers
14 during testing.
15 [Slide.]
16 In terms of the discrepant testing that we will
17 perform during a study, this table simply summarizes the
18 possibilities for the types of discrepant results that can
19 be obtained. The column over on the far right-hand side
20 represents the maximum number of specimens that would go
21 through discrepant testing.
22 I guess maybe one of the most important of these,
23 of course, would be contained in the first row, the PCR-
24 positive and antibody-negative donors. They will have
25 discrepant testing as well as follow up. Discrepant

1 testing, as defined here, would include PCR testing by three
2 alternate targets; the 5-prime UTR, the core and the E-1
3 regions of the HCV genome.
4 For the other categories of discrepancy, a maximum
5 of 250 of these specimens or donors will be tested with the
6 exception of the NAT-negative NIHCV test and confirmatory-
7 test-negative category in which no further discrepant
8 testing would be performed.
9 [Slide.]
10 This is the final slide. In terms of donor follow
11 up, HCV-RNA-positive anti-HCV-negative donors will be
12 deferred and enrolled in the follow-up study. A different
13 patient-consent form is used for this study. Subjects in
14 this study, as we said before, will be followed on a monthly
15 basis. The testing at each monthly visit will include the
16 licensed anti-HCV test, RIBA for confirmation and, lastly,
17 the COBAS AmpliScreen HCV test and, if necessary, additional
18 testing for genotyping or other alternate primer pair will
19 be done.
20 Follow up, again, will continue for twelve months
21 or until such time that the subject has seroconverted.
22 Lastly, follow-up subjects who have negative HCV RNA test
23 results and non-reactive anti-HCV and negative RIBA, after
24 twelve months of participation in the follow-up study, are
25 being proposed as being stated as blood donors.

1 Thank you.

2 DR. HOLLINGER: Thank you.

3 This concludes the open session this morning. We
4 are going to take a break and then, after we return, we will
5 have some open public hearing and then into the open
6 committee discussion. So we are going to take a break for
7 twenty minutes.

8 [Break.]

9 **Open Public Hearing**

10 DR. SMALLWOOD: We will hear from the National
11 Genetics Institute, Dr. Andrew Conrad; Baxter Health Care,
12 Dr. Susan Cushing; Centeon, Dr. Charles Watson; America's
13 Blood Centers, Dr. Celso Bianco; American Association of
14 Blood Banks, Dr. Steven Kleinman; and the Hospital and IRB
15 Association, Dr. David Pittman. That is the order of
16 presentations. If any of those individuals have overheads,
17 would you please let us know.

18 DR. HOLLINGER: Thank you, Linda. Each of the
19 speakers for this open public hearing will have five minutes
20 for their talk. I had to laugh. We said ten minutes.
21 Everybody did real well the first session, but everybody
22 just speaks faster when they have ten minutes. It is sort
23 of like submitting a grant when they tell you have five
24 pages. So you give it to them in 5-point type so you can
25 get the ten pages into the five pages.

1 I also want to commend the American Red Cross for
2 relinquishing the word GAT for NAT so we now just have to
3 talk about one type of thing. Actually, I think NAT is a
4 more preferred terminology anyway. But now we can all just
5 talk about nucleic acid amplification testing.
6 So we will start with the open public hearing
7 today. Our first speaker will be Andy Conrad from the
8 National Genetics Institute.
9 Andy?
10 DR. CONRAD: Thank you. I am just going to give
11 everyone the summary of the 6 million donations that we have
12 tested in the plasma arena. So, as our brethren in the
13 whole-blood arena begin this arduous task, I will give you
14 some of the experiences we have had testing 6 million
15 donations for HCV.
16 [Slide.]
17 We have tested approximately--these are pools of
18 500, so 300,000 donations for HBV and about 2 million
19 donations for HIV This is the summary of the total number
20 of donations that we found positive. I am going to go over,
21 literally in five minutes, some of the data that we have.
22 [Slide.]
23 Basically, the sensitivity of the assay we are
24 using in a 512 pool--we have a mean sensitivity of
25 1.4 copies for HIV, 3.1 for HCV. That is with some fancy

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1 centrifugation et cetera.

2 [Slide.]

3 This is the prevalence in donors in two study-

4 group donors we looked at for HBV, HCV and HIV. You can get

5 those numbers. These are not qualified donors. These are

6 anybody walking in the door, but the prevalence of these

7 window-period donations is higher than we really would once

8 have imagined.

9 [Slide.]

10 About each of the different viruses and the way

11 the constructs of those window periods--for hepatitis C, we

12 have learned some very interesting things. We have seen

13 window periods where we had pre-NAT-positive samples and

14 window periods up to 120 and 103 days. I think the longest

15 one has now gone up to 160 days with seroconversion. Dr.

16 Cushing from Baxter wants to talk to you about the fact that

17 we have had some donors without seroconversion using one

18 antibody test but they really, truly had seroconverted.

19 So the importance of this real finding is that, if

20 you use enough antibody tests, everyone actually does

21 seroconvert. We never found anyone who didn't seroconvert.

22 We found high viral loads and relatively long window

23 periods. So this was an interesting thing which really

24 points to the need for NAT testing.

25 The viral loads, or the viremic levels--they

1 become highly viremic very quickly and then they wobble
2 around. But they are substantially viremic samples for HCV.
3 [Slide.]
4 For HIV, this is the case as well. These are the
5 NAT-positive. The yellow is NAT and p24 positive. The red
6 is just seroconversion. These donors we were unable to
7 follow up on. They just didn't come back and let us follow
8 them up.
9 [Slide.]
10 But, again, in cases like this, the important
11 thing about HIV--and Sue Preston from Alpha will talk more
12 about this--is that, of all the HIV samples we have
13 encountered, we have never found one that is positive by p24
14 but not positive by pooled PCR, even at 512.
15 There has never been, in all our experience, Dr.
16 Epstein--never--a sample that was positive for p24
17 individually that was not positive by pooled PCR. I think
18 that is an important message. Dr. Preston from Alpha will
19 really go into detail on that.
20 [Slide.]
21 For HBV, we have encountered four different
22 scenarios. We have followed these donors up fairly
23 carefully and looked at the serology in them. We found four
24 different types of serology in these HBV-NAT-positive
25 donors. These eleven donors were all discovered in these

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1 pools and NAT positive and had various serology statuses.

2 We had a group that was HVC-core-antibody negative

3 and S-antigen negative. We had some that were core-antibody

4 positive and S-antigen negative. We obviously had all four

5 scenarios. These ones were just ones that were quite close

6 to cutoff on S-antigen but the original laboratory, the

7 screening laboratory, missed them.

8 [Slide.]

9 What is important about these is that these,

10 arguably, represent, at least in this case--that is, core-

11 antibody S-antigen negative incidence information. These

12 are new infections. Obviously, these are acute early

13 infections. We are encountering them much more frequently

14 than we ever thought we would.

15 The viral loads are extraordinarily low for

16 hepatitis B. What is interesting about these is, as we will

17 follow them up further, we don't know if this just

18 represents an early phase or there truly is. There used to

19 be some arguments that, with hepatitis B, there was a long

20 gestation period with relatively low viral loads.

21 As we follow these people along, we will see if

22 that is the case. These viral loads are nothing compared to

23 what we see, really, with someone with an acute hepatitis--

24 with a clinically acute hepatitis B.

25 [Slide.]

1 The next group looks like people who are resolving
2 their infection. They are S-antigen negative so they are
3 the hallmark of seroconversion with core antibody
4 positivity. In the ones that we were measuring, we could
5 see their viral loads drop. These were ones that we, then,
6 subsequently collected where they weren't always positive by
7 PCR and their viral loads were decaying.
8 These look like people who were in the process of
9 getting rid of the 95 percent of HBV acutely infected
10 patients who are in the process of going ahead and getting
11 of their infection.
12 That was my last slide for my five minutes. But
13 what was important about this is that in 6 million
14 donations, we found HCV, high viral loads, long window
15 periods, HIV, p24 brought nothing to the table and a new
16 emerging issue, which was really a surprising amount of HBV
17 which looks like new infection.
18 The importance about HBV is that we haven't seen
19 anybody with high viral loads and no S-antigen which would
20 have been the hallmark of an S-antigen mutant. We have not
21 seen that yet, but we are constantly on vigil for that.
22 So that is all for us.
23 DR. HOLLINGER: Thank you, Andy.
24 The next speaker is Susan Cushing from Baxter.
25 DR. CUSHING: Thank you.

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1 [Slide.]

2 I am going to give you a brief summary of the
3 clinical study that we did in conjunction with NGI. This
4 study is completed and it was done in two phases. The first
5 phase would be the screening phase of the study and the
6 duration for this phase from which we found the donors for
7 the second seroconversion phase was about four months.

8 The donor qualifications for this were to be EIA
9 negative and p24 negative. If the serology was positive,
10 they were not included in the pool for PCR. We had 46
11 plasma centers participating. We screened approximately
12 341,000 donations and about 43,000 donors. That came to
13 about 666 plasma pools, master pools, which were the 512
14 samples. That was a mean donation of about eight per donor.

15 [Slide.]

16 The seroconversion phase was done with donors who
17 were found eligible by being either HCV or HIV PCR positive
18 and antibody negative. These donors were then invited to
19 enroll in this phase. They would return to the donor center
20 weekly for blood draws and we would do PCR and antibody
21 testing on them.

22 Of the 46 centers, we found ten centers had
23 eligible donors. This study duration was for up to six
24 months or seroconversion, whichever came first.

25 [Slide.]

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1 The results from this are here. Because we knew
2 we probably wouldn't find that many donors, we added blinded
3 samples. They were either positive or negative for HCV and
4 HIV and we added them randomly to the pools. We did
5 accurately identify all 50 that were added.
6 We had no HIV-positive donors to enroll in our
7 phase II clinical trial but we did have 17 HCV-PCR-positive
8 donors. Five of these donors did not enroll. Only two of
9 them declined to enroll. The other three, we were not able
10 to find. Four of the donors seroconverted prior to
11 enrollment and we had six donors who did enroll and
12 seroconverted within the six-month time frame.
13 We had two donors, as Andy just mentioned, who
14 were consistently positive by PCR but never did seroconvert
15 within the time frame of six months.
16 [Slide.]
17 So, of the ten donors that were seroconverting,
18 the time range between the first HCV-PCR-positive test to
19 seroconversion was 30 to 115 days. Now, the time range for
20 the elevated ALT levels was 30 to 110 days. There was a
21 general correlation between elevated or deferable ALT levels
22 and seroconversion.
23 However, we did have three donors whose ALT levels
24 were elevated prior to seroconversion and we did have two
25 donors whose ALT levels were never elevated.

1 [Slide.]

2 The viral loads for the seroconverting donors was
3 also variable. We did quantitative PCR testing and, at
4 seroconversion, the donors had anywhere between 100 genomes
5 per ml to greater than 5 million genomes per ml.

6 We also had two other donors who exhibited a
7 transient negative PCR test following positive PCR test
8 results and with one donor, the PCR-negative test came one
9 month prior to seroconversion. Then the viral load rose to
10 290,000 genomes per ml. Again, he was PCR negative one week
11 after seroconversion.

12 In the second donor, the PCR negativity came at
13 seroconversion but, a week later, he had a viral load of
14 30,000 genomes per ml.

15 The seroconverting individuals in our study were
16 all male. However, the mean male-to-female donor ratio at
17 the centers was 68 to 32. We didn't find any correlation
18 with the number of prior donations that these donors had
19 made and becoming infected with HCV. It ranged all the way
20 from one donor who it was their first time to donate up to
21 three donors who had donated between 61 and 80 times in the
22 past.

23 [Slide.]

24 Now, the non-seroconverting donors; interestingly,
25 they were both female. Their HCV PCR test results were

1 positive, greater than six months. Their viral load, by
2 quantitative PCR during that time ranged between 140,000 to
3 4.5 million genomes per ml. We also went back and did
4 branch-chain DNA testing on them and they were consistently
5 positive by branch-chain DNA testing.

6 Their ALT levels were normal the entire six
7 months. The test that we use for screening is the Ortho HCV
8 EIA antibody test. I'm sorry; the test that we use is the
9 Abbott 2.0. It was negative the entire time.

10 When we went back and did the Ortho 3.0 test, we
11 found that they were positive and, in fact, they were
12 positive at the very first time they came into the center.
13 This is not to say that one test is better than the other
14 because since we use the Abbott test for screening, we were
15 not able to see if the reverse might hold true.

16 I do know that another clinical trial that is
17 being conducted by a manufacturer has an individual who has
18 not seroconverted according to either test for up to twelve
19 months and they have been consistently PCR positive.

20 Both of our donors had different genotypes, 2b and
21 3a. The other donor I just referred to is 1a. So I think
22 that what this says is that the implementing PCR is really
23 going to make quite a difference because these donors, based
24 on the Abbott screening test, would very likely still be
25 donating otherwise.

1 [Slide.]

2 So, in conclusion, we have demonstrated that PCR
3 testing of the pooled plasma can detect HCV-infected donors.
4 We have also validated the process of our pooling and the
5 testing of the samples by PCR and linking them back to the
6 donations and the donor. We have collected some data on the
7 seroconversion of donors who are positive by PCR and
8 nonreactive by HCV antibody testing.

9 Thank you.

10 DR. HOLLINGER: Thank you.

11 The next speaker is Charles Watson, Dr. Watson,
12 from Centeon.

13 DR. WATSON: Good morning.

14 [Slide.]

15 This morning, I am going to update you on our
16 experience with PCR testing which we have been doing now for
17 about a year.

18 [Slide.]

19 The system that we use tests all plasma that we
20 collect for fractionation for HCV, HIV and HBV. It was
21 developed by our research organization in Germany and is now
22 being currently used in two laboratories, one in the United
23 States and one in Germany.

24 We call it a system because when you collect large
25 numbers, one of the most important things that you have to

1 work out is a logistic system, to obtain the specimens,
2 identify them, get them to where they are supposed to go,
3 make sure you test them properly and then make sure they go
4 back to the right location.

5 Then, the identification of the donor falls into
6 the normal notification, as you would for serology. So we
7 consider PCR a system, not just a test. In July, '97, we
8 started in Germany and, in April of '98, we started in the
9 United States. To date, we have tested approximately a
10 little less than 3 million units of plasma.

11 [Slide.]

12 We take out all serology positives and only test
13 units that are serology negative. We want to interdict all
14 positive units prior to pooling for fractionation. We also
15 want to notify the donors so they can receive counseling.
16 And then, in the manufacturing process, we only want to
17 manufacturer with non-reactive PCR units.

18 [Slide.]

19 This is the viral load required in the donation
20 for us to find it positive on a routine basis. That
21 includes all of our dilution protocols.

22 [Slide.]

23 These are the results. What have we done so far?
24 It is broken out. The first slide is the United States and
25 the second slide is from Germany. In the United States, we

1 have tested a little more than 1.6 million units. We had 96
2 positive donors and you can see the breakout by virus. I
3 have also shown the interdicted units; how many units have
4 we stopped going through the manufacturing process that
5 would have gone through the manufacturing process if PCR was
6 not being used.

7 You can see that that is 458 units. The only
8 thing that is counted here on the interdicted units, if the
9 donor became serology positive, and that unit would not have
10 gone to manufacturing due to the lookback process from
11 serology, that was not counted for this number for
12 interdicted units.

13 So, for example, the three HIV-positive donors,
14 two became serology positive within 30 days. Those units
15 were not counted. One donor never came back so never became
16 serology positive. Those four units are all from that one
17 donor.

18 You can see our frequency, from we see in the
19 United States based upon what we tested, let's say one donor
20 per 200,000 for HBV, five donors per 100,000 for HCV and one
21 donor in a million of HIV.

22 [Slide.]

23 From Europe, they have tested a little less;
24 approximately the same number of positives. One of the key
25 things on this slide here is that Europe is where we do our

1 fractionation pool testing. We have taken 340 consecutive
2 fractional pools from the manufacturing plants. We have
3 tested them by PCR for all three viruses and all 340
4 fractionation pools have been negative.
5 [Slide.]
6 We also do a substudy. As you have heard this
7 morning, all of the INDs have a substudy, a clinical part of
8 it. Ours consists of following positive donors for six
9 months on a monthly basis or until they seroconvert. We
10 bring them back. We repeat the PCR testing for that virus.
11 We repeat the serology testing for that virus and we also do
12 the confirmation test for that virus.
13 We started with eight centers. We have extended
14 that to all of our locations, all 32 collection centers.
15 [Slide.]
16 The next slide shows you the results of that,
17 where we are at right now. If you notice, there are only 51
18 donors that are eligible. That is because we started with
19 the eight and then we extended to everyone. So, of the 96,
20 we found 51 have been eligible. We have enrolled 20. To
21 date, seven have completed the study either by finishing the
22 six months or by seroconverting. Five of those seven have
23 seroconverted.
24 There was one HBV that did not seroconvert and one
25 HCV that did not seroconvert. And we had one dropout. It

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1 was an HCV positive. They came back. They were PCR-repeat
2 positive and then they decided not to come back again.
3 In addition to this number, we have seven HCV-
4 positive donors who seroconverted but declined to enroll.
5 The status of the ones that are not finished yet; some are
6 first time. Some have repeat positives. Some have come
7 back and been PCR negative.
8 What I have tried to do here is give you a real-
9 world experience, what can PCR do, is it beneficial? Can
10 PCR, in a pool environment, improve the safety over the
11 licensed tests that are performed today. I think that we
12 have shown that and, hopefully, this information is of
13 benefit to you.
14 Thank you.
15 DR. HOLLINGER: Thank you.
16 The next speaker is Dr. Bianco representing
17 America's Blood Centers.
18 DR. BIANCO: I will dispense with it.
19 DR. HOLLINGER: That was a good talk, Celso.
20 The next talk, then, is Dr. Kleinman from the
21 AABB. I'll bet Steve will have something to say.
22 DR. KLEINMAN: The major risk of transfusion-
23 transmitted HIV, HBV and HCV infection results from
24 collection of a unit of blood during the infectious window
25 period for these agents. This window period represents the

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1 time in early infection when virus is circulating in the
2 blood but conventional tests are unable to detect viral
3 antigens or antibodies.
4 During at least a portion of this window period,
5 viruses can be detected by nucleic-acid amplification
6 techniques. Data on the seronegative viremic window period
7 and the dynamics of viral replication suggest pooled NAT for
8 HCV will offer the greatest reduction in the number of
9 potentially infectious units.
10 It has been estimated that such testing could
11 reduce the window period for HCV from the current 70 to 80
12 days to ten to 30 days, thereby reducing the per-unit risk
13 of HCV transmission from the current estimate of about one
14 in 100,000 to one in half a million to a million.
15 In the case of HIV, preliminary data suggest
16 pooled NAT testing may reduce the window period from the
17 current estimate of 16 days to about 13 to 14 days with a
18 best-case scenario of ten days for individual unit NAT
19 testing. Given the very low incidence of HIV infections in
20 the volunteer blood-donor setting and this small window-
21 period reduction, the introduction of pooled NAT for HIV
22 will result in few detected infections.
23 This projected low yield is supported by the
24 actual low yield is supported by the actual low yield of HIV
25 infected units in the three years following introduction of

1 HIV-1 p24-antigen testing. I would say that there have only
2 been five units that we know about.
3 Nonetheless, continued public concern over the
4 threat of transmission of HIV through the blood supply
5 appears to support the implementation of pooled NAT for HIV.
6 The low level of HBV viremia present during the window
7 period prior to positive surface-antigen results makes it
8 unlikely that HBV DNA will be detectable by NAT applied to
9 pooled plasma specimens, although we have seen some examples
10 today from NGI in plasma donors where it has been detected.
11 HBV NAT will most likely require single donation
12 testing to significantly impact residual HBV risk. At this
13 time, the complexity of NAT and the lack of widely available
14 automated testing equipment and reagents make it impossible
15 to perform single donation testing.
16 The approach of pooled sample testing is currently
17 practical and, in the case of HCV, has relatively little
18 impact on the ability of the technology to detect infection
19 earlier since HCV nucleic acids reach high levels rapidly
20 after infection is established.
21 The ultimate goal for operational NAT programs is
22 to complete testing prior to issuance of blood components
23 for transfusion. However, in the early phases of NAT
24 implementation, the logistics may require the release of
25 blood components before NAT results are known in order to

1 avoid shortages of labile cellular blood components with
2 short dating periods such as platelets.
3 The turnaround time for pooled NAT is likely to be
4 longer than for current blood-donor screening assays due to
5 the time required for pooling, the performance of the test,
6 itself, and the additional testing required to identify the
7 reactive unit in a reactive pool.
8 The AABB agrees with FDA's policy to allow for
9 release of blood components prior to obtaining NAT results
10 until the logistics of the operational NAT programs permit
11 the more rapid turnaround time required to complete testing
12 before component release.
13 Due to these logistics, there is a possibility
14 that a component that is negative by all required
15 serological assays will be found to test NAT positive after
16 it is transfused. In these rare instances, it is important
17 to remember that such a component would have been transfused
18 in the absence of pooled NAT testing.
19 In such cases, the AABB believes that the
20 management of recipients who have received such units should
21 be similar to the management of other lookback cases with
22 the exception that the rapid availability of information
23 about the transfusion event may allow early intervention to
24 treat infection in the recipient and prevent secondary
25 transmission.

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1 Potential issues to be addressed by FDA. The AABB
2 recommends that the FDA establish a standard for NAT
3 sensitivity for each analyte, HCV and HIV, based on the
4 requirement that an operational pooling algorithm must
5 detect a given number of copies in an individual donation at
6 a 95 percent frequency.

7 I think we have heard today that there is a
8 suggestion that the FDA is considering a 5,000 copies per ml
9 number. This type of standard would allow for variability
10 in analytic sensitivity and in pool size in different NAT
11 programs as long as the product of the analytic sensitivity
12 and the dilution factor introduced by pooling meets the
13 minimum sensitivity standard.

14 Consequently, this type of standard would insure
15 that any individual donation interpreted as NAT negative for
16 a given analyte would have less than a designated number of
17 copies per ml of viral nucleic acid at a 95 percent
18 probability.

19 Although the ultimate goal in setting an NAT
20 sensitivity standard is to detect a large majority, if not
21 all infectious viremic window donations, the standard set in
22 the initial stages of pooled NAT must be achievable using
23 current technology. As the technology continues to evolve,
24 the standard can be evaluated and adjusted, if needed.

25 In light of the anticipated use of several

1 different NAT pooling and testing algorithms for donor
2 screening and the significant actions that will be triggered
3 by a reactive NAT result, the AABB urges the FDA to adopt
4 standard nomenclature to describe test results and to define
5 various stages of testing.
6 A suggested nomenclature is as follows, and maybe
7 the specific terms can be altered but I think the principles
8 are correct. In our suggested nomenclature, master pools
9 are the pools of plasma from individual donations so it the
10 first pool that is made, that is initially tested by NAT.
11 Master pools, once tested, are either negative or
12 reactive. In some programs, intermediate pools are prepared
13 from individual donations and then pooled to make a master
14 pool. When a master pool tests reactive, either the
15 individual samples comprising the master pool or the
16 intermediate pools comprising that master pool are then
17 tested. If intermediate pools are tested, the results are
18 either negative or reactive.
19 Both master and intermediate pools generate
20 interim results in the testing process that is designed to
21 identify and test specific individual donations. Individual
22 donations, when tested, will be either negative or reactive.
23 The definition of a positive test result should be
24 reserved for results obtained on an individual donation that
25 is reactive by NAT and confirmed. Confirmation is currently

1 not really defined but may either be by subsequent
2 seroconversion or by a different NAT procedure.
3 This definition of a positive NAT result is likely
4 to evolve as experience with NAT is gained and donor follow-
5 up data are obtained. Pooled NAT methodology involves
6 testing samples with progressively higher concentrations of
7 viral nucleic acid as the testing proceeds from master pool
8 through intermediate pool to individual donation.
9 In contrast, current individual unit blood-donor
10 serological screening assays require repeat testing of the
11 same sample source if initially reactive results are
12 obtained. The AABB believes that there are sufficient
13 differences between pooled NAT and conventional EIA testing
14 such that it urges the FDA to consider interpretation of NAT
15 reactivity differently from current EIA algorithms.
16 Specifically, if all individual donations in a
17 reactive pool tests negative on individual donation testing
18 and no implicated unit can be found to explain the reactive
19 pool result, the AABB urges that mechanisms be designed to
20 allow such units to be released for transfusion.
21 The AABB urges that the policies with FDA adopts
22 concerning notification of consignees of previous donations
23 from NAT-reactive donors and policies for donor notification
24 and counseling be based on reactive NAT results at the level
25 of the individual donation and not on results obtained at

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1 previous stages of the NAT resolution algorithm. In fact,
2 this seems to be the case with all the INDs described today.
3 The AABB urges the FDA to encourage and support
4 the development and validation of supplemental testing
5 algorithms and follow-up protocols for donor counseling and
6 donor reinstatement. Protocols for reinstatement of donors
7 who are negative on licensed serological screening assays
8 and have false reactive NAT results should be consistent
9 with the following principles; failure to demonstrate
10 persistent NAT reactivity or seroconversion after a six to
11 twelve-month period offers a high degree of assurance that
12 the donor is not infected; that is, follow-up serological
13 testing with FDA-licensed tests for HIV or HCV should become
14 positive if the donor really has been infected.
15 Negative NAT results on a single sample are more
16 specific than a reactive result in a sample pool and, with
17 respect to HCV, the unusual individual who does not develop
18 detectable HCV antibody, and I think we have heard of at
19 least one case today in the plasma sector, should, however,
20 reveal persistent viremia on repeat NAT testing and be
21 reactive by a different NAT test.
22 The AABB requests that the FDA also consider
23 eliminating the requirement for specific serological tests
24 subsequent to the implementation of NAT. Such decisions, of
25 course, will need to be supported by data. Existing data

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1 suggests that elimination of HIV antibody and HCV antibody
2 testing will not be possible.
3 Now, although ALT testing has never been required
4 by FDA, and an NIH consensus conference recommended its
5 discontinuation in 1995, such testing is still performed by
6 most blood-collection agencies in the U.S. for the purpose
7 of conforming with German regulatory requirements for
8 importation of recovered plasma or manufactured plasma
9 derivatives.
10 Data from pooled HCV NAT programs may be helpful
11 in influencing the German regulatory agency to modify its
12 ALT testing requirement. With regard to pooled HIV NAT,
13 existing data suggest that elimination of HIV p24-antigen
14 assay may be feasible. This topic will be discussed later
15 today.
16 The AABB commends the FDA for initiating such open
17 public discussions at this early juncture about the
18 elimination of p24-antigen testing.
19 A final comment; the AABB is sponsoring a
20 conference on April 7, a one-day conference, in Crystal City
21 to talk about nucleic-acid testing primarily for the blood-
22 transfusion user community, but I think there are people in
23 this room who may be interested in attending.
24 Thank you.
25 DR. HOLLINGER: Thank you, Steve.

1 The final speaker today is Dr. David Pittman
2 representing the Hospital and IRB Committee.
3 DR. PITTMAN: I am addressing the committee
4 regarding concerns with NAT testing, its IND process--not
5 the eventual outcome but the logistics of implementing it.
6 I am the transfusion medical director at a 350-bed hospital
7 in Columbia, Missouri and the transfusion medicine
8 consultant for sixteen other pathologists in my group who
9 are responsible for 17 hospitals and about 1500 beds. So we
10 are consumers, essentially.
11 This bridges both the Red Cross and community
12 blood-center supply. I am also the chairman of the Medical
13 Advisory Committee for the Missouri-Illinois region of the
14 Red Cross based on St. Louis which covers between 75 and 100
15 hospitals.
16 I am been chairman of my hospital IRB for four
17 years. I am here at my own expense. I am not paid by any
18 of these except the patients but I represent what I believe,
19 if you look at web sites and list serves are a lot of
20 hospital tranfusionists in my position as well as hospital
21 IRB chairmen.
22 What I am about to tell you is from a practical,
23 hands-on practice of transfusion medicine and the
24 incorporation of views of these other people. I believe
25 that the FDA has impugned its own standards of research

1 conduct in forcing hospitals to participate in this
2 research.
3 I and probably other transfusion-medicine
4 professionals do not wish to withhold a test which makes
5 blood safer, even this very small amount of greater safety,
6 as this test will do for HIV. However, what research in
7 this century has been approved by the FDA without informed
8 consent of the subject, perhaps short of syphilis research
9 down south.
10 There seems to be a great desire by the FDA, blood
11 and blood-derivative industry, to rush this research despite
12 little incremental benefit to the American public. I have
13 been told that this committee ignores cost issues and so I
14 am sure that this doesn't relate to any European time tables
15 for the NAT testing.
16 However, the annual cost to the United States
17 hospitals, many of whom are not profitable and many of whom
18 fold each month, as you know, will be asked to absorb a
19 $75 million bill during this research period per year being
20 able to recoup only a small percent because of prospective
21 medical reimbursement from inpatients and operative
22 patients.
23 The FDA has approved this IND believing the donor
24 is the only subject. If this is so, why are transfusion
25 services across America being asked to add a two-paragraph

1 statement of risk to our transfusion consents? Those of you
2 who don't transfuse blood every day should be aware that
3 nearly 40 percent of American hospitals do not have separate
4 transfusion consents, separate from an admission consent.
5 Why, then, am I asked to "advise the NAT-positive
6 patient of the implications of the NAT test result for their
7 health and any treatment that may be appropriate?" How can
8 I do that if my hospital has not agreed to participate or if
9 the investigational subject is not informed and if the
10 implications, such as false positives, are not known since
11 that is what this research is trying to figure out.
12 How many on this committee have had to sit in a
13 room with a patient that has developed a positive test after
14 transfusion and tell them that they are HIV positive. Now
15 we know that up to 5 percent of those confirmed Western Blot
16 positives were not positives at all.
17 These people have gone and told their families.
18 They may have told their workers and been discriminated
19 against and that wasn't even a research test. This is kind
20 of analogous to me of not having the recipient of the blood,
21 the investigational subject, as designing a protocol to test
22 new bumpers for GMP suburbans. They are new soft bumpers.
23 They are supposed to hurt pedestrians less if they run into
24 them and so you consent the driver, the volunteer driver, of
25 the car.

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1 It is ridiculous. FDA is violating their own
2 standards. Statisticians and many scientists recognize that
3 the lower the prevalence of the disease, the higher the
4 false-positive rate. For HIV, you have heard prevalence of
5 1 in a million and for HCV 1 in 20,000 to 100,000. That is
6 great that our tests have got us that low.
7 But, furthermore, just based on ABO Rh clerical
8 errors in transfusion medicine, we know the clerical rate is
9 closer, the error, to 1 in 20,000 for ABO Rh. How many of
10 you on the committee have made 20,000 in your checkbook,
11 which is pretty important to you, and not found that you
12 have made an error?
13 I think that is what a lot of the false positives
14 are going to end up being. Please make your decision
15 carefully. You should know that many of us who transfuse as
16 physicians, not as industry, not as government, not with
17 conflicts of interest are amazed at your vote last quarter
18 on universal leukodepletion which has a minuscule scientific
19 validity for indications other than what we already
20 selectively leukodeplete for.
21 Finally, as an IRB chairman, I often deny local
22 researchers with protocols that are far superior to this IND
23 protocol that I have seen because I, as an extension of the
24 FDA for my hospital, read your rules and enforce them. This
25 IND is not acceptable to physicians, blood banks and

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1 hospitals responsible for daily transfusing America's blood
2 and it shouldn't be acceptable to you on this committee.
3 We petition that you withdraw this until there is
4 revision and I'll bet you there are about 100 IRB chairmen
5 that would be glad to help the FDA figure out how to revise
6 this.
7 Thank you.
8 DR. HOLLINGER: Thank you, Dr. Pittman.
9 The final item in this open public session--there
10 is a letter that the committee has from the American Society
11 of Clinical Pathologists. Dr. James Linder is president. I
12 am reading it into the minutes. I am not going to read the
13 whole thing but I do want to point out a couple of aspects
14 of it.
15 He states that, "The American Society of Clinical
16 Pathologists is made up of board-certified pathologists,
17 other physicians, clinical scientists and certified
18 technologists and technicians." He is concerned about--it
19 is very similar to what Dr. Pittman says about, "requiring
20 that all derivatives be prepared from plasma, that this is
21 being promulgated by the European regulatory agencies."
22 The concern that he talks about is, "It is
23 apparent that the rush for implementation of the gene-
24 amplification technology will require the release of blood
25 and its components before test results are known." He says,

1 "The management of patients in potential lookback cases
2 raises concerns for patients in the laboratory."
3 He goes on further and says, "To conduct this
4 research protocol under an investigational new-drug process,
5 donors must be informed of the investigational nature of the
6 testing." It says, "ASCP agrees that donors must be
7 informed. However, concern arises when it is noted that
8 recipients of nucleic-acid amplification-tested blood may
9 receive blood or blood components before the test results
10 are complete."
11 He then says, "It has been suggested that
12 laboratories have patients sign documents acknowledging that
13 the blood they may receive through this investigational
14 process may be contaminated. This is just not feasible,
15 especially in very large facilities. Getting informed
16 consent from blood recipients is likely to create anxiety in
17 patients that may cause them to refuse blood completely
18 which may place them at greater harm than the theoretical
19 risk of a nucleic-acid-tested positive unit transfused
20 before the test result is known."
21 Then he gives a solution. He says, "We suggest
22 that clinicians transfusing blood should be educated about
23 the nucleic-acid testing issue. Patients should not be
24 charged for the testing during the investigational procedure
25 or period and testing should continue to be unlinked until

1 it can be performed uniformly prior to transfusion."

2 He then completes this by saying, "These comments

3 should not be construed to be speaking against nucleic-

4 amplification testing. Rather than relying on the pressure

5 from the European community, we urge that more time be given

6 to assess patient needs and laboratory concerns in the

7 United States."

8 That's basically the gist of that letter.

9 Is there anyone else from the public that wants to

10 make a statement or anything at this point before I turn it

11 over and close it and then open it up for discussion among

12 the committee?

13 State your name and association.

14 DR. SCHOCHETMAN: Jerry Schochetman, Abbott

15 Laboratories. I just wanted to raise the issue--we heard

16 this morning that our serologic EIA 1.0 tests require HIV-1

17 Group M, HIV-1 Group O and HIV-2 detection and must have

18 antigens in them. We heard this morning that nucleic-acid

19 amplification testing apparently does not require HIV-2

20 testing and seems to only require HIV-1 Group M and possibly

21 detection of Group O in those cases where the assays can

22 detect the Group O.

23 In rapid testing, we heard that the FDA may only

24 require HIV-1 Group M, no Group O and HIV-2. We now have a

25 whole series of standards and the rules seem to be changing

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1 as we go along and sends a very complicated message to
2 manufacturers who start along a particular path and then the
3 rules change and either have to pull tests that are before
4 the FDA or certainly would have to come back in and modify
5 them as we go along.

6 I am wondering if somebody from FDA would like to
7 comment on this varied standard which doesn't seem to be
8 occurring, as we can tell, within Europe.

9 Thank you.

10 DR. HOLLINGER: Anyone wish to comment from the
11 FDA?

12 DR. HEWLETT: I just wanted to make a comment in
13 regard to the nucleic-acid test. We are actually asking
14 manufacturers to test the Group M variants for the nucleic-
15 acid test. HIV-2 has been an optional requirement. In
16 regard to the blood-screening assays, of course, you know
17 that the antibody tests are also required to be validated
18 against the Group M variants.

19 In that instance, of course, we are also requiring
20 Group O. But that is primarily because of their broader
21 utility. They are the primary screen and we view nucleic-
22 acid test as an add-on screen for the window period.

23 DR. EPSTEIN: I agree with Dr. Hewlett's
24 statement. Let me just add that we are aware of this
25 disparity and that we have a dialogue ongoing with the

1 sponsors of the nucleic-acid tests. We will obtain
2 commitments that these tests will be further modified to
3 broaden the sensitivity to include other virus variants.
4 We do think that is appropriate although it is
5 true that the vast majority of window-period cases currently
6 seen are Group M. So I guess the problem is always a moving
7 target. Had we decided a year or two ago that we would make
8 it an up-front requirement, we simply would have delayed the
9 development that we are now seeing moving into the clinical
10 domain.
11 So we agree with Dr. Schochetman. Right now, we
12 do have a set of different standards in different contexts
13 but we do see this as evolving stages of technology and the
14 standards will evolve.
15 DR. HOLLINGER: Anyone else under the public
16 hearing have a comment?
17 If not, then we will open this up for committee
18 discussion.
19 **Committee Discussion**
20 I'm sorry we didn't have time--unfortunately, we
21 don't know how long each of these talks are going to take
22 and so on. If you are like me, I really would much prefer
23 to ask questions as speakers present things because it is
24 fresh in my mind, but I would like to see if anyone can
25 comment on some of the items that have been brought up this

1 morning, both in initial talks as well as from the public
2 hearing, too.
3 DR. NELSON: A couple of issues were raised but
4 just in the context of a case or two, and that is disparate
5 results between PCR and antibody, particularly with
6 hepatitis C where patients were persistently antibody
7 negative, PCR positive, and then some where the PCR result
8 was intermittent in the face of antibody.
9 Individual cases--that issue has been known for
10 some time, those two scenarios. But the real issue is is
11 there any data on how frequently that occurs. As I recall,
12 Miriam Alter's data suggested a fairly high rate of PCR
13 positivity or at least infection with no antibody occurring
14 for up to a year or longer.
15 The rate, as I remember, was something in the
16 range of 10 percent. I think that is probably much higher
17 than reality. But, with the data that were presented, I
18 couldn't really get a handle on how frequently this is.
19 There were large numbers of people screened and then a few
20 cases were presented. But I wonder if anybody could put any
21 quantitative figures on the disparity, at least for some
22 period of time, on those two scenarios for hep C.
23 DR. CONRAD: I self-elected myself to answer this
24 just because those data that you are referring to were
25 derived in my laboratory. It is very important that you

1 know that the two women that we saw how never seroconverted,
2 they never seroconverted only by a single assay, which was
3 the Abbott assay.

4 When we ran them on the Ortho assay, they had
5 seroconverted from the original moment. So those are truly
6 not cases of non-seroconversion. They are just non-
7 seroconversion by a single screening assay.

8 We did not look for the inverse, so it is entirely
9 possible that, had we screened with Ortho, found PCR
10 positivity for a long period of time and then tested with
11 Abbott, some of those would have been.

12 So it is our experience that in every single donor
13 who we have identified in these periods of follow-up
14 clinical study seroconverted. So we did not see anyone who
15 did not seroconvert. In the careful clinical follow-up
16 period where we followed all donors up to six months, that
17 is 32 people that we followed from pre-NAT positivity all
18 the way through, and all of them seroconverted.

19 The issue of transient positivity is to be
20 expected with some people--remember that was transient
21 positivity at the time of seroconversion. It is well known
22 that some people resolve their hepatitis C infections. They
23 would remain antibody positive but nucleic-acid negative.
24 That is expected. And so we saw nothing out of the ordinary
25 and nothing that didn't seem to make sense.

1 And so the original supposition by Miriam Alter
2 that there was a persistent window-period patient that never
3 seroconverted is probably not the case and, in fact, from
4 some sedimentation studies, many of these patients are
5 actually manufacturing antibody. It is just not detected
6 yet. In other words, it looks like it is immune complex to
7 the way how fast it precipitates.
8 So it is not as bad as it would seem from that
9 data.
10 DR. NELSON: We have been following a cohort of
11 injection-drug users who, as you know, are commonly infected
12 with hep C. We do find, not only during the seroconversion
13 period, but we find people who are PCR positive, lose their
14 PCR positivity and then it reoccurs. It is possible that
15 some of these could be reinfections, but we have done some
16 sequencing and I think that that is not always the case.
17 I think that there is, not only during the
18 seroconversion period but in the natural history of hep C,
19 people who become PCR positive, it goes away, it comes back
20 again. So I think, from a practical standpoint, I don't
21 think that it is likely, as Dr. Kleinman mentioned, that we
22 would be able to replace antibody testing, at least for hep
23 C, with PCR because, if we did, we would miss maybe not
24 people that were infectious at the moment but certainly were
25 at high risk and were infected and, perhaps, possibly,

1 infectious by just doing PCR testing.

2 DR. CONRAD: None of us advocate replacing
3 antibody with PCR for a host of reasons, especially pooled
4 testing because it would become prohibitively expensive in
5 the resolution algorithms. We only recommend this and
6 certainly advocate it as an addition, with the exception of
7 some of the antigen tests which we find to be less than
8 effective. But not the antibody tests.

9 DR. HOLLINGER: A comment on that, too. As you
10 know, Jack Stapleton has done some studies which are
11 reported in, I think, March or this month's edition of the
12 Journal of Clinical Microbiology but also had reported a
13 year or two ago in the Journal of Infectious Disease using
14 whole blood for PCR testing.

15 The one in the Journal of Clinical Microbiology,
16 they found six of 16 individuals, about 38 percent,
17 actually, of the patients with clinical hepatitis now who
18 were PCR positive, antibody negative, which they followed
19 for a period of time.

20 They felt that a majority of that was maybe due to
21 cryglobulins formed. But that was only in three of them.
22 The earlier paper, however, followed patients for a period
23 of time that remained PCR positive, antibody negative. This
24 often wasn't the case. These were patients who were not
25 initially felt to have hepatitis C. They cloned them and

1 sequenced the samples. Some of them were just sampled in
2 the core regions, and so on.
3 But the issue that has come up is--and his feeling
4 is that, because they used whole blood and since hepatitis C
5 can be found in not only leukocytes, PBMCs as well as in red
6 cells, possibly platelets, et cetera, that that might be why
7 they are finding this kind of thing.
8 I think it is too early. I think we need to
9 really look at it but it is a very interesting concept. So
10 I might ask you, Andy, did they look for cryglobulins in
11 those two patients?
12 DR. CONRAD: Yes. It was interesting. That was
13 obviously one of the confounders and neither of them
14 exhibited that. So we did find that confounder there.
15 DR. KHABBAZ: I thought the speaker who followed
16 you mentioned an additional HCV-positive genotype 1A was
17 negative by both Ortho and Abbott. Was that done and, I
18 presume, followed? Was this person persistently HCV
19 positive?
20 DR. CONRAD: That donor was not in my group, in my
21 study. She mentioned that someone had reported that. I
22 don't know whose group that was in, but we never saw that.
23 DR. HOLLINGER: Just one thing, while you are up,
24 Andy. There were some what I thought were discrepancies,
25 not in your numbers but--you stated something like 11 out of

1 43,000 donors were HBV positive, PCR positive, antibody
2 negative; is that correct?
3 DR. CONRAD: That's correct.
4 DR. HOLLINGER: Then the speaker from Centeon
5 stated that it was a half per 100,000.
6 DR. CONRAD: I think he gave donor per donation
7 numbers. I did donor-donor. He went donor-donations which
8 are different. So, obviously, in the plasmapheresis
9 setting, donors can donate--
10 DR. HOLLINGER: Could the person from Centeon go
11 to the microphone just a moment and clarify if that was per
12 donation and, if it was, how many positives were there per
13 donor?
14 DR. WATSON: That was donors per donation because
15 I did not have a figures for the number of donors. That is
16 in a different computer system in the company that I
17 couldn't get in the short time prior to the talk.
18 DR. HOLLINGER: Thank you.
19 DR. CONRAD: If we were to look at the donor-
20 donation numbers, they are quite similar. It is the donor
21 to donor.
22 DR. STRONCEK: I would like to congratulate all
23 the groups this morning. I think this is outstanding data
24 and it shows outstanding cooperation between a number of
25 groups. It is really a unique situation for blood banking

1 and transfusion medicine in that we have an outstanding test
2 that we know can improve the safety of the blood supply.
3 But it is far from universally available. Where
4 it is available, it is really under INDs. They are fairly
5 tightly defined on how you can submit tests through these.
6 These INDs will work very well for the large blood centers
7 but, in the interim, until this technology does expand, we
8 are going to see a number of potential problems with smaller
9 centers, particularly hospital transfusion services that do
10 specialized collections and transfusions, platelet things,
11 stem-cell donors, organ donors, where this testing won't be
12 available.
13 I would encourage all the groups to continue to
14 work together to develop, advance the technology quickly
15 even further so we have a low-cost test that is widely
16 available as a licensed test so all appropriate donors can
17 be tested with this technology.
18 DR. HOLLINGER: Do you, David or Gene, perhaps
19 even Dr. Fitzpatrick or any others here on the committee,
20 want to comment about the informed consents that were
21 discussed both from the donor standpoint, or give some
22 comments about that from the donor standpoint as well as
23 from the recipient standpoint, if this is going to be
24 required by most hospitals or not, or what the feelings are?
25 I know it is real early in this, but I think that

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1 would be helpful.

2 DR. STRONCEK: I think, because it is a research

3 test, all donors have to be told that an experimental test

4 is going to be done. But I don't see that as a problem.

5 These donors are wonderful people that will virtually sign

6 anything.

7 As far as a transfusion recipient, most hospitals

8 do have some informed consent process. But this is going to

9 be such a rare event that we have a person that is tested,

10 gets a blood transfusion from someone tested positive by NAT

11 testing and negative by antibody that I don't see the need

12 to add that specific information to the informed consent.

13 We, as physicians who run these transfusion

14 services, can deal with these cases on a case-by-case basis.

15 DR. EPSTEIN: I just wanted to comment on this

16 same point. Dr. Pittman raised some very pertinent and

17 difficult issues that, of course, the FDA was aware of. I

18 guess that there were a couple of factors that led us to

19 think that allowing the INDs on a very large, indeed near

20 national, scale was the appropriate thing to do.

21 One of those is the point of view that there was

22 no added risk from the blood to the recipient. In other

23 words, the recipients could only ever get the same screened

24 blood they would have gotten otherwise or blood that had

25 been additionally screened by the experimental test with

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1 some potential benefit.

2 The second point is that the FDA felt that, with

3 all of the concern that we have heard for a number of years

4 about window-period risk, that we wanted to bring that

5 potential benefit, albeit at the investigational stage, to

6 the maximum number of blood recipients as soon as possible.

7 Third, recognizing Dr. Stroncek's point, we

8 recognize that, because of the very complex logistics

9 involved with NAT testing, particularly if done on fairly

10 large pools and in centralized labs, that it would be

11 important to shorten the time from the investigation to full

12 implementation to allow, again, as many centers as possible

13 to be participating in those logistic developments so that

14 they would be ready to roll out very quickly.

15 Lastly, a point of clarification about the

16 informed consent. There is, perhaps, a little bit of

17 misnomer or misinterpretation. FDA's point of view was that

18 the local institution, the hospital, should make its own

19 decision whether any change was needed in its own practices

20 of transfusion informed consent because, really, there is

21 not an independent informed consent for whether you do or

22 don't get an NAT-screened unit.

23 You don't have the option of rejecting the unit

24 that the blood center provides to the hospital. It was more

25 a question of allowing hospitals the awareness that this

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1 practice was going to go on in donor screening and to allow
2 independent local determinations whether that necessitated
3 any change in what was told to the recipient or prospective
4 recipient.

5 Indeed, some hospitals have no message to
6 recipients. They don't do informed consent. Other
7 hospitals do and thought it was appropriate to add mention
8 of NAT.

9 I wouldn't disagree with Dr. Pittman's point that
10 there is a certain risk to the recipient in that same very
11 small number of recipients may be told that they got blood
12 that had a reactive investigation of result. That is true
13 and, unfortunately, that is unavoidable given the current
14 logistics and stage of development.

15 But our point of view is that that factor would be
16 something known to hospital risk committees and they could
17 then decide whether or not it merited additional information
18 to the recipient within the transfusion practices of the
19 hospital.

20 So it is a bit subtle because it is not quite what
21 we normally think of as informed consent.

22 DR. ELLISON: I have a question. Dr. Linder's
23 letter, at the bottom of page 1, implies that we are
24 responding to a global market and the force of the European
25 community make it a deadline of July 1 and we are meeting

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1 that. That is not a consideration, then, in this?

2 DR. EPSTEIN: I think that it was not the driver

3 for FDA but it didn't surprise us how many of the

4 organizations in the private sector became highly motivated

5 to develop their PCR testing or NAT testing strategies.

6 The requirement that has been put in place for

7 July 1 pertains to plasma for fractionation. So it is not a

8 surprise that American-licensed fractionators sought to have

9 in place their PCR testing in time to provide PCR-screened

10 pools for fractionation by July.

11 There, then, was a secondary effect in that there

12 is sale of recovery plasma off whole-blood collection.

13 Collection centers had the choice either to stop selling

14 that plasma for European fractionation or to the

15 fractionators in the U.S. who would potentially market in

16 Europe or to try to move themselves.

17 I think that FDA's point of view in this was

18 really not related to the European requirement except to

19 introduce the notion that if PCR were implemented on plasma

20 for fractionation, we would regard that as a donor-screening

21 test subject to validation and ultimate approval under a

22 license.

23 That has been where the FDA has been coming from,

24 not simply to regard it as a process control on

25 fractionation but to regard it as part of fundamental donor

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1 screening and to put forward the goal of achieving it for
2 transfusable components as soon as possible.
3 DR. KHABBAZ: I, too, was intrigued by a point
4 raised by both Drs. Linder and Pittman. I realize that the
5 issue of recipient is a temporary one but we can hopefully
6 move soon that people will not get blood that is NAT
7 positive before the test results are out.
8 But what I found a little odd is that, at this
9 point, at least, the recipients of components--they may not
10 be of benefit to them in that the results are not out yet.
11 Yet, it seems that the cost is being passed to the users.
12 So if there is not benefit, I felt that it is odd that we
13 will pass the cost.
14 DR. HOLLINGER: I think that is an important
15 issue. I have seen this more and more, now, in studies
16 where commercial companies--for example, in hepatitis C--
17 doing studies out in the community in which the costs of
18 those studies are being passed on to the healthcare system
19 in test being asked to be done and things which we would
20 never do if we were just following patients, treating them
21 ordinarily, asking for monthly tests, except for, perhaps,
22 the medications, and so on.
23 I think this is a very important issue. I would
24 like to hear what the FDA has to say about that.
25 DR. EPSTEIN: It is difficult and, perhaps, it is

1 also a novel paradigm. But I think the way we understand it
2 is that 70 to 80 percent of the recipients are benefitting
3 from the investigational test. A percent of individuals, of
4 course, don't.
5 But, with certain exceptions, particularly
6 platelets, the majority of products released will be after
7 the NAT result. That will be true for all frozen components
8 and it will be true for well over half of red cells. So,
9 yes, it is true that not every individual benefits but the
10 population, as a whole, does benefit.
11 Unfortunately, these trials needed to be done on a
12 very large scale because to measure any actual benefit, you
13 have to look at huge denominators. You have to remember
14 that the expected pickup rate for this testing was low. One
15 had to be thinking in terms of hundreds of thousands to
16 millions in order to get the validation that we are talking
17 about.
18 So putting these things together, I guess the
19 answer is that, on the average, the recipient benefits and,
20 therefore, on the average, the recipient is also paying. It
21 is true that there will be a small number of recipients who
22 paid through reimbursement of care but who didn't actually
23 benefit. But they benefitted future recipients because the
24 studies benefit everyone.
25 So it is tricky. I do think these are very

1 legitimate points and well worth reflecting on. This isn't
2 the last time we are going to face novel technology in a
3 large scale.

4 DR. LINDEN: Dr. Busch, could you give us a little
5 bit more information in terms of the question of how many
6 products we are talking about that would be released without
7 the benefit of this testing and what type of time would be
8 involved in phase I, and what about phase II? When you
9 talked about selecting specifically units from first-time
10 donors to hold off on testing, are you going to be making
11 platelets selectively out of repeat donors or is the time
12 all going to be over five days so that none of the platelets
13 are going to be tested anyway.

14 Can you explain that a little bit better?

15 DR. BUSCH: You have several questions there. I
16 think in terms of the programs during this so-called phase I
17 when products may be released based on serology with NAT
18 data following several days later, the risk to these
19 recipients is really the risk today which we have been
20 projecting at around 1 per 100,000 for HCV and much lower,
21 probably 1 in a million, for HIV.

22 The truth is, in the whole blood-sector screening
23 so far, we haven't seen that yield of HCV. In the plasma
24 industry, we are seeing a very good yield, or high rates of
25 viremic seronegative units for HCV, essentially as would

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1 have been predicted by their incidence rates.

2 So I think that models, the approaches to measure

3 and estimate yield are accurate but, perhaps, it is just

4 that we haven't tested enough. But, as we heard from Sue

5 Stramer, they have tested, now, several hundred thousand and

6 have yet to pick up an HCV viremic seronegative.

7 In Europe and in Germany, several programs have

8 picked up in the rates of 1 in 200,000 to 1 in 300,000. So

9 we are in that ballpark of risk. So the truth is that we

10 are willing to get a unit from a NAT unscreened,

11 serologically screened donation. The probability that that

12 recipient will subsequently be told they got a NAT-positive

13 unit is exceedingly small.

14 Most of the programs are designed to move beyond

15 phase I in the three to six months following implementation.

16 So I think, reasonably, one could say that by the end of

17 '99, all of the programs will be designed and operating in

18 an on-line mode that will not release product other than

19 after NAT testing other than in exceptional circumstances.

20 One of the things that we had to build in is the

21 potential reaction to the fact that we are dealing with both

22 manufacturers and test reagents that have never been tried

23 in the massive scale that we are going to be facing.

24 So we don't know whether we may be testing for six

25 months; fine. And then, all of a sudden, there is a problem

1 with respect to reagents or other issues. So we have to
2 build in the reflex that if, after we have transitioned to
3 phase II, that it may be necessary, on some interim basis,
4 to release based on serology again. So all the programs
5 have kind of designed in that potential reaction.
6 In terms of the specific program I described where
7 we are looking at trying to sort first-time and repeat
8 donations and parallel test the donations from the 80
9 percent of repeat donors, yes, indeed, the programs are
10 being designed to predominantly prepare both--obviously, our
11 pheresis donors are all repeat donors, but, in addition, the
12 whole-blood-derived platelets will be predominantly derived
13 or exclusively, in many of the centers, from the repeat
14 donor subset.
15 Again, the systems are designed such that even
16 that 20 percent of first-time donations, the NAT data will
17 follow within about 36 to 48 hours of time of collection,
18 so, literally within 12 to 24 hours of the serology data.
19 So that 20 percent of whole-blood collection of red cells
20 from the first-time donors will be entering active inventory
21 very shortly after collection.
22 DR. KHABBAZ: I am a little confused. Can you
23 clarify for me? You said you are going to exclude
24 seropositive from NAT testing. Yet, later on in your talk,
25 you said that you are going to follow some maybe

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1 seropositive, NAT-negative--

2 DR. BUSCH: Actually, as I indicated, our trial,

3 itself, has two components. Two of the testing laboratories

4 will test all comers, will not sort first-time and repeat.

5 We will pool them altogether. The other program is

6 devaluating this strategy add will formally evaluate the

7 benefits of the strategy that sorts.

8 In addition, we are planning to test all

9 seropositive donations from first-time donors as a single

10 donation NAT independent of the pool testing designed to

11 release product. So all donations will be tested. One of

12 the peripheral values of NAT will be as an adjunct assay to

13 more properly counsel serologically reactive donors for HCV

14 and HIV most of whom are false positive or indeterminate.

15 So now we are fortunate to have an RNA test to

16 better counsel those donors.

17 DR. HOLLINGER: I would like to pose a question,

18 then, also. Does somebody else have something?

19 DR. STRONCEK: Just one more comment. You asked

20 about the informed consent from a transfusion-medicine point

21 of view. I don't think that is a huge issue. I think what

22 is going to be the biggest issue down the line is when we

23 move to using this, to using NAT testing to release red

24 cells and platelets. Everyone is going to try and move to

25 that as quickly as possible, but there probably is going to

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1 be an extra day of quarantine for these products and there
2 maybe shortages.
3 There may be issues where centers may elect to
4 have emergency releases. So I trust that will go well and
5 that will be a short period of time. But that is going to
6 be a major problem for a while with the blood supply.
7 DR. HOLLINGER: I would like to ask a question to
8 either Sue Stramer, Mike Busch or Dr. Gammon. In dealing
9 with a shipment of samples, I would like to know what is in
10 place in terms of shipments getting lost and so on. I have
11 had a fair amount of experience in shipping things across
12 the country for proficiency testing and receiving huge
13 numbers of samples in some studies being done with the CDC.
14 I will tell you that shipments get lost. Samples
15 get lots. The question of cold and hot. They sit in a
16 warehouse in certain places. It may be very hot. It may be
17 cold. I would like to know what you have in place for
18 documenting and determining the temperature of the sample,
19 whether it gets frozen, whether it gets too hot, what
20 happens when it is lost, it is shipped to Minneapolis
21 instead of San Diego and it sits there, or they can't find
22 it in all or it ends up in Puerto Rico.
23 Why don't you give us some ideas of what you have
24 in place, what the problems are that you anticipate, et
25 cetera.

1 DR. STRAMER: Blaine, you asked a series of
2 questions. Let me first address lost shipments and then
3 return to temperature recording, et cetera. While the
4 testing is going on under IND and this is not required,
5 obviously it is our goal to test all of the collections by
6 NAT. But, under IND, we will be collecting a separate tube
7 for the entire program. So, if that separate tube gets
8 lost, we basically have two options; not to use the products
9 or to have released to products based on serology.

10 As Mike Busch said, during the IND phase, it is
11 certainly an option to release products based on serology
12 while we are working through the kinks in the system. Once
13 this becomes an FDA-licensed test, if a shipment gets lost,
14 as it does now for serology, the test isn't performed, the
15 unit isn't released and we don't have the product available.

16 As far as temperature recording, we do that today
17 and we record times and temperatures because we have other
18 requirements for other serologic tests that require those.
19 We will be using the same validated shippers, as an example,
20 we use today to ship tubes around the country for serology.
21 So we will be using systems that are already in place.

22 DR. HOLLINGER: But it is obviously not just one
23 sample that is going to be lost. There are going to be
24 samples that might be sent from a regional site that might
25 have 500 samples in it. I don't know what your largest

1 numbers are. They are going to be shipped on any one-day
2 basis. So you have a huge number of samples coming from one
3 site.

4 DR. STRAMER: I can't tell you what the maximum
5 number of tubes for shipment for an example. But these are
6 the kinds of studies and these are the kinds of other
7 logistics that will also have to be worked out during the
8 IND phase.

9 DR. BUSCH: The only other comment is all of these
10 programs have what is called retention tubes built in. So
11 whenever samples are shipped, in the case of the Red Cross,
12 they are already centralized in the national testing labs.
13 Each of the collection centers hold back one tube that is,
14 then, potentially available were there a lost or discarded
15 shipment.

16 At present, that tube is not a PPT. It is not
17 designed in this early IND phase but, obviously, once it is
18 a required assay, I think the retention tube will have to be
19 of a nature that is amenable to lab testing as well as
20 serologic testing. Non-Red-Cross programs who are not using
21 PPTs, the retention tube will be an EDTA tube that could be
22 used for NAT.

23 DR. GAMMON: We are trying to minimize the loss of
24 samples by having the blood-collection centers ship their
25 specimens by direct flight. A large number of our specimens

1 will be coming by courier, so it will be ground
2 transportation directly to the NAT collection laboratory.
3 So we will try to reduce loss of specimens that way.
4 Temperature indicators can be put on the specimens
5 when they are shipped. When we receive the specimens, we
6 will know what the maximum temperature was that the specimen
7 was received. We did do some validation studies to try to
8 determine what size shipment containers would be most
9 appropriate for receiving any of these specimens.
10 DR. BIANCO: Blaine, you would have to change
11 shippers. There is a lot of movement of samples and units
12 of blood that go around. For instance, we outsource all our
13 testing at the present time for New York Blood Center, over
14 600,000 a year. There are no losses. It is rare to have an
15 event when there is a snowstorm or something that would
16 delay the shipment or the arrival of a sample.
17 Those systems are much better than they were in
18 the past. Actually, I can say one of the major carriers for
19 all those are companies that carry checks around to exchange
20 with banks. They never lose anything.
21 DR. MITCHELL: I think that the AABB brought up a
22 good point about the sensitivity of the NAT testing that the
23 FDA is proposing, 100 copies per ml of viral units to be
24 detected. They are proposing that it be much higher and
25 that, rather than 100 percent, that it be 95 percent.

1 I wanted to find out whether there is a basis for
2 deciding what the level of the sensitivity should be and if
3 there is going to be a difference between what is going to
4 be required of the pooled sample versus the individual
5 sample. Is there a level, on an individual sample, for
6 example, where the number of virus particles may be low
7 enough that it will be considered non-infectious, I guess.
8 I don't know if FDA or CDC might be able to answer
9 that.
10 DR. HOLLINGER: Any comment?
11 DR. EPSTEIN: FDA does have the intention, as Dr.
12 Hewlett explained, to set a minimum sensitivity for
13 detection of the individual sample, regardless whether it is
14 tested in a minipool or as a single unit.
15 That is not to say that, below that level, the
16 unit is not infectious. It is just that the way that you
17 set it is by looking at how fast does the viremia come up.
18 If you can figure out a practical minimum level of detection
19 which captures virtually the whole viremic period, then you
20 succeed in setting a useful standard.
21 Data have been presented, including publicly by
22 Mike Busch, both for HIV and for HCV which have suggested
23 that if you can detect in the pooled format individual units
24 which have 5,000 or greater copies per milliliter, then that
25 assay will capture virtually the entire viremic period

1 detectable by a gene amplification.

2 So we are not saying that below that level units
3 are not infectious. We are just saying that at that level
4 you will capture the vast majority of units that are
5 infectious.

6 So there are two sensitivity standards then being
7 set. One is the sensitivity for the assay per se on the
8 pooled sample. That is the 100 copy per milliliter level.
9 That is what is achievable right now with state-of-the-art
10 technologies although we are starting to see some that are
11 better.

12 And then, secondly, in terms of being able to
13 interdict infectious components for transfusion, we are
14 saying there has to also be a sensitivity limit set for the
15 system, as a whole, such that it could detect any individual
16 unit when it contains that number of copies of 5,000
17 regardless of what the pooling and the extraction and the
18 amplification and the assay scheme are.

19 So that is a system sensitivity to defined as a
20 threshold for individual units.

21 DR. HEWLETT: I just wanted to add a couple of
22 comments to what Jay was discussing and that is that the
23 5,000 limit at the present is, again, a proposed limit and
24 it is based on data that we have seen presented at various
25 meetings, particularly by Mike Busch.

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1 I think that there are efforts ongoing to look at
2 infectivity--that is, how much virus is, infectious, in the
3 individual donation. Obviously, this limit that we are
4 setting at this point is, again, going to evolve as these
5 tests develop and we learn more about the infectivity titers
6 in terms of RNA copies.

7 So, at this point, the 5,000 limit seems to be the
8 best number that we can come up with.

9 DR. McCURDY: While we are talking about standards
10 and copies per ml, I wonder why it wouldn't be equally good
11 or, perhaps, better to reference the international standards
12 that are available and talk about international units rather
13 than copies per ml. I think the rest of the world is going
14 to the units.

15 DR. EPSTEIN: The international units have only,
16 as yet, been defined for hepatitis C. Based on the assays
17 in our hands at CBER, we believe that one international unit
18 represents four genome equivalents. I think you are correct
19 that, as international units are defined for various agents,
20 we should start to speak in terms of them.

21 It is just that we had set forth our sensitivity
22 standard prior to the development of the international unit.
23 Let me also remark that the European standard for single-
24 unit detection for hepatitis C, as defined by the CPMP, is
25 5,000 international units which would then be, in our hands,

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1 fourfold less sensitive than what the FDA standard is likely
2 to be.
3 So I take your point that, as the international
4 units are defined, we will start talking in terms of them.
5 It is just when things happened.
6 DR. NELSON: How are these standards, then,
7 developed into a pool size. It would seem to me that if you
8 take those criteria and the fact that hepatitis C,
9 particularly in a serologically negative--or HIV in a
10 serologically negative--there shouldn't be more, probably
11 rarely, more than one unit positive in a hundred, even.
12 So would that dictate a pool size of 50, or 5,000
13 and 100 because there could be--maybe it is a small point
14 and maybe the practical issues of cost and how you can
15 detect a positive, a needle in a haystack, if you will. But
16 shouldn't the criteria, somehow, relate to the pool size?
17 Maybe not. I don't know.
18 DR. EPSTEIN: The beauty of setting the standard
19 for the system is then it liberates you from defining the
20 pool size and you can then have a different range of
21 sensitivities, of the analytic sensitivity of the assay. So
22 what is going on, in effect, is that if you have a pool size
23 of 500, you are going to need a ten-copy sensitivity on the
24 pool to detect neat samples at 5,000.
25 Conversely, if you have only an assay at 100-copy

1 sensitivity on the minipool, then you can't get your pools
2 bigger than 50 to comply with that individual unit standard.
3 So the virtue in having a standard for the system is that it
4 relieves us of the burden of attempting to define to pool
5 size. That can then vary.

6 We did feel, however, that, at a practical level,
7 it was necessary for us to set some minimum for the analytic
8 sensitivity of the assay that could be used on the pool
9 because there are assays that are very insensitive and can't
10 pick up under 50,000.

11 So we set 100-copy sensitivity limit knowing that
12 there might be better assays and that better assays might
13 permit larger minipools. But assays that met that standard
14 would, ultimately, require smaller minipools. So we are
15 allowing some tradeoff and then that permits us to allow
16 development of varying systems which have different virtues.

17 DR. FITZPATRICK: I have a question for Sue
18 Stramer along that same line. One panels 6211 and 6213,
19 there is a marked difference between the neat and the
20 diluted results. Could you explain that, or say what you
21 have done to look into that?

22 DR. STRAMER: I think that the panel that you are
23 describing is the one I showed where the neat sample was
24 reactive. And then, in the following bleed, the neat sample
25 was reactive and the first pooled diluted sample was not

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1 reactive, then, until the third bleed.

2 Our explanation for this, through reproducibly
3 seeing this type of finding for some HCV-positive
4 individuals is we see a degree of aggregation. So the
5 degree of aggregation, obviously, has a greater impact of
6 your using larger pools but, in this degree, with 128-member
7 pools, we only saw this on two individuals that have copy
8 numbers, that we would have predicted that we should have
9 been able to detect them, we didn't.

10 And, again, we attribute this to aggregation but
11 we haven't done disaggregation studies yet to actually say
12 that that is, in fact, the cause.

13 I hope that answers your question.

14 DR. FITZPATRICK: That is a good start. There
15 will more late, I'm sure. Thanks.

16 DR. BIANCO: Coming back to the number of copies
17 in international units, there is a certain variability of
18 methods both to determine the units and the copy numbers.
19 Does the agency plan to provide those that are using the
20 test with a standard, a reference sample, that would, for
21 instance, have these numbers of copies so we could adjust
22 our systems.

23 I remember in the meeting, I think we had last
24 September, the international unit was 2.7 copies. Now it is
25 4.

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1 DR. YU: This is Mei-Ying Yu from the Division of
2 Hematology. I just want to tell you that we do have a HCV
3 panel in CBER but it is not really formally accepted as a
4 panel. This panel consists of ten members and the
5 concentration is from 10^5 copies per ml to none. So there
6 are some negative.

7 Now, one of the members, which is member No. 1
8 which contains 1,000 copies per ml, has just been
9 standardized in a collaborative study that is really,
10 mainly, carried out by NIBAC. It is an international study.
11 So that particular panel member No. 1 of CBER has been
12 assigned as 250 international units per ml.

13 So we do have such a standard that is assigned
14 with international units assigned already. Now, it is true
15 it depends on nucleic-acid test methods. So, based on John
16 Savannah's data he recently presented at a couple of
17 meetings, one international unit can be a high as more than
18 6 genomic equivalents and as low as 2 genomic equivalents.

19 So we rely on the manufacturer's validation data
20 with various standards available, at least for HCV because
21 there is an international standard available.

22 DR. BIANCO: Mei, it would be much easier for all
23 of us if you gave each one of us a little bit of that panel
24 member and you told us this is what you are going to call a
25 unit, and we will do it. It will allow for standardization

1 of the entire system if one, or a group, of those samples
2 were made available to all the manufacturers and people
3 working in the field.
4 DR. YU: The first member is 250 international
5 units per ml.
6 DR. HEWLETT: I just wanted to talk about the HIV
7 reference reagent that CBER has developed. Obviously,
8 people in the field are aware that there is no international
9 unit at this point for HIV RNA quantitation. But there are
10 intensive efforts within the WHO and they are collaborating,
11 in fact, with FDA, and the NIBAC is putting this effort
12 together to actually develop a candidate reference reagent
13 for the WHO and, from that point on, to establish the
14 international unit.
15 But, in terms of copy numbers, the CBER panels are
16 configured to include members that are at 100 copies per ml
17 and at 5,000 copies per ml which we can actually provide to
18 manufacturers and have provided to manufacturers in the past
19 to calibrate and to validate their tests.
20 DR. HOLLINGER: It is a very complex issue,
21 obviously, because there are so many types. It is not like
22 having a very pure protein like albumin from which you can
23 have an international standard. I am not even sure how you
24 can have an international standard with so many types and
25 subtypes and other things that go on.

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1 But at least it would be a start to have something
2 based on certain primers and so on.
3 Sue Cushing, are you going to be here through this
4 afternoon? I will save my question until then. If not, I
5 am going to ask it to you now. Is she even here now? Maybe
6 Andy, some of the data may be yours. She presented a slide
7 which showed people who had been followed for a long period
8 of time, some of which had donated multiple times and then
9 became positive.
10 The only question I was going to ask her is why
11 did they become positive. They obviously were asked
12 questions like anyone else on donation about safety and so
13 on, about their history and a donor questionnaire. The
14 question is what was their transmission route. Don't tell
15 me it is sexual transmission.
16 Did they look for that and try to evaluate it in
17 any way because some persons donated multiple times and then
18 became positive.
19 DR. CONRAD: Blaine, in those finger plats that I
20 showed you, many people donated prior to--and if you look at
21 the graph that Sue showed, it didn't matter if it was their
22 first, fifth, tenth, sixtieth donation. So the answer is
23 they must have lied because they didn't claim they did
24 something or they did something that they didn't know. You
25 know those donor questionnaires as well as I do.

1 DR. HOLLINGER: But did they follow up on it
2 afterwards to ask them and try to seek that information
3 DR. CONRAD: Oh, yeah.
4 DR. HOLLINGER: And?
5 DR. CONRAD: Nothing came of it. They just said,
6 "I don't know." I don't think anyone was willing to admit--
7 although there was some early data that showed that there
8 was an odd break or a lapse in the timing between the
9 donations. In other words, they had been donating regularly
10 at some pace and usually there was some early data. It is
11 just anecdotal. It is not enough to be statistically
12 significant.
13 But there seemed to be a lapse. In other words,
14 there was some behavioral indication of that conversion,
15 that there was this greater time in between donations
16 surrounding that conversion to NAT positivity.
17 DR. KLEINMAN: I think that is an important
18 research issue. I don't know, in the plasma-donor sector
19 whether they have really done the donor follow up with
20 detailed questionnaires. Certainly, that is something we
21 hope to do in the whole-blood sector to try to find out what
22 people's risk factors are.
23 Maybe the plasma-collection agencies are also
24 talking about more formal questionnaires to be given to
25 these donors after the fact to try to get to what you are describing.

at

1 DR. EPSTEIN: I believe that at previously
2 meetings, we have seen data from the CDC that approximately
3 half of all acute HCV infections, whether community-acquired
4 or in donors have no identifiable risk. The problem is that
5 we don't ascertain it with questioning.
6 We think we know most of the underlying mechanisms
7 but, when you ask people, they cannot identify the risk.
8 DR. HOLLINGER: That's not true. I won't let that
9 stand at the present time. You can get that information
10 and, in fact, it is not being done. That is because the
11 patient might not tell it to individuals who are acquiring
12 that information in the first place.
13 Our experience has been that almost all of them
14 have a risk factor.
15 With that in mind, it is now 12:45 and we are
16 going to take a break now until 1:45 for lunch. We will
17 meet back here at that time and begin our deliberations on
18 the p24 antigen.
19 [Whereupon, at 12:45 p.m., the proceedings were
20 recessed, to be resumed at 1:45 p.m.]

1 A F T E R N O O N S E S S I O N

2 [2:01 p.m.]

3 DR. SMALLWOOD: We will proceed with our afternoon

4 session.

5 DR. HOLLINGER: The first session is on HIV p24

6 antigen testing, potential criteria for discontinuation.

7 The first speaker is going to be Dr. Hewlett who will give

8 us an introduction and background to this particular

9 session.

10 **II. HIV p24 ANTIGEN TESTING:**

11 **POTENTIAL CRITERIA FOR DISCONTINUATION**

12 **Introduction and Background**

13 DR. HEWLETT: Good afternoon, everyone. I am

14 going to actually provide you with a very brief background

15 and introduction to the issue.

16 [Slide.]

17 Today, we are going to initiate a discussion of

18 the feasibility of replacing HIV p24 antigen testing by

19 nucleic acid testing of minipools in the U.S. plasma blood

20 donors settings.

21 I want to emphasize that this is also an

22 informational session like the one this morning. FDA is

23 seeking feedback in the form of discussion on the issue of

24 replacing p24 antigen with pooled NAT and the adequacy of

25 the criteria proposed by the FDA should such replacement be

1 considered feasible or appropriate.

2 At such time as the sponsor submits an IND to us
3 for replacing HIV p24 antigen by NAT, we intend to bring the
4 issue before BPAC for formal advice. Consequently, today,
5 we invite your discussion, but we are not posing specific
6 questions to be voted on.

7 [Slide.]

8 When HIV p24 antigen testing was instituted three
9 years ago, it was recognized that antigen tests were less
10 sensitive than NAT, particularly NAT for viral RNA. Based
11 on seroconverted data, it was estimated that NAT could
12 eventually reduce the window period for HIV by an additional
13 five days over the reduction achieved by antigen testing.
14 However, NAT was only feasible at the time in a research
15 setting, and it was decided to adopt p24 antigen testing as
16 an interim measure for interdicting window period donations.

17 Since the initiation of antigen testing, a total
18 of five window period units have been interdicted by HIV
19 antigen testing in the U.S.A. and Puerto Rico, and this is
20 data that we obtained from the Red Cross.

21 [Slide.]

22 With the imminent implementation of NAT testing of
23 U.S. volunteer donor blood using pooled donor plasma, which
24 has been sparked by European requirements, the feasibility
25 of replacing HIV p24 antigen testing with NAT testing for

1 early detection of window period donations has been raised
2 by many in the field.
3 NAT for HIV and HCV is currently being performed
4 by plasma collection facilities towards further improving
5 the safety of the blood supply, and, in addition, as you
6 heard this morning, establishments that collect whole blood
7 and transfusable components are also initiating NAT.
8 Although FDA has no stated position on this topic
9 at the present time, we have begun to discuss the issue both
10 internally and externally. Today's presentations are part
11 of this discussion.
12 [Slide.]
13 Here, outlined on this slide, are some
14 considerations that relevant to this topic for the committee
15 to bear in mind.
16 One. NAT testing be pooled or single unit testing
17 must be able to detect all available specimens which are
18 antigen positive, antibody negative, that is, window period
19 specimens. In other words, NAT sensitivity should be equal
20 to or greater than p24 antigen testing for the window
21 period, and this is NAT testing on minipools.
22 Comparisons can be made between HIV detection by
23 NAT versus p24 in the course of clinical trials of pooled
24 NAT technologies. We expect this data to be collected
25 prospectively over the course of a year during which

1 individual sponsors are expected to test over roughly six
2 million donations.
3 An analysis of this prospective data will include,
4 amongst other considerations, analysis of antigen-positive
5 antibody positive and antigen negative antibody-positive
6 specimens.
7 [Slide.]
8 Also, NAT minipool testing must be able to detect
9 appropriate samples from seroconversion panels. NAT
10 minipool testing must also be able to detect HIV variants
11 that would be detected by p24 antigen tests, and this can be
12 demonstrated on selected HIV antibody-positive samples and
13 on cultured virus spiked into normal plasma or sera.
14 We are working with industry to identify and
15 collect such specimens and to use them to possibly establish
16 a validation panel. Details of administration of this panel
17 have yet to be determined.
18 Finally, individual testing organizations will
19 submit INDs to replace HIV p24 antigen testing with NAT.
20 With that brief outline, I will conclude my
21 presentation and look forward to some interesting
22 presentations today, to continued cooperation from industry,
23 and to input from BPAC on this important issue.
24 Thank you.
25 DR. HOLLINGER: Thank you, Dr. Hewlett.

1 The first speaker is from the American Red Cross,
2 Dr. Susan Stramer.

3 **American Red Cross**

4 [Slide.]
5 DR. STRAMER: As you hear earlier this morning, I
6 mentioned one of our IND goals for the NAT test IND at the
7 American Red Cross was the replacement of p24 antigen, and
8 studies to be presented to FDA in PLA to support those
9 claims. I will describe some of those now.
10 [Slide.]
11 But first to give you some background in our use
12 of p24 antigen, Indira basically said we had five yield
13 samples. Let me describe the experience in a little bit
14 more detail with p24 antigen since its implementation on 3-
15 14-96.
16 We have been using the test for three years. The
17 three-year experience in the United States has been 5 p24
18 antigen confirmed positive/HIV antibody negative samples per
19 approximately 36 million donations screened in the United
20 States, and that yield is 1 per 9 million if you exclude the
21 1 donor from these 5 who was CUE, who had self-deferred
22 because he had other risk factors. So, that unit would not
23 have been used. Including, then, those 4 and 36 million
24 screened, we have a yield of 1 per 9 million.
25 What I presented in detail at the AABB is

1 summarized in this bullet. Our two-year experience with p24
2 antigen at the Red Cross, we have 132 total confirmed
3 positive. That is neutralized positives by p24 antigen. Of
4 those 132, they break out as follows: 74 have been in
5 antibody positive individuals, so these antibody positive
6 individuals were also antigen positive, and per our
7 procedures, we repeat the neutralization, so we know this is
8 a real finding that is repeated in duplicate, and the
9 particular individual was also RNA positive. So, this is
10 our benchmark for really establishing HIV infection in this
11 individual, a combination here of antibody, antigen, and
12 RNA.

13 We have also had, in contrast, 54 false positives.
14 The way we define false positives is these neutralize once
15 in the index sample, but then when that same sample is
16 repeated, the antigen test does not repeat in duplicate, it
17 is RNA negative, and there is no seroconversion of the
18 individual on follow up.

19 So, in addition to these 74 and 54, then, over
20 this two-year time, we have 4 index case p24 antigen-
21 confirmed antibody negative.

22 So, let me show those, and I will come back then
23 to my next bullet.

24 [Slide.]

25 This slide summarizes what we know about these

1 four yield samples, that is P24 antigen confirmed antibody
2 negative. Here is their index and time of donation, RNA
3 viral load, p24 antigen signal indicated in yellow here
4 except this one should be yellow, too.
5 So, these are all the positives, percent
6 neutralization on confirmatory testing, development of
7 antibody, and then development of bands on Western Blot.
8 So, what is important to note here, if we are
9 talking about the p24 antigen positives, which you can see
10 here, by either start at the peak viral load, if you look at
11 the concentration, the minimum concentration here is 100,000
12 copies per mL, so in our p24 antigen positives, the minimum
13 concentration was 100,000 copies per mL.
14 [Slide.]
15 Another feature of p24 antigen testing, since we
16 have implemented it, has been the lack of a negative result
17 on repeat reactive samples. In most confirmatory strategies
18 after a sample is repeat reactive and it goes on to
19 supplemental testing, you have the ability to call the donor
20 either negative or positive, and with western blots we all
21 know there is indeterminate. But in this case, actually,
22 there is no negative criteria. If a donor is repeat
23 reactive, that individual goes on to neutralization testing
24 and is either called confirmed positive or indeterminate.
25 [Slide.]

1 To further indeterminate donors, the Red Cross, in
2 collaboration with REDS, did a large study looking at the
3 repeat reactive donors coming from 6.97 million screened,
4 and of those, we had 1,500 repeat reactive donations, 1,157
5 of those were submitted for PCR, and on PCR testing, all of
6 these were negative.
7 So, we do know from the study that indeterminate
8 donors do not represent HIV infection that is for p24
9 antigen, but it represents a challenge to the assay because
10 it is now very difficult to counsel an individual.
11 [Slide.]
12 We do know that when FDA licensed the p24 antigen
13 test, it was licensed as a interim recommendation, and we do
14 also understand or we believe that this will require
15 replacement of p24 antigen, will require an FDA licensed NAT
16 test and, of course, with that the release of all products
17 based on NAT, as I described for the Red Cross program Phase
18 II.
19 Now, to go into specifics of how p24 antigen
20 compares with NAT, at least NAT on pools because that is
21 what is relevant in this discussion, what we have submitted
22 in the IND is really four types of studies.
23 One. We know that NAT has brought subtype
24 detection, at least by the Gen-Probe methods as Christina
25 Giachetti described this morning, including testing of

1 greater than 219 samples from Subtypes A through F, Group O,
2 and Group N samples.
3 Also, NAT has a broad detection of RNA as compared
4 to p24 antigen. For example, you have seen in
5 seroconversion data--and I will show you more--that RNA is
6 picked up first, prior to p24 antigen. In addition, on the
7 other side of the coin, as people seroconvert and become p24
8 antibody positive, RNA is also detected, so it has a broader
9 base of detection, and therefore, an increased number of
10 samples would be detected by RNA as opposed to p24.
11 [Slide.]
12 Looking at a seroconversion profile--and these are
13 all very reproducible--what you see here again is the
14 frequent donation on a plasma donor. Here is the antibody
15 test for HIV 1/2, the antigen test, and then in red you see
16 the quantitative RNA values.
17 As you can see clearly from this, the p24 antigen
18 represents a subset of the total that is detected by RNA.
19 [Slide.]
20 If you now add the TMA data that we will be using
21 per our IND, here again is the p24 antigen line, so even
22 using a pool size in this study of 128, the pool test picked
23 up p24 antigen two days prior to the p24 test, and then
24 there was another five-day window from the 128 to detecting
25 the donor in a neat sample.

1 So, in this case, and in all the cases we have
2 looked at, as I have showed you, p24 relative to diluted NAT
3 diluted NAT is always more sensitive than the individual
4 testing of p24 antigen.
5 [Slide.]
6 Looking at all of the samples we did combined in a
7 larger data sat, this is our NGI data set from the first
8 IND, so this is all from quantitative PCR, these are the
9 different stages that an individual goes through in
10 seroconversion, so here we would first have PCR positive,
11 antigen negative, antibody negative followed by PCR
12 positive, antigen positive, antibody negative.
13 So, in this case, this is the case that we are
14 talking about here, here, the median value of p24 antigen
15 was 100,000, which again was the minimum number that we
16 detected in our p24 antigen yield samples.
17 So, we believe there is adequate levels of RNA to
18 detect if p24 antigen was not present.
19 [Slide.]
20 Looking at the data now in our Gen-Probe IND, we
21 tested samples undiluted, diluted to 1:128, and p24 antigen.
22 So, if you look at 25 panels that were tested on two
23 different master lots, of the world of positives in these 25
24 panels, we could detect on one lot 162 positives, and on
25 another lot 167 positives.

1 When diluted, we detected 90 percent of these
2 samples and 89 percent of these samples, but when we looked
3 at p24 antigen, we only could detect 82 across both lots,
4 and all 82 of these were reactive when tested in pools of
5 128, so we didn't miss any, and this represents again a
6 smaller subset of this population.
7 [Slide.]
8 Looking at just the seronegative bleeds on a 2 by
9 2 plot with p24 antigen against the undiluted test, here you
10 can see the undiluted NAT test reactive samples, none of
11 which were p24 antigen reactive, so we have many low-level
12 positive samples here by the NAT assay that could not be
13 detected by p24.
14 [Slide.]
15 So, what happens when you do a 1:128 dilution?
16 These same samples here that are weakly positive by NAT
17 remain weakly positive at 1:128 dilution again, but nothing
18 is reactive by p24 antigen. So, there is a whole population
19 of samples here that can be detected by the multiplexed
20 diluted assays that are not detected by p24 antigen.
21 [Slide.]
22 In addition to those studies, what we plan to do,
23 although our yield from p24 antigen screening is very low,
24 we hope as we get additional p24 antigen positive donors, we
25 will submit those sample for pooling in our prospective

1 study to introduce into the pooling mechanism and then test
2 on-line as it were a routine donation.
3 In addition to that, the last thing we are doing
4 are NAT reproducibility studies to demonstrate that even a
5 weakly reactive p24 antigen sample will be detected by the
6 pooled NAT test across multiple days, instrument systems,
7 technician, and product lots.
8 In order to do that, we are building a control, an
9 external control sample which will fit into an external
10 control panel, and that sample is a combination of three
11 weakly reactive p24 antigen units that start with an S to CO
12 of 1 to 2. they are pooled, diluted to 1:16 in negative
13 plasma, and we have the quantitative data before and after
14 dilution.
15 [Slide.]
16 They will be included in your LINK study, and we
17 have the opportunity to replicate this 3,000 times. So, in
18 our external control panel, we have an HIV-1 RNA positive
19 sample and a HCV RNA positive sample, a negative sample, and
20 we have added this weakly reactive HIV-1 p24 antigen sample
21 that, when diluted, had a quantity of 2400. So, with each
22 and every test, we will guarantee detection of that one
23 sample.
24 Thank you.
25 DR. HOLLINGER: Thank you, Sue.

1 The next speaker is Sue Preston from Alpha
2 Therapeutics.
3 **Alpha Therapeutics**
4 MS. PRESTON: Good afternoon, ladies and
5 gentlemen.
6 [Slide.]
7 We are very pleased to be invited today to speak
8 to you on the results of our clinical trial and comparison
9 of the p24 antigen to HIV RNA results in our pooled sample
10 PCR testing.
11 [Slide.]
12 The prospective clinical study was sponsored by
13 the National Genetics Institute, and conducted jointly with
14 Alpha Therapeutic Corporation. ICRC, Inc., was contracted
15 to run the clinical trials. The IND was filed February 17,
16 1997. The study was actually conducted for HIV from June
17 through September of 1997.
18 [Slide.]
19 The design of the clinical trial was to enroll
20 anyone who was antibody negative and p24 antigen positive
21 and/or PCR positive, and follow three months or to
22 seroconversion.
23 [Slide.]
24 The clinical participation included 33 of our
25 plasmapheresis centers. We have 63 licensed, so

1 approximately half of our centers were enrolled in the
2 study. We tested over 342,000 donations over that four
3 months and greater than 10,000 donors were tested in the
4 study.

5 [Slide.]

6 Our source plasma screening program includes about
7 close to 3 million donations per year. They are collected
8 in 4% sodium citrate. For our testing new donor plasma
9 units or the applicant donors have their viral marker
10 serology performed and they are found negative before those
11 samples for pooled for PCR screening.

12 For applicants donors or repeat donors, those
13 units are pooled concurrently with the serology for the PCR.

14 [Slide.]

15 I decided not to show you the cube today, but I
16 tried to do it a little differently. We do have a cubic
17 matrix, eight primary pools in each of three dimensions.
18 That includes the rows, columns, and layers.

19 There are 24 primary pools with 64 samples per
20 primary pool, and aliquots from each primary pool contribute
21 to the formation of the master pool. So, there are a total
22 of 512 samples per master pool.

23 [Slide.]

24 In terms of the stability that we found for the
25 source plasma donations, we have tested that with NGI, and

1 we can store up to 60 days at minus 15 degrees, up to 7 days
2 at minus 5 degrees, up to 7 days at plus 8 degrees, up to 10
3 hours at 24 degrees, and it will withstand 5 freeze-thaw
4 cycles, sample will withstand 5 freeze-thaw cycles.
5 The actual logistics for the testing, the plasma
6 samples are shipped to the Memphis laboratory, which is the
7 Alpha Therapeutic Corporation's central testing laboratory,
8 where plasma samples are pooled. We have T-can equipment to
9 assist with that.
10 The master pools are then shipped to National
11 Genetics Institute for the PCR testing where they undergo
12 preparation, amplification, and detection.
13 [Slide.]
14 Following the PCR testing at NGI, the results are
15 reported back to the Memphis laboratory. Positive master
16 pools are retrieved or we retrieve the primary pools from
17 the positive master pools, so there are 24 primary pools per
18 master pool that are shipped back to NGI.
19 The PCR test results are then reported to our
20 Memphis laboratory where we identify the donations and
21 confirm with the individual sample.
22 It takes right now a mean of 20 days to resolve,
23 and that is well within, for the source plasma, the 60-day
24 inventory hold, so that does not present a problem to us
25 because there are several back and forths with respect to

1 samples.

2 [Slide.]

3 For the clinical study itself, we had four
4 eligible subjects, two enrolled and two did not. The number
5 of donations that were found to be PCR positive were 10 from
6 the two enrolled and 6 from the two that were not enrolled,
7 and that is presented in the next overhead, which is a
8 finger plot that Dr. Conrad showed earlier today, but I will
9 go through and describe a little bit in more detail.

10 [Slide.]

11 Each little tick mark there represents a sample or
12 donation, so each of the black marks. In green, all of
13 these units were tested in the 512 pool. They were by PCR,
14 and they were negative.

15 So, plotted at the day of the first positive
16 result, we can see that blue represents PCR positive only,
17 that yellow represents PCR positive in the 512 pool, as well
18 as p24 antigen positive, and red is the PCR positive, p24
19 positive, and antibody positive donations.

20 For each of four donors, we did detect by PCR
21 prior to p24 antigen test results becoming positive.
22 However, this was only four. That is a small number. We
23 worked through, and if we can have the next overhead--

24 [Slide.]

25 -- additional samples and the sources for these

1 window period samples included the clinical study period
2 subjects, additional subjects that were HIV antibody or
3 antigen positive, some of the plasma units we had in
4 seroconversion panels.
5 So, what I am going to present you now is in the
6 process of being finalized for a report, so I would all it a
7 preliminary analysis.
8 [Slide.]
9 This is a description of how we actually selected
10 these window period units. NGI performed their quantitative
11 reverse transcriptase PCR. If they were positive, then,
12 these units were diluted to 512, and the qualitative test
13 was performed. This is a test that we do on the 512 for the
14 donor screening.
15 If they were negative, however, by the
16 quantitative, we then did them by the qualitative method,
17 and again if they were positive, diluted to the 512 to
18 obtain the test results.
19 [Slide.]
20 This overhead is a 2 by 2 contingency table. PCR
21 along here is PCR positive or PCR negative. It was either
22 positive by Coulter or Abbott, we didn't care which one, but
23 just as long as it was positive by at least one of those,
24 and these are for antibody negative specimens. We found 61
25 of these specimens were concordant, they were positive for

1 PCR, and also positive by p24.

2 There were 32 samples that were positive for PCR,
3 but negative on p24. There were 71 that were concordant
4 being negative for both p24 and PCR, and as Dr. Conrad
5 pointed out, there were none that were positive for p24 and
6 negative for PCR.

7 [Slide.]

8 This overhead is the same table, but for all
9 samples, so there were antibody positive samples also
10 included in this, and as we look at this, there were 140
11 concordant samples PCR positive and p24 positive.

12 There were 91 samples that were p24 negative and
13 PCR positive, 109 that were negative by both tests, and
14 again zero where p24 would have picked them up and PCR
15 didn't, so there was absolutely none.

16 I think another important thing, since we talked a
17 little bit about this, and you discussed it a little bit
18 earlier, there were 6 samples that were antibody positive
19 only, in other words, they were not p24 positive, nor were
20 they PCR positive, however, all of these--I want to make the
21 point that all of these would have been caught by lookback
22 in our 60-day hold. But I think that is an important point
23 as to why we are not requesting consideration for deleting
24 the antibody test.

25 [Slide.]

1 This is a plot just to show these are the number
2 of incidences, the number of donors, if you will, and a plot
3 as to the days that they were detected before p24. Now,
4 this doesn't mean that this was sampled every day in between
5 there, but this is the way these panels broke out.
6 There were 27 donors that were detected basically
7 the same day they were p24 antigen positive, they were also
8 PCR positive, and then there were 36 donors that were
9 represented in here where PCR detected the viremia earlier
10 than p24.
11 The mean turns out to be about three days here
12 with the median of about two days earlier, and during the
13 quantitative analysis of these samples, they ranged from
14 anywhere from 100 copies per mL to 20 million copies per mL
15 in the PCR positive donations.
16 [Slide.]
17 I would just like to acknowledge all of the
18 collaborators on this study - Andrew Conrad, Peter Schmid,
19 Jeffrey Albrecht, and Richard Smith from NGI; and then Alpha
20 Therapeutics, Bill Craig, Chuck Frisbie, Chuck Heldebrant,
21 Lorraine Peddada, and Lolita Mercado.
22 Thank you. I will be glad to answer any
23 questions.
24 DR. HOLLINGER: Just at this point--I should have
25 done this the first time around--but any questions for Sue

1 Preston on the presentation here?

2 [No response.]

3 DR. HOLLINGER: If not, let's move on to the next

4 speaker, Michael Busch from the Blood Centers of the

5 Pacific, Irwin Center.

6 **Blood Centers of the Pacific, Irwin Center**

7 DR. BUSCH: Thanks, Blaine.

8 Just a few I think sort of historical comments. I

9 think many of you in the audience were probably here about

10 five years ago or so when the antigen issue was first

11 debated, and I think it is worth going back and remembering

12 that the Advisory Committee to FDA voted based on the

13 projected yield data from the models that we had developed

14 and that I will briefly review now that indicated that the

15 yield would be something in the range of five or so antigen

16 positives per year, and that the cost effectiveness of

17 antigen testing would be extremely poor, voted against

18 introducing antigen testing. I think, as I recall, the vote

19 was something like 12 to 5 or something like that.

20 Within several weeks of that vote, the

21 Congressional Oversight Committee, chaired by Shays, issued

22 a letter instructing FDA to, in essence, override the

23 committee's decision.

24 In that letter, somehow projections were derived

25 that estimated that there would be something in the range of

1 65 antigen-only donations detected in the whole sector per
2 year. I think, as we have come to see, the antigen yield is
3 actually much lower than projected, and I will briefly
4 address a few studies that have tried to understand why has
5 the yield been lower than we originally projected.
6 Just another comment. The focus of discussion on
7 antigen implementation at the time was exclusively focused
8 on the whole blood sector. I don't recall any
9 considerations at the time because there has not been an HIV
10 transmission from plasma derivatives since essentially
11 screening was introduced in '85. Any discussion about
12 requiring antigen testing of source plasma donors, and many
13 people including myself were very surprised when the FDA
14 memo came out and actually required antigen testing of
15 source plasma donors.
16 As we have seen, actually, there continues to be
17 yield in the source plasma industry, but not in the whole
18 blood sector. So, with that background, if you would turn
19 on the slides, please.
20 [Slide.]
21 As we saw from Sue Stramer's data, the yield has
22 actually more in the range of one to two per year rather
23 than the five to 10 per year predicted, and we wondered why
24 that is. One possibility is that actually, the modeling
25 that we use to estimate yield assumes that the incidence

1 rate in the donor population, the rate of seroconversions or
2 new infections is constant over time, and also that when a
3 donor is giving, that they are giving in a steady-state rate
4 throughout the evolution of seroconversion, and the models
5 estimate the duration of each of these windows, and then
6 multiplying by the incidence, project the rate at which
7 people may give during that brief window phase here, the
8 antigenemic phase.
9 So, one assumption is that the rate at which
10 people seroconvert overall can be assumed to be predictive
11 of the rate at which they would give during that very
12 transient antigenemic window.
13 So, as we realized that the yield wasn't coming
14 toward what we had projected, we began to wonder, one,
15 whether the incidence rates had dropped; two, the question
16 of whether the donations may not be consistently given
17 during the antigenemic phase either due to people's self-
18 deferring due to recent risk or to symptoms or deferral at
19 the time of blood donation because we take people's
20 temperature and ask them about things like recent night
21 sweats, and as most of you know, HIV primary infection,
22 particularly during the antigenemic phase, is associated
23 with an elevated temperature and with symptoms, and in
24 addition, these people may be aware of recent risk.
25 [Slide.]

1 So, to look at these issues, a couple of analyses.
2 One is actually REDS has continued to monitor incidence.
3 The incidence rates that we use to project the yield of
4 antigen were an incidence rate about 4 per 100,000 per year
5 based on data from this '91 to '93 time period.
6 As we have continued to monitor incidence, you can
7 see there has been a small, although insignificant, drop in
8 incidence rates, and we are really running these days more
9 in the range of 1 per 100,000 person years, so, indeed, the
10 incidence of HIV has declined in the donor pool, which may
11 partly explain the lower than projected yield.
12 [Slide.]
13 Another clue actually comes from the panels that
14 were actually studied in generating the original model data
15 that led to antigen introduction, and this slide was
16 actually made back in probably '94 and before we had any
17 consideration of this, just selecting four of the
18 seroconverting plasma donor panels from BBI that were
19 representative of the panels, just to illustrate the ramp-up
20 of RNA, the increase in antigen levels, and then the
21 appearance of antibody.
22 What I want to point here is something that is
23 frequently seen in these panels, and specifically, it is
24 actually the X axis. What you see here are data points
25 corresponding to when these donors were giving, and you see

1 that these donors were giving at essentially a twice a week
2 frequency, which is the rate that they are allowed to give,
3 and then they don't give for a week. They give it twice a
4 week, twice a week, and they don't give, twice a week, twice
5 a week, and then they skip a week. Over here, this person
6 skipped several weeks.

7 What you can see is the weeks they skip are fairly
8 consistently when they would have the peak antigenemic
9 titer. So, what we suspect is going on is a fair bit of
10 self-deferral, attributable organ donor center deferral. We
11 actually looked back at donors who didn't give to see if
12 they had come to the center and perhaps were deferred due to
13 temperature, things like that, and there was no evidence of
14 that.

15 So, what we actually think is many people, because
16 they are sick, may not come in to give blood during that
17 week they are maximally antigenemic.

18 [Slide.]

19 This is the plasma donor sector, and we have
20 looked at this in the whole blood donor sector, as well, in
21 the REDS study, and this is an analysis that George
22 Schreiber did, where we looked at our seroconverters to all
23 of the viruses, and we looked at their interdonation
24 intervals, the time between their first positive donation
25 and their prior negative donation, and this was based on

1 antibody testing, and we did this in HbsAg for the four
2 major agents.
3 Just to make a long story short, what we observed
4 was that the HIV seroconverters had significantly longer
5 interdonational intervals in their immediate pre-
6 seroconversion donation than the general donor pool, and
7 specifically, most powerfully, is donors who were giving
8 serially, when we looked at their interdonation interval
9 immediately prior to seroconversion, it was much longer, 388
10 days, compared to these very same donors' usual pattern of
11 donation, which was about 140 days, and that was highly
12 significant.
13 This observation was true for HIV, but not true
14 for any of the other viruses. So, it really does look as if
15 HIV seroconverters, both in the whole blood and plasma
16 sector selectively defer immediately prior to seroconversion
17 either due to some awareness of risk behaviors or because of
18 this symptom issue.
19 [Slide.]
20 One last slide, which is to lead us into the newer
21 data. This is data again that was generated from panels
22 immediately before the licensure of HIV antigen testing when
23 we were trying to understand the durations of the RNA and
24 antigen window characterizing lots of panels, and now we are
25 focused back on these because the real issue we are focused

1 on today is whether we can comfortably discontinue antigen
2 testing given the availability of direct nucleic acid
3 screening.
4 What this slide shows is what is termed at box and
5 whisker plot showing the distribution of RNA among donations
6 in these plasma panels that were detected only by RNA versus
7 by p24 antigen during the pre-antibody window period. It is
8 this kind of data that I will go into in more detail with
9 newer analyses in the overhead.
10 [Slide.]
11 The first slide is actually the same data as was
12 in those first two box and whiskers on that earlier plot,
13 just directly comparing the RNA distribution. Now, this was
14 from approximately about 80 samples from 50 seroconversion
15 panels. Again, these were archived panels that had been
16 identified in the period of like '85 through '95, and then
17 testing back, we identified these RNA only or p24 antigen
18 positive samples.
19 What you can see from this analysis is that there
20 is a highly significant difference with the RNA-only samples
21 having a much lower viral load on average. This, by the
22 way, is Roche quantitative monitor PCR data versus Abbott
23 p24 antigen results. We can see that the RNA-only had a
24 average copy number of about 1,000, whereas, the p24 antigen
25 had an average copy number of about 200,000.

1 [Slide.]

2 On this slide there are actually just some sort of
3 scribbled statistics from this distribution plot focused on
4 the antigen positive donations, and the critical point here
5 is again the average copy number of these antigen positive,
6 antigen negative donations is over 200,000, and the lower 95
7 percent confidence bound is about 25,000.

8 So, in other words, if you had an RNA assay that
9 could detect samples with 25,000 copies based on this data
10 set, you would detect 95 percent of the antigenemic
11 donations. You would detect 97.5 percent if you had an RNA
12 assay that had about 2,000 copy sensitivity. You would
13 detect 99 percent with an RNA assay of about 1,000 copies.

14 [Slide.]

15 Then, one can look at these samples again from
16 this earlier historical data set, plotting out the log of
17 concentration of RNA versus the p24 antigen reactivity, and
18 you can see that there is a moderate number of samples down
19 here that are antigen nonreactive that were RNA positive,
20 very similar to what Sue Stramer showed, and then once you
21 get into the samples that are antigenemic, you see a very
22 close relationship between the levels of RNA and the levels
23 of antigen.

24 [Slide.]

25 If one does a regression analysis on this data,

1 you can then begin to try to estimate what the RNA load is
2 at the point of the antigen cutoff, and this is focused on
3 the antigen positive, RNA positive samples, and based on
4 this analysis, the estimated intercept is around--I think it
5 was around 30,000 copies.
6 But this was very old data, so what we wanted to
7 do was to really update and expand this analysis, and
8 fortunately, Sue Preston and Andy Conrad from Alpha and NGI
9 were comfortable with sharing their newer data, which is
10 much more exhaustive.
11 [Slide.]
12 This slide summarizes a similar analytical
13 approach to get an understanding of the distribution of the
14 antigen positive units and the cutoff value at which the
15 antigen test becomes reactive, so that we can ask the
16 question of at what level of RNA would we be comfortable
17 discontinuing antigen.
18 I think this very same data is actually the data
19 that is the basis for defining the cutoff that we want NAT
20 to perform at. We want NAT to clearly be a substantial
21 improvement relative to RNA, and interdict most of these
22 RNA-only samples that are detected by single donation
23 testing. So, these kind of analyses are the kind of data
24 that yield the 5,000 recommendation.
25 But to focus first on the antigen-only phase,

1 there were 85 specimens in this data set that were negative
2 on the third generation antibody Combi test, specifically
3 Abbott's HIV 1/2 Combi test that were positive on p24
4 antigen. In this case, it was the Coulter p24 antigen
5 assay.
6 This slide then shows the distribution with the
7 median copy number of about 100,000--we will look at those
8 statistics in a moment--and the vast majority of samples
9 having copy numbers well over 10,000 copies, really with
10 only a single outlier specimen.
11 In contrast, the RNA-only samples have a much
12 lower copy number, an average copy number of around 20,000
13 with samples detected as low as 100 copies or less.
14 [Slide.]
15 This is statistics again not for people to see.
16 If you actually push that up. This is basically for me to
17 just comment. The same kind of analyses, then focusing on
18 the antigen-only samples, would tell us that an assay
19 sensitivity of 10,000 would pick up 95 percent of the
20 antigen-positive samples that Alpha and NGI detected.
21 As you want to pick up 97.5 percent, an assay
22 would have to have a sensitivity on an individual donation
23 of 7,000 RNA copies, and if you wanted to pick up 99 percent
24 of the antigenemic specimens, the assay would have to be
25 able to pick up around 2,400 copies per mL in the individual

1 donation samples.

2 [Slide.]

3 Then next thing we wanted to understand was more
4 precisely what the RNA load is at the cutoff of the antigen
5 assay. The data that Sue Preston presented, extremely
6 positive reassuring, essentially, every single positive
7 antigen sample was detected by RNA at a pool of 512, and
8 empirically, as I just showed, if you take a cross-section
9 of samples picked up as antigen only, the lower 95 percent
10 confidence found on that distribution is around 10,000
11 copies. So, you would pick up 95 percent of real world
12 samples with an assay of 10,000 copies.

13 But we wanted to go a little further and try to
14 really understand the antigen intercept, meaning at what
15 concentration of RNA did the antigen assay become reactive.

16 Based on this regression analysis, we could
17 estimate almost exactly 10,000 copies is where the antigen
18 test first becomes reactive. So, clearly, setting a cutoff
19 at or below the limit of sensitivity of the antigen assay
20 would be a very reasonable and conservative strategy to
21 allow discontinuation of this assay.

22 [Slide.]

23 This just shows confidence intervals analyses
24 around that cutoff, but again, the bottom line is that
25 virtually all the samples are detected at 10,000. You will

1 note this one outlier sample that actually had a copy number
2 of only 500, and yet was detected at on the antigen assay.
3 [Slide.]
4 This is a similar plot of the distribution, but
5 now this is limited to 32 of these approximately 45
6 seroconverters where we had 3 samples that were RNA positive
7 prior to antibody. This then distributes their individual
8 subject RNA versus antigen reactivity.
9 The point I want to make here is that virtually
10 all of these people, all of their antigen RNA data is
11 consistent with a very tight cutoff sensitivity of the
12 antigen test at 10,000 copies. So, almost all of these
13 people crossed this antigen cutoff line right at that 10,000
14 copy sensitivity. So, very reassuring that a 10,000
15 sensitivity assay would comfortably detect all of the
16 samples even if they were diluted down to the cutoff of the
17 assay. But there was this one sample, and interestingly,
18 this one person is actually represented three times in a
19 panel, and all three samples from this person showed a low
20 RNA copy number on this assay relative to the antigen in
21 single intensity.
22 So, the point here, this is one out of 32 people.
23 There may be rare individuals who, on a particular RNA
24 assay, may give you relatively low RNA antigen load, but why
25 that is, is under investigation, but these are extremely

1 rare, and again, this sample was picked up at a 512 pool,
2 but my bottom line message here is that based on the
3 analysis we have been doing, we would be very comfortable
4 that a cutoff as high as 10,000 should allow discontinuation
5 of p24 antigen testing, and certainly setting a cutoff half
6 that, at 5,000, would be an even more conservative and
7 appropriate position.
8 Thank you.
9 DR. HOLLINGER: Thank you, Mike.
10 Any questions of Dr. Busch?
11 [No response.]
12 DR. HOLLINGER: The final speaker in this session
13 is Dr. Schochetman from Abbott Laboratories.
14 **Abbott Laboratories**
15 DR. SCHOCHETMAN: Thank you.
16 I think my role here is to sort of provide the
17 counterpoint to this and to provide possibly a cautionary
18 note about premature termination of antigen testing, and
19 thereby probably sending a disincentive message to
20 manufacturers to not bring forth new and more sensitive
21 antigen tests.
22 [Slide.]
23 What I hope to be able to do today is to convince
24 you that the gap in detection between individual antigen
25 testing, using a new and more sensitive assay with broad HIV

1 variant detection, and NAT testing of pooled samples may not
2 be as significant as we may have originally thought.
3 [Slide.]
4 Before I begin with that part of it, I would like
5 to come back to the HIV variant issue. I am sure most of
6 you are aware of the fact that HIV variants are rapidly
7 spreading into developed countries. If you are not aware,
8 currently, only at 1/30th of the global infections in the
9 world are due to HIV-1 group M subtype.
10 In Europe now, it is estimated that up to 25
11 percent of new infections are due to non-subtype B HIV-1
12 group M infections, and in the U.S., that number of non-
13 subtype B HIV infections is also increasing, and according
14 to the CDC, there may be in excess of 3,200 cases that were
15 actually detected that were non-subtype B.
16 [Slide.]
17 I think the challenge to manufacturers certainly
18 is to develop sensitive assays with broad HIV variant
19 detection. In particular, for NAT assays, they must be able
20 to detect all HIV variants efficiently, and must have
21 adequate sensitivity to address dilution factor due to
22 pooling.
23 [Slide.]
24 What I would like to do now is address all HIV
25 variants efficiently. What I have provided you here is a

1 comparison of two assays, two quantitative assays, the LCx
2 assay from Abbott and the test of record assay here in the
3 United States, the FDA-licensed test.
4 What I would like to do is point out really the
5 upper lefthand quadrant here, that there are 71 samples out
6 of a total of 278 that we actually looked at, which were
7 positive in the LCx assay and negative in the test of record
8 here in the United States including at least five Group O
9 specimens shown in red here.
10 [Slide.]
11 I think you can see here that those 71, when you
12 break them down, you find out that in terms of HIV subtypes,
13 that they run the gamut of subtypes from all the A through
14 G, HIV-1 group M subtypes and including the Group O. The
15 mosaics would be either mosaic or recombinant viruses.
16 I think when one looks at which assay you are
17 using, I think it is imperative that actually one pay
18 attention to and realize the broadness of the cross-
19 reactivity of the assays that are being used and whether
20 they can detect all subtypes.
21 [Slide.]
22 What about the issue adequate sensitivity to
23 address the dilution factor due to pooling?
24 I have just taken three examples here of actual
25 specimens. These happen to be mosaic viruses A/G/A, and

1 these are specimens with low copy number. In this case, the
2 copy number is just over 1,000, again here over 1,000, and
3 this one is actually less than 1,000.
4 You can see here as we begin to dilute, certainly,
5 if you are looking at 50 copies per mL, that as you reach
6 about 1 to 50 in a pool of 128, you actually would be
7 negative, and if you are looking at a sensitivity of 100
8 copies per mL, you would actually lose your sensitivity more
9 like 1 in 20.
10 [Slide.]
11 What about antigen testing? Well, we have gone
12 ahead and actually developed a new and more sensitive
13 antigen test, and you can see here the sensitivity begins to
14 approach about a picogram/mL for p24.
15 When you look at the ability of this assay to
16 actually detect a variety of subtypes, the group M subtypes
17 A through G, and including O, you can see that this assay is
18 very sensitive and can efficiently quantitate really all the
19 variants, and not just simply the HIV group M subtype B.
20 So, here, we have an assay that actually is very
21 sensitive and has very broad detection.
22 [Slide.]
23 Well, what about the comparison between a
24 sensitive antigen assay and genetic testing? A lot of data
25 we heard today was really with the currently licensed tests

1 which have been around for a while.

2 If you talk about the sensitivity of an antigen
3 assay, such as the one I showed, which is about a picogram
4 of p24, you are talking about somewhere in the neighborhood
5 of around 10,000 copies of viral RNA.

6 So, even at a sensitivity of 50 copies per mL for
7 a NAT test, and you are talking about a pool of 128, the
8 sample must have at least 6,400 copies of viral RNA. I
9 think there can be variability as much as half a log between
10 assays and maybe between runs, so that the difference of
11 10,000 copies picked up by a more sensitive antigen assay
12 and 6,400 copies may really not be all that significant.

13 [Slide.]

14 In terms of the advantages of individual testing
15 in pooled versus NAT testing, I think certainly the antigen
16 testing is a fully automated system. It provides rapid
17 results, and as I show you, can actually provide very
18 efficient detection of all HIV variants including the group
19 O, really does not have issues related to sample
20 preparation, contamination issues. We heard this morning
21 issues of possible transportation, temperature controls, et
22 cetera, et cetera. The assay has the ability to be
23 confirmed using a neutralization test, and in terms of
24 simplicity for implementation, there would be no pools
25 needed to dilute the sensitivity, and there would be no

1 dissection of pools.

2 I think I would leave you with the comment that
3 although we now have an assay that can get us down to about
4 a picogram of p24, I think that by no means is that the
5 theoretical limit, and we feel that we can actually go more
6 sensitive, and I will come back to my original point, that
7 is, that I think if we decide to send a message that nucleic
8 acid testing should be removed, then, we may send a
9 disincentive to the development of new technology, and I
10 will leave it at that.

11 DR. HOLLINGER: Thank you, Dr. Schochetman.

12 Any questions on this presentation for now?

13 [No response.]

14 DR. HOLLINGER: In the open public hearing, we
15 have one person who stated he wanted to speak, and that is
16 Dr. Kleinman from the AABB.

17 **Open Public Hearing**

18 DR. KLEINMAN: The AABB commends the FDA for
19 initiating open public discussions about the potential
20 elimination of the p24 antigen assay. The major requirement
21 for establishing that the HIV-1 p24 antigen assay can be
22 safely discontinued is to demonstrate that it elimination
23 would not introduce additional HIV infectious units into the
24 blood supply. The AABB would like to take this opportunity
25 to present a proposed approach to acquiring the data

1 necessary to evaluate this issue.

2 The AABB recognizes that elimination of the p24
3 antigen assay will not be possible until all donated units
4 are screened by an assay that is of equivalent or greater
5 sensitivity for detecting window period infection.

6 In the case of pooled NAT, this would mean that
7 NAT would need to be completed prior to component release.
8 Furthermore, the AABB believes that pooled NAT would need to
9 demonstrate satisfactory performance characteristics in
10 routine operational settings before it can be considered as
11 a replacement for the p24 antigen test.

12 It is unclear exactly what requirements would need
13 to be met to fulfill this criterion; at a minimum, the
14 pooled NAT system would need to have the required level of
15 sensitivity, as determined by previous studies comparing p24
16 antigen results with quantitative viral nucleic acid assays.

17 In the view of the FDA, satisfactory performance
18 may require that a pooled HIV NAT system be licensed prior
19 to considering replacing the p24 antigen assay. However,
20 other approaches to demonstrating satisfactory performance,
21 such as compiling performance data over an extended time
22 frame while still under IND, for example, 6 to 12 months,
23 should also be considered.

24 The rationale for the introduction of p24 antigen
25 testing was based on modeled data from plasma seroconversion

1 panels that demonstrated the ability of the assay to shorten
2 the window period for HIV infection by approximately six
3 days relative to the estimated 22-day window with the most
4 sensitive antibody assays.

5 Data from the same seroconversion panels have
6 indicated that all HIV-1 p24 antigen positive window period
7 units also were positive by research RNA PCR assays and that
8 these assays further shorten the window period by an
9 additional three to five days.

10 Furthermore, quantitative PCR assays indicate that
11 p24 antigen positive units contain at least 10,000 copies
12 per ml of HIV RNA. These combined data suggest that pooled
13 NAT programs using assays with 50 copy/ml sensitivity and
14 pool sizes of less than or equal to 128, which is the
15 maximum pool size proposed by the volunteer blood sector,
16 will be able to detect all window period units that are p24
17 antigen positive.

18 As you heard today, using the incidence window
19 period model developed by the REDS, it was projected that up
20 to eight HIV p24 antigen positive, antibody negative units
21 would be detected annually in the U.S.

22 Actual experience over the past three years has
23 demonstrated that fewer than two units per year have been
24 detected in volunteer donors. This low yield indicates that
25 it would take many years to accumulate a sufficient number

1 of p24 antigen positive window period units to substantiate
2 that pooled NAT will detect all such units.
3 The AABB believes that an alternative approach for
4 data acquisition is needed. We suggest that test
5 performance on commercial plasma donor seroconversion panels
6 and on samples obtained from HIV screening performed by the
7 commercial plasma donor sector serve as the basis of
8 assessing the performance of a pooled HIV NAT system versus
9 the p24 antigen assay.
10 Satisfactory performance of a pooled NAT system
11 relative to p24 antigen testing could first be demonstrated
12 in a research laboratory and then could be validated by the
13 testing of blinded seroconversion panel samples in clinical
14 trial protocols conducted by the operational NAT
15 laboratories.
16 The number of antigen positive window period units
17 needed should be determined by statistical evaluation and
18 agreed upon in advance by FDA and the testing laboratories.
19 Such an approach would yield data that should duplicate
20 prospective blood donor screening performance, but in a very
21 much shorter time frame.
22 This approach would permit rapid evaluation of the
23 feasibility of replacing the p24 antigen assay without
24 increasing risk to recipients. If the data support such an
25 approach, rapid elimination of an unnecessary test would

1 have the benefits of simplifying the blood donor screening
2 process and reducing the costs of supplying blood
3 components.
4 Thank you.
5 DR. HOLLINGER: Thank you, Steve.
6 Any questions of Dr. Kleinman?
7 [No response.]
8 DR. HOLLINGER: Is there anyone in the audience
9 also then during the open public hearing that would like to
10 make a presentation?
11 Yes, please state your name and organization.
12 DR. HEALEY: Yes. Good afternoon. My name is
13 Chris Healey, and I am the Director of Government Affairs
14 for ABRA, which represents the source plasma collection
15 industry.
16 We are encouraged by the fact that FDA has
17 initiated the dialogue about discontinuation of p24 antigen
18 testing, and we concur that the time is right to begin
19 discussing the specifics of discontinuation criteria.
20 Of course, first among them must be that p24
21 antigen testing is discontinued only if there is no
22 sacrifice in the safety of source plasma, which means that
23 the NAT testing must be demonstrated to be equal to or
24 better than the current p24 antigen testing.
25 Other key issues to the industry must be addressed

1 early on in this dialogue, and among them are included the
2 implementation of discontinuation of p24 antigen testing.
3 What I mean by that is that industry believes it should be
4 done industrywide, and not piecemeal. That is to say, we
5 believe that FDA should consider withdrawing its policy
6 industrywide, and not according to specific manufacturers or
7 specific collectors.

8 To that end, we think that discontinuation should
9 not be linked to specific IND amendments, and the
10 perspective here is that the logistics associated with
11 tracking specific units of plasma as to whether they should
12 be p24 tested or tested according to NAT is just
13 overburdensome and would basically eliminate this good work
14 or discontinuation. It would make it unworkable
15 essentially.

16 We believe that FDA can take a perspective of
17 looking at the aggregate data. We believe that industry
18 working together with the agency can collect data over some
19 period of time, six months, a year, and that based on the
20 aggregate industry data, industry and FDA can agree that the
21 time is right to withdraw the policy industrywide.

22 Other issues pertain to the development of the
23 seroconversion panel. Primary among them is that the panel
24 ought to be internationally recognized. We believe that we
25 should be working with European and Japanese partners to

1 make sure that whatever seroconversion panel is developed to
2 assess NAT testing is recognized by our foreign
3 counterparts.
4 Finally, we believe that whatever panel is
5 developed, that it should be used only as a reference panel,
6 and shouldn't be used at all to evaluate sensitivity of
7 current NAT tests.
8 We look forward to working with the agency on this
9 initiative, and look forward to reporting back to the BPAC.
10 DR. HOLLINGER: Thank you.
11 DR. EPSTEIN: Jay Epstein, FDA.
12 I understand at a practical level why it would be
13 easier to just have a blanket removal of antigen for the
14 fractionation industry, but the reality is that if different
15 testing systems are going to be used, we can only get to
16 that point once we are assured that all of the ones in use
17 are adequately sensitive to replace antigen. That is just a
18 logical requirement. So, you know, if we were to have a
19 blanket policy and we looked at it your way, we would have
20 to wait until all assays available met that standard.
21 DR. HOLLINGER: Other comments?
22 [No response.]
23 DR. HOLLINGER: I think then we will close the
24 open public hearing.
25 Now, we will open it for the committee for their

1 discussions. Anyone would like to make some comments about
2 the issue on p24 antigen testing, the potential criteria for
3 discontinuation or continuation?
4 Yes, Dr. Fitzpatrick.
5 **Committee Discussion**
6 DR. FITZPATRICK: Abbott has raised a point here
7 that I think needs to be considered, and that is that the
8 focus is on elimination of p24 antigen in deference to PCR
9 testing, but if they can demonstrate equal sensitivity and
10 narrowing of the window by detecting p24 antigen, now you
11 have two equivalent tests, and it is a matter of economics
12 and selection as to which test you are going to use to
13 select and test for HIV.
14 I didn't hear that argument presented by anybody,
15 but I think that needs to be considered.
16 DR. HOLLINGER: Does that pose a problem if there
17 are comparable sensitivities and it can be demonstrated
18 either that the comparable sensitivities or that one picks
19 up some that are positive by antigen and negative by RNA,
20 and vice versa?
21 DR. EPSTEIN: I guess we will have to cross that
22 bridge when we come to it. The question that will arise is
23 whether if you have two different assays and they each pick
24 up the same number of antibody negative infectious samples,
25 should they coexist and be used as alternatives or should

1 they both be used versus the simple case where they pick up
2 the same samples.
3 If they pick up the same samples, the question is
4 easy because you could easily allow alternative use, but if
5 they pick up the same number or approximately so, but they
6 are not the same sample, then, it is difficult, and I think
7 that the logic would tend to drive us to keep both tests.
8 DR. HOLLINGER: Jay, while you are here, in Europe
9 they require p24 antigen testing, so it is not an issue, a
10 regulatory issue at all.
11 DR. EPSTEIN: They have not introduced it in
12 Europe to my knowledge.
13 DR. HOLLINGER: And not into other countries?
14 Does Canada require it?
15 DR. EPSTEIN: I believe Canada followed the U.S.
16 model. I believe that Canada followed the U.S.
17 recommendation, but to my knowledge, no European country is
18 testing for p24.
19 DR. HOLLINGER: Other questions? Yes, Dr. Nelson.
20 DR. NELSON: The data seem to indicate that under
21 most circumstances, the window period is shorter with the
22 PCR testing, but I am still disturbed by the data showing
23 negative PCR with other than non-group B viruses.
24 The Abbott presented those data, and there seems
25 to be some disagreement on that.

1 DR. HOLLINGER: Is there any other way of knowing
2 whether those samples are infectious or not either by
3 culture or other--possibly not by culture, but other ways of
4 knowing that? Gerald.
5 DR. SCHOCHETMAN: Well, certainly the specimens
6 are isolated from HIV-infected individuals, and as we
7 sequence across the genome, we don't see any premature
8 termination signals, so our assumption is that these are
9 probably viruses that would be infectious.
10 DR. HOLLINGER: Say it again, that what?
11 DR. SCHOCHETMAN: These would in essence be
12 infectious viruses. We have no indication that they are not
13 infectious. The evidence would probably be the other way.
14 They are isolated from people who replicating virus, and as
15 we sequence across the genome, we see no premature
16 termination, and we see only open reading frames, so we are
17 assuming that these are infectious agents.
18 DR. HOLLINGER: I am sorry, these are antigen
19 positive, but RNA negative?
20 DR. SCHOCHETMAN: No.
21 DR. HOLLINGER: They are low level.
22 DR. SCHOCHETMAN: They are picked up by the Abbott
23 assay, they are missed by the other assay.
24 DR. HOLLINGER: But low level PCR positive?
25 DR. SCHOCHETMAN: Well, they are not necessarily

1 low level. They are pretty good level. It is just the
2 other assay doesn't have the variant detection capability.
3 The broadness of the detection is more limited.
4 DR. HOLLINGER: Did you present also some
5 information, though, that suggested that some were very low
6 level?
7 DR. SCHOCHETMAN: I also presented some additional
8 data on three samples that were low copy number to start
9 with. What I was suggesting was that if you start diluting
10 those, even at a 1 to 20 dilution with a sensitivity of 100
11 copies per ml, which is what we heard today, is that those
12 would go negative.
13 DR. HOLLINGER: Did you do that?
14 DR. SCHOCHETMAN: I presented the data.
15 DR. HOLLINGER: No, but did you dilute them and
16 then test them?
17 DR. SCHOCHETMAN: Yes.
18 DR. HOLLINGER: And they were negative?
19 DR. SCHOCHETMAN: Yes.
20 DR. HOLLINGER: Thank you.
21 DR. SCHOCHETMAN: I mean they were positive in the
22 assay, but negative if you assume a cutoff of 100 copies per
23 ml.
24 DR. HOLLINGER: I guess my question is did you
25 specifically dilute them.

1 DR. SCHOCHETMAN: We specifically diluted them and
2 did the experiment.
3 DR. HOLLINGER: And retested them and they were
4 negative.
5 DR. SCHOCHETMAN: Yes.
6 DR. HOLLINGER: Thank you.
7 DR. NELSON: Could I ask Dr. Schochetman one
8 additional question? You used the Roche monitor. Was that
9 Version 1 or Version 1.5 that was used, because we have had
10 experience in Thailand that subtype e, the Version 1 doesn't
11 work very well, but 1.5 does.
12 Which assay was used for that determination?
13 DR. SCHOCHETMAN: Specifically, in this case, used
14 the 1.0 because it is the licensed kit here in the United
15 States, and the reason the E is missing is because in the
16 GAG region it is A.
17 DR. HOLLINGER: Do you want to respond to these
18 issues, Mike? Yes, and then Andy.
19 DR. BUSCH: I think we have really got an apples
20 to oranges. The data you saw was LCx, which is the Abbott
21 noncommercially available at this point amplification assay
22 versus the Roche 1.0 monitor assay.
23 We did not see p24 antigen data versus the 1.0
24 monitor assay. I wouldn't doubt that they would have false
25 negatives on the 1.0 monitor test because, as Ken indicated,

1 Looking at it, in the past, in the early days of
2 blood transfusion, medical history was it. We had no basis
3 for selecting donors except through medical history. We
4 shouldn't forget that only in the late sixties, early
5 seventies, that we came, except for syphilis that was
6 introduced in the forties, that we came with the came with
7 the first test that really started addressing the major
8 problems of blood transfusion, that was hepatitis B.
9 There were no screening assays except for blood
10 typing, and the history of infectious diseases focused on
11 hepatitis.
12 In the 1950's, in New York City, in a study that
13 was published by the New York Academy of Medicine, 25
14 percent of the people that received multiple blood
15 transfusions had clinical evidence of hepatitis.
16 [Slide.]
17 This left us with a heritage that I think affects
18 very much our thinking today. It is the extreme desire that
19 we have, and because of that need to rely on medical
20 history, and the success of the change from paid donors to
21 volunteer donors created unrealistic expectations in terms
22 of medical history, and it perpetuated a number of
23 assumptions that are not based on data.
24 Those assumptions obviously are all questions are
25 understood by all donors, all donors are truthful in their

1 that test had serious subtype sensitivity problems which
2 have been fixed with the commercially not yet available, but
3 I believe submitted 1.5 or 2.0 monitor, which is the
4 quantitative assay, and certainly all the data I have seen
5 from both Roche and Gen-Probe looking at a large number of
6 subtype-defined specimens has indicated 100 percent
7 sensitivity of the assays that are in development and being
8 implemented in donor screening.
9 So, these samples that we saw were all Abbott
10 source samples, and I think it is a beautiful panel and
11 would be outstanding to be able to apply that panel to the
12 assays we are talking about, but until that is done, I have
13 never seen a single contemporary antigen positive sample
14 that is missed by either the Gen-Probe or the Roche systems.
15 DR. CONRAD: Andy Conrad from NGI.
16 I just wanted to echo what Dr. Busch said, that
17 that slide was again the Abbott LCx amplification system
18 versus Amplicore 1.0, I think it is not exactly what we have
19 been talking about here. In our clinical experience,
20 looking at thousands and millions of donations, we have
21 never seen a case when the antigen was positive and the PCR
22 was not, and I think that is a much more telling thing.
23 As far as subtype detection, most of the
24 manufacturers who are using nucleic acid-based detection
25 systems now are very, very comfortable detecting, and have

1 tremendous specificity and sensitivity throughout the entire
2 genomic range of subtypes, and I think that would obviously
3 be forwarded in the submissions.
4 DR. HOLLINGER: And both you and Dr. Busch would
5 indicate that the levels are such in those antigen positives
6 that they would be detected with a pool system?
7 DR. CONRAD: Even with the 1 picogram thing that
8 we saw here, it is 10,000 copies, and the NAT, we will show
9 you the sensitivities that nucleic acid systems are getting,
10 that would be easily detected even in larger pools than the
11 ones proposed.
12 DR. HOLLINGER: Thank you.
13 DR. NELSON: Our experience in Thailand in testing
14 people with Version 1, we found a fair number of negatives
15 that went up 3 or 4 logs with the 1.5. So, they had high
16 levels of virus, it was just the wrong primer.
17 DR. HOLLINGER: David, you had a question?
18 DR. STRONCEK: A question for Jay. The topic of
19 this was criteria for discontinuation of the antigen test.
20 I assume when companies do comparison to show the NAT test
21 is equivalent or better than antigen testing, they are going
22 to have to test all samples, they can't exclude some that
23 were positive for HCV or something like that.
24 The other issue is the first NAT test that shows
25 it can detect, you know, in a rigorous study with a licensed

1 test, that shows it can detect everything and additional
2 viruses that p24 can't, will that open up the category for
3 all assays or all NAT testing tests approved have to show
4 that.

5 So, I guess what I am asking for is, if we get to
6 a time where p24 testing is eliminated, does that go in all
7 cases or is it going to be only for one licensed NAT test at
8 a time?

9 DR. EPSTEIN: I don't know the answer. I just
10 think that we have to validate each test system. Now, if we
11 have a validated test system and any such system should be
12 able to detect all p24 positives, but if we have a single,
13 say, first validated system, we will then have a choice.

14 We will have a choice whether to go ahead and
15 label it such that if you screen with that system, you do
16 not need additionally to do p24, or we will have the choice
17 to wait until we think that there are enough such systems to
18 satisfy the entire blood collection industry and then
19 recommend it uniformly, assuming that only validated systems
20 would be used for that purpose.

21 We would probably bring that very question back to
22 the Advisory Committee, because there will be a choice
23 available there. But my own thinking is that probably the
24 decisionmaking would be driven by the individual test
25 systems and their validation. We are not going to deny the

1 use of validated systems as they become available.

2 But again, we don't have to make that decision

3 today. Let's see the data first. We will be back with that

4 question, I am sure.

5 DR. HOLLINGER: Not seeing any other responses

6 from the committee, we will take 20 minutes for a break, and

7 we will start at 3:30, the appointed time.

8 [Recess.]

9 DR. HOLLINGER: This session is on validation of

10 donor history questions. It is an important issue. Any of

11 you who have recently gone to donate blood and found all the

12 questions that are being asked of you, and sometimes how

13 they are different from different centers, I think this is

14 an important topic.

15 We are going to start out. Captain Mary Gustafson

16 is going to introduce the topic, and then we will move

17 forward with the other presenters. We have two

18 presentations and one person who has asked to speak in the

19 open public hearing.

20 **III. VALIDATION OF DONOR HISTORY QUESTIONS**

21 **Introduction**

22 CPT GUSTAFSON: Thank you. Actually since we were

23 running so far behind, I apologize to the committee because

24 I am not going to go in the order of the slides that I gave

25 you, but I am going to abbreviate my presentation, so that

1 we can spend the time listening to our invited guests and
2 the interested public, as well as leaving time for some
3 committee discussion.
4 I will skip the background that is in your
5 presentation on exactly what donor history questioning is
6 and where it fits within the overlapping layers of safety
7 that protect the blood supply.
8 But to cut to the chase, why are we bringing this
9 topic before you today? There is a couple of reasons. You
10 were provided a copy of the American Association of Blood
11 Bank's Uniform Donor History Questionnaire in your mailing.
12 This form is approved by us as suitable for use by
13 blood establishments, but we do not mandate its use or any
14 other standardized form, and as Dr. Hollinger said, there
15 are variations. We have standards, we have regulations, we
16 have recommendations that people need to abide by in making
17 up their donor history questionnaire, but we do allow a
18 great deal of variability.
19 Another reason for bringing this topic to you is
20 that a fairly recent oversight report faulted us, the
21 agency, for not requiring the Uniform Donor History
22 Questionnaire.
23 This was one of the deficiencies noted by the
24 General Accounting Office in its February 1997 Report to the
25 Ranking Minority Member of the Committee on Commerce in the

1 House of Representatives, entitled "Blood Supply, FDA
2 Oversight and Remaining Issues of Safety."
3 Although this observation was not included in the
4 list of the GAO recommendations to the Secretary of the
5 Health and Human Services, it is an issue that has been
6 discussed before and merits further discussion.
7 The other reason for presenting this topic is that
8 we know that not all information obtained from donors at the
9 time of donation is accurate. The 1997 JAMA article that
10 was in your mailing discusses data from the REDS survey,
11 which will likely be discussed more by Dr. Williams in his
12 presentation, but it showed that nearly 2 percent of donors
13 provided inaccurate information at donation.
14 [Slide.]
15 We in the FDA also know from our own error and
16 accident reporting system that donors fail to give accurate
17 information at donation, but may make information available
18 at a later date. These reports are called Post-Donation
19 Reports.
20 In 1998, 61 percent of all error and accident
21 reports received in the Center for Biologics were Post-
22 Donation Reports. Slightly less than 80 percent of these
23 involved information picked up at subsequent donation that
24 was not revealed in an earlier donation.
25 About 15 percent are donor callbacks and the rest

1 are third-party reports. Again, nearly 80 percent, it's
2 78.4 percent of the reports are concerning information that
3 was known to the donor or should have been known to the
4 donor at the time of the earlier donation, and include such
5 things as having had a tattoo or ear or body piercing within
6 a year of donation.
7 These are types of data that indicate that there
8 is room for improvement in the donor screening process. One
9 of the problems is that we often find that these types of
10 reports are not fully investigated. There is always oops
11 factor or, if I could embarrass Andy Conrad if he is still
12 around, there is the idea that the donors lie, and it is
13 just one of those things that we really can't do much about.
14 So, the follow up is usually incomplete whereby
15 they could look at their processes, is it particular
16 questions that donors are missing or is it particular
17 screeners, is it the day of the week, certain donor
18 demographics, fixed site versus mobile sites, maybe an issue
19 of privacy, or even other issues within the donor behavior
20 that we, as regulators, and also I think in blood bank, you
21 know, are just not comfortable with.
22 Let's face it, we are far more interested in
23 discussing the types of things that we discussed earlier
24 today, where there is real, real scientific data rather than
25 donor behavior, and we are really excited that we got Dr.

1 Jane Piliavin back today to sit with the BPAC, because she
2 is a behavioral scientist and can help much in the
3 discussion of these areas.
4 [Slide.]
5 As background, I am going to briefly discuss donor
6 studies that were sponsored by FDA in the past. In the late
7 1980s and early 1990s, FDA sponsored two donor studies with
8 the purposes of intercepting the at-risk donors and
9 increasing and improving donor screening effectiveness.
10 Both of these studies were performed under
11 contract by the American Institute for Research.
12 [Slide.]
13 The first study was entitled "Intercepting
14 Potential Donors as Risk for AIDS or Other Infections,"
15 which was completed in 1990. The purpose of this study was
16 to get at-risk donors to not donate or prevent their
17 donations from being used by using the confidential unit
18 exclusion and to study methods to communicate more
19 effectively with donors.
20 [Slide.]
21 The study involved testing five types of screening
22 material to improve the effectiveness of screening donors
23 for risk behaviors at different points in the process.
24 These materials included AIDS information
25 brochures designed specifically for men or women, utilizing

1 line drawings of risk behaviors and simple tests, and AIDS
2 information video incorporating motivational material in the
3 form of testimonials from persons who have correctly decided
4 not to donate, behavior questions asked orally and answered
5 with paper and pencil about a donor's participation in
6 specific risk behaviors, comprehension questions asked and
7 answered orally that ask donors if they understand that they
8 should not donate blood if they have engaged in specific
9 risk behaviors, and a revised Confidential Unit Exclusion
10 form containing pictures to emphasize the ramifications of
11 the choice the donor makes.

12 [Slide.]

13 In the study, the interventions were compared to
14 one another and to existing materials in terms of the
15 numbers of at-risk persons who did or did not donate for
16 transfusion, the amount of attention paid to materials, the
17 scores on a comprehension test, and the self-reports by the
18 subjects of attitudes toward the various behaviors.

19 To summarize, investigators found that people
20 responded well to the pictures, and they were able to score
21 higher on the comprehension test after exposure to the
22 brochures.

23 [Slide.]

24 However, increased comprehension related to the
25 materials did not affect their behavior in terms of making

1 the correct decision to donate or not.

2 Likewise, it was demonstrated that even if people
3 stated orally that they understood that they should not
4 donate if they engaged in risk behaviors, this did not
5 affect whether or not they decided to give blood.

6 The only intervention that seemed to make a
7 difference in screening out at-risk donors was the very
8 direct behavior questions.

9 Another observation from the study is that people
10 don't read information provided, and even when the donor
11 claims to have read the material, observation of the donor
12 during the process did not support the donor's self-
13 reporting of having read the material.

14 The results of this study were the basis for FDA's
15 December 5th, 1990 recommendation to blood establishments
16 that donor screening include the list of direct questions to
17 be asked of the donor orally if possible.

18 These recommendations were later combined in a
19 comprehensive April 23rd, 1992 revised recommendations for
20 the prevention of human immunodeficiency virus transmission
21 by blood and blood product. This was the first time that
22 FDA had provided the exact wording for questions to be asked
23 during the interview process, and the first time that
24 questions were actually field-tested prior to general use
25 for comprehension and effect on donor deferral.

1 [Slide.]

2 In the early 1990s, the American Institute for
3 Research performed another study under contract with FDA,
4 this study, optimistically entitled "Increasing the Safety
5 of the Blood Supply by Screening Donors More Effectively."

6 The study was completed in 1993, and was the
7 subject of BPAC discussions in 1993 and 1994. The goal of
8 the study was to improve donor screening by developing new
9 processes that would hopefully increase the validity of the
10 donor interview process, provide for the different needs of
11 the first-time donor versus the repeat donor as one
12 complaint from donors since adding length to the donor
13 questionnaire with the addition of the direct, high-risk
14 questions has been the amount of time required to donate
15 blood, an increased knowledge of both the donor and the
16 health historian via educational materials and training.

17 [Slide.]

18 The material studied during the contract included
19 a computer-assisted donor interview, an abbreviated donor
20 history for repeat donors, prototype donor information cards
21 for per- and post-donations, and a curriculum for health
22 history training.

23 The study was conducted at blood centers and a
24 plasma center, and included over 7,000 donors. At the end
25 of the study, the results did not support the title of the

1 study, that is, there was no demonstration that use of any
2 of the materials could increase the safety of the blood
3 supply by screening methods.
4 [Slide.]
5 However, the study did demonstrate the feasibility
6 of using a computer-assisted donor interview and provided
7 materials that could be used by blood centers in developing
8 their own procedures for a computer-assisted donor
9 interview, abbreviated donor history for repeat donors,
10 donor educational materials, and a curriculum for training
11 health history technicians.
12 In retrospect, neither study fully met FDA's
13 expectations. Particularly with the second study, there
14 were problems in study design, randomization, definition of
15 endpoints and statistical methods. However, the greatest
16 obstacle in performing donor studies is that the risk of
17 infectivity in the blood donor population is extremely low.
18 I am sure one would like to see a study that links
19 the effectiveness of donor screening to recipient outcome,
20 that is, infections in recipients or even a less dragged out
21 deferral of donors who have positive markers, however, the
22 blood donor population currently is a very healthy, low-risk
23 population.
24 You can tell from the numbers of samples tested
25 this morning in the NAT testing, we were talking about

1 hundreds of thousands to a million donors to get that type
2 of data, and behavioral data is even more difficult to come
3 by.
4 Therefore, to design a study to test the effect of
5 any screening method based on outcome measures requires a
6 prohibitively large number of donors. But like I said
7 before, we know that there is room for improvement
8 nevertheless. We know from REDS data that nearly 2 percent
9 of donors interviewed provided incorrect information at the
10 time of donation, and we know from our own error and
11 accident reporting that information obtained during the
12 donor interview is not always complete and accurate.
13 Even so, as Dr. Hollinger pointed out earlier
14 also, we keep adding to the donor interview process without
15 removing anything. Since the early 1990s when the amount of
16 information presented to the donor and the length of the
17 donation process were concerned, we have added additional
18 questions to the form.
19 Among the questions added are questions about
20 recent incarceration, questions about risk of CJD, and
21 geographical questions to tease out risk of HIV-1 group O
22 infection.
23 Today's topic--it is late in the day--and this is
24 an introductory discussion for the committee. We are not
25 going to ask the committee to provide a formal

1 recommendation or vote on anything today. However, as you
2 listen to Dr. Williams' and Dr. Bianco's presentations, and
3 as you prepare for committee discussion, I will show you a
4 few questions that you might keep in mind.

5 [Slide.]

6 The first I mention with great trepidation.
7 Should FDA support a study or studies to validate the donor
8 history questions? Of course, the short answer would be
9 yes. This is akin to asking you if you support motherhood,
10 apple pie, and white picket fences, and eternal youth.

11 However, as I mentioned earlier, blood donors are
12 currently a very healthy population. With the redundant
13 layers of safety provided by blood centers today, the
14 expectation that we can perform a study that truly links
15 donor screening effectiveness with outcome measures in the
16 recipient is probably not realistic.

17 So, with this in mind, given that efficacy studies
18 based on final outcome, which would be infection in
19 recipients, are impractical, what suggestions do the
20 committee members have for appropriate areas of study?

21 Would the committee view a stratification of
22 questions based on risk outcomes a useful exercise? Are
23 there ways to tease out questions that may no longer be
24 useful, on one hand, and questions that are so critical that
25 we need to study these questions linked to outcome in

1 recipients?

2 Finally, does the committee view a mandated

3 national donor questionnaire desirable? I will share with

4 you that in looking at the transcript from the BPAC in March

5 of 1994, when the second AIR study was discussed, and there

6 were materials for computer-assisted donor interview and

7 pre- and post-donation information, one of the fears of both

8 the committee members and of industry in public session was

9 that FDA would actually mandate the use of these materials,

10 and they felt that this would inhibit innovation in the

11 field.

12 So, it will be interesting to see if things have

13 changed in the past five years.

14 With that, I will turn this over to our invited

15 speakers. Thank you.

16 DR. HOLLINGER: Thank you.

17 The first presentation will be by Alan Williams

18 representing the American Association of Blood Banks.

19 **American Association of Blood Banks**

20 DR. WILLIAMS: Thank you, Blaine.

21 [Slide.]

22 As Mary outlined, the topic is a challenging one.

23 Validation of a process is going to have many elements, and

24 this is a particularly difficult one to look at. Lack of

25 outcome measures is only one of the difficulties.

1 I hope as I go through the talk, I will be able to
2 point out some other inherent problems of definition of the
3 process which I think need to be resolved before one can
4 really talk about validation, if that in fact is possible.
5 What I want to do is pitch my talk from a
6 behavioral and research standpoint, and I think you will see
7 some parallels between my presentation and Dr. Bianco's.
8 His is going to cover more the blood center perspective.
9 [Slide.]
10 As we move increasingly toward considering blood
11 collection as a manufacturing process, I think it is worth
12 reminding ourselves that blood donors aren't raw materials.
13 They are thinking, feeling, motivated individuals who don't
14 always do what we anticipate they might do, and there are
15 many aspects of our discipline which very much could be
16 considered as having a large behavioral science component.
17 These include donor recruitment and retention,
18 certainly a major issue for blood banking, pre-donation
19 education, donor qualification, which we are talking about
20 today, confidential unit exclusion, test result
21 notification, also a major issue, the whole issue of
22 informed consent, and this has to do with donation,
23 transfusion to recipients, and the research process, and
24 again another major issue, risk education, public, patients,
25 media, elected officials, and one could give examples from

1 the HIV and HCV experiences, but I won't take time to go
2 into that.
3 The reason I am going into this is the major take-
4 home points that I want to leave is that with all this
5 behavioral science interaction, there really are very few
6 behavioral scientists involved in the blood banking
7 discipline.
8 There have been consultants along the way,
9 individuals who have had blood banking association, but no
10 one working full time in our field, and I think that is
11 probably resulting in some of the difficulties that we have
12 right now.
13 [Slide.]
14 So, to move into donor qualification, why is
15 accurate donor qualification important? Some of these are
16 certainly very self-evident. To maximize blood safety is
17 the big one, both for known agents which have a laboratory
18 screen, it serves as another layer of protection, as you all
19 know.
20 Probably looking toward the future, one of the
21 major reasons to optimize our screening process by donor
22 questioning is to face unknown threats in the future which
23 have no laboratory screen.
24 CJD took us a few years ago by surprise as being
25 an unconventional agent, and hopefully, there may be a test

1 in the next few years.

2 From an operational perspective, certainly you
3 want to minimize donor loss due to inappropriate deferrals.
4 You want to minimize negative operational impact. Mary
5 showed some of the statistics for contribution of the
6 questionnaire process to post-donation information and
7 market withdrawals and recalls, an important issue for
8 center operations.

9 One that often gets passed over is to minimize
10 staff exposure to infectious donations. Although you can
11 certainly test out donations, you don't necessarily want
12 hepatitis infectious and HIV infectious materials collected
13 in the first place and handled by staff members.

14 [Slide.]

15 There have been a lot of discussions about some of
16 these areas. I put some of the major ones down because I am
17 going to base some of my comments on some of the proceedings
18 that have taken place.

19 There has been a major study of HIV seropositive
20 donors sponsored by the CDC. That started in 1988 and still
21 is occurring, and has produced a lot of epidemiologic data
22 about HIV seropositive blood donors.

23 As you know, REDS has conducted donor survey
24 research since 1990, getting at risk factors and other
25 characteristics of the blood supply donors.

1 National Heart, Lung, and Blood Institute has
2 sponsored two major activities. There was a behavioral
3 workshop in November of '97, which got together behavioral
4 scientists and blood banking experts and regulators, and we
5 all discussed some of these issues, and some of the points I
6 am going to bring up today came out of that workshop.
7 FDA has held several BPAC sessions, as well as a
8 donor suitability workshop at the end of last year,
9 discussing some of the issues.
10 AABB, as the national blood banking organization,
11 has ongoing review of the donor screening activities through
12 its scientific and administrative coordinating committees,
13 its Standards and TTD and other committees, and its
14 professional staff and board.
15 In addition, they recently added a national blood
16 data resource center, which collects information from blood
17 centers, which is relevant to this subject and could be an
18 important data collection element in the future as we go
19 into some of these activities.
20 [Slide.]
21 What are some of the successes of behavioral
22 screening? I think it is fair to say donor screening has
23 contributed to unprecedented safety in the blood supply in
24 combination with other factors.
25 It has contributed to documented reduction over

1 time of markers in accepted first-time blood donors, and I
2 think in some data that will be presented by Dr. Bianco, you
3 can see that the prevalence of donor risk and infection is
4 much lower than the general population, and this is
5 documented.

6 [Slide.]

7 What are some of the deficiencies? Interviews
8 with seropositive donors reveal behavioral risks that should
9 have prevented donation. There have been a lot of case
10 control studies done on seropositive donors. They are
11 relatively easy to conduct and through the years a lot have
12 been done.

13 Two that I will mention specifically are both the
14 NIH and the REDS study of HCV-infected donors. Both came to
15 the same major conclusion that injecting drug use, a major,
16 if not the major risk factor of HCV infection.

17 [Slide.]

18 Also, the CDC HIV positive donor interview study
19 has produced data similarly showing that individuals who are
20 interviewed and found to have risk factors should not have
21 been accepted as blood donors, and something happened during
22 that process where the appropriate information didn't come
23 to light and result in that donor's either self-deferral or
24 staff-based deferral.

25 These are risk factors from recent data from the

1 CDC interview study. Males found to be HIV seropositive, 38
2 percent on subsequent interview reported having a sexual
3 contact with other male risk. This is down proportionately
4 from approximately 60 to 65 percent when these studies were
5 first taking place in the late '80s.
6 These individuals should not have been accepted as
7 blood donors, that is a clear deferral criteria.
8 A small proportion, similar to HCV-infected
9 donors, report injecting drug use. Again, these individuals
10 should not have been accepted as blood donors, the point
11 being that there is some leakage of individuals at risk
12 through the screening process, and that gives us a target to
13 address.
14 [Slide.]
15 Another interesting bit of information about HIV
16 seropositive donors, and I give credit to Ken Clark who put
17 these data and these slides together. Although the overall
18 number of positives enrolled in the study, 1990 versus 1997,
19 is much lower, 129 in 1990 and 29 in 1997, those who report
20 male contact with other males in the previous year is
21 higher, 90 percent of those with the risk factor had recent
22 activity, and I think that is an important consideration.
23 [Slide.]
24 From the REDS study, we have been conducting
25 surveys. The first major study was in 1993, ran a smaller

1 pilot in 1995, and again a major survey last year. The data
2 from the '98 survey have not yet been extensively analyzed,
3 but we have some preliminary analysis, and I will show them
4 in a comparative basis with the 1993 study.
5 [Slide.]
6 In 1998, we studied 104,000 sampled donors at
7 eight different sites, seven monthly waves, April through
8 October, and one of the main reasons we ran the study was to
9 update the 1993 survey data, which was the JAMA publication,
10 and see how the deferrable risk variable identified in that
11 survey held in 1998 time period compared to other donation
12 variables get at some aspects why donors didn't reveal risk
13 and importantly, we wanted to, in a major way, look at
14 donation incentives and see if we could bring some answers
15 to the question as to whether incentives do or do not
16 increase risk in a blood donor population, and also got
17 additional information on HIV test-seeking.
18 [Slide.]
19 Prevalence of reported behavioral risks, the
20 overall cumulative prevalence of risk that should have
21 resulted in deferral, as Mary mentioned, was 1.9 percent in
22 1993. It is about the same value, actually closer to 2
23 percent in 1998, but because there are a few additional
24 centers and we have a few more questions involved, I think
25 it is going to take further analysis to see if there is any

1 change over time, so we can address that.

2 You can see here in 1993 data, the final data,

3 half percent of individuals accepted as donors in responding

4 to the survey admitted drug use ever in their lifetime, and

5 that is a deferral criteria.

6 A little lower in the preliminary data for 1998,

7 but I think we need to look at the final data and complete

8 that analysis.

9 The bottom line here is some of the risk factors

10 observed in '93 are still there in the 1998 data. I think

11 as we look at the data over time, we will be able to

12 determine if there are any trends present.

13 One that we are watching in particular is the

14 apparent possible higher trend in donors who have sexual

15 contact with other males.

16 [Slide.]

17 Donors report insufficient privacy at screening.

18 Privacy is one thing that can potentially compromise the

19 donor history. All donors in the '98 survey, 4 percent

20 reported that they had some concerns about the privacy at

21 the time of the screening at the blood center.

22 These vary according to donors who report

23 different risk factors, and the highest are those who had

24 sexual contact either with another male since '77 or sex

25 with CSWs, commercial sex worker or a prostitute, 12.8

1 percent reported that they had concerns about privacy.

2 So, you see some association is going on there

3 between risk and some of the operational processes that we

4 have.

5 [Slide.]

6 Similar data in terms of donors who reported that

7 they donated either ever or in the past year to receive the

8 results of an HIV test. The data for 1993, we had I believe

9 6.2 percent who reported ever donating blood to receive an

10 HIV test, and 3.5 percent in the past year.

11 This number appears to be reduced somewhat in

12 1998. We will have to see if that holds as the data are

13 finalized. One thing to keep in mind is that some of the

14 home HIV tests became available, so this potentially could

15 have contributed to a drop in this figure.

16 But again you see variation, again some of the

17 risk factors that were also reported in the survey, and you

18 can see again the same three groups here that reported

19 sexual contact and might have been worried about something

20 at the time of donation report significantly higher rates of

21 HIV test-seeking.

22 [Slide.]

23 What are some of the deficiencies as well from the

24 donor perspective? I think it is pretty clear that donors

25 tend to make their own judgments about their personal risk.

1 Some of it might be an inherent tendency, denial that you
2 don't really mean me, and I feel fine, and this person
3 really couldn't have had any problems that I was with. So,
4 it might be an inherent tendency to make your own judgment.
5 In addition, I think another thing of potentially
6 a factor is that the scientific basis of screening questions
7 either may not be understood by the individual being
8 screened or they might tend to make their own judgments
9 about risk if they feel that the scientific basis of
10 screening is not accurate because it is politically
11 motivated or discriminatory in some way.
12 I think in some elements of the donor population,
13 this might be coming into play that individuals feel that
14 there is no scientific basis for certain questions and they
15 don't take them seriously. We don't have direct data for
16 that, but I think some of the indirect data points in that
17 direction.
18 [Slide.]
19 What are some of the other elements from the donor
20 side? Donors seek to gain or preserve something of value by
21 proceeding with donation. Here, we get into the test-
22 seeking issue, blood centers are a free, confidential,
23 reliable source of HIV testing.
24 Certainly, donors get a healthy feeling and an
25 altruistic feeling from the donation itself. It is

1 something that we use to encourage donation, and certainly
2 there is some motivation attached to it for all donors, even
3 those who have risk.

4 There is an element of saving face in a peer
5 environment, particularly in a work site type collection
6 where your supervisor is rounding up donors. That factor is
7 also well known.

8 I put other possibilities here because there are
9 some areas that are charged with controversy and emotion,
10 but very little data. Here, I would classify elements like
11 incentives, donation for therapeutic phlebotomy, directed
12 donation, some of those areas where what is the donor
13 perspective, what is the value of the donation, and does it
14 supersede their perspective of making risk known at the time
15 of donor screening.

16 These are areas that need further data collection.
17 As I mentioned, the REDS study is really concentrated on
18 incentive use and for the HHS Safety and Availability
19 meeting in April, we are trying to put together a major
20 analysis of the 1998 to address the issue.

21 [Slide.]

22 From a donor perspective, our questionnaires are
23 complex and lengthy. There are undoubtedly some educational
24 barriers for some of the wording that is used. There are
25 cultural differences. As Donna Mayo mentioned in her

1 publication to the AIR study, people don't read, they don't
2 like to read, and for repeat donors there is a certain
3 redundancy when they come to the blood center multiple times
4 and have to go through this long questionnaire and oral
5 history each time.

6 [Slide.]

7 Also, screening deficiencies here looking from the
8 blood center's perspective. To measure the parameters of
9 performance of anything, you have to compare it to a gold
10 standard whether you are looking at predictive accuracy,
11 sensitivity, specificity, you need a gold standard for
12 comparison, and I think some of the gold standards for some
13 of the screening questions are a little ambiguous.

14 Are we looking for the true existence of a defined
15 risk factor or are we looking for the ability to transmit a
16 seronegative infection to a recipient? The first one is
17 reasonably easy to validate, the second one is almost
18 impossible to validate, but what is the gold standard that
19 we are looking at?

20 Just as an example, I used history of syphilis as
21 one indication, and I think you can recognize the
22 possibilities for different interpretations, why that
23 question might be asked.

24 In a sense, we are relying on surrogate value of
25 questions. Just the surrogate value of testing got a bad

1 name with respect to non-A, non-B hepatitis. I think we are
2 doing a little bit of that in terms of questioning of
3 donors. It complicates scientific credibility and also may
4 be viewed as political or discriminatory.
5 One example of this might be the consideration of
6 deferring males who have had sexual contact with other males
7 since 1977. I am not aware of any window period for HIV
8 infection that exceeds or even comes close to one year. Why
9 the deferral should go back to '77, there has been a lot of
10 discussion about it, but it is not based on the window
11 period of HIV, because scientific data argues against that.
12 [Slide.]
13 From a behavioral perspective, I just wanted to
14 mention that this is a major problem in the field of AIDS-
15 related research. Getting information about personal risk
16 is inherently difficult. Response rates tend to be low.
17 Missing data happens frequently. Even if you get someone to
18 complete a questionnaire, often there is about 20 percent
19 missing data, and internal inconsistencies are frequent.
20 [Slide.]
21 I wanted to say something about the AIR study, but
22 Mary covered it quite well. I think particularly the first
23 AIR contract, there is some valuable information there, and
24 as I say later, I hope some of that, that was not published,
25 can be made available, because I think that first contract

1 was pretty well done. There was a lot of meat in the data
2 that emerged from that.
3 Out of the NHLBI discussion, there were some
4 discussions of current research going on. Charles Turner
5 was at that meeting and described the use of what is known
6 as Audio-CASI. CASI stands for computer-assisted self-
7 interview. This is increasingly being used for risk
8 behavior data collection in HIV-related studies that has the
9 advantage of being fully private, does not require literacy.
10 It can be standardized, so there is no interviewer
11 variability. It can be done in any language. It can have
12 visual aids, and the respondent, in essence, is in control
13 rather than having an interviewer who is controlling the
14 situation.
15 This work was published just about a year ago in
16 Science. Those of you who are interested, I think it is
17 really good to see the detailed write-up of how that works
18 somewhat better in collecting risk-related information.
19 [Slide.]
20 Also at the meeting was Dr. Catalina from UCSF,
21 the Center for AIDS Prevention Studies, who went into some
22 of the more behavioral aspects of designing questions and
23 proposed that pre-identifying some of the threats that a
24 question might have to an interviewee and trying to preempt
25 those in way you introduce the question can have a big

1 impact in terms of relaxing the individual and getting them
2 to give you an answer or the correct answer.
3 He also brought forward the idea of using enhanced
4 questions which give a little background before asking the
5 basic question that you want to have answered, and showed
6 some data, I am not sure if it is published yet, that in an
7 HIV risk situation, not with blood donors, but with other
8 subjects, that they get more reliable and better information
9 completion by doing this.
10 One of the areas that we can validate key
11 questions is through the structure, content, and
12 comprehension of current blood donor screening questions.
13 [Slide.]
14 Again, getting back to the recall and market
15 withdrawal importance of questions, within Red Cross there
16 has been an effort in our department to do some of this with
17 a key set of questions. This has been spearheaded by Sharyn
18 Orton, who is in the audience here. Victoria Virvos is a
19 facilitator for the focus groups that we used.
20 [Slide.]
21 The idea was to use focus group discussions with
22 individuals in this case who have never donated blood to
23 evaluate the structure, content and comprehension of seven
24 selected questions. These weren't AIDS risk related
25 questions, but they were seven questions which made the

1 major contribution to Red Cross recalls and market
2 withdrawals, and had PDI information concerns.
3 [Slide.]
4 What are the goals? The introduction to this
5 session was participants were asked what is the question
6 asking, are all of the terms and the way the question is
7 written clear, if not, would they ask for more information,
8 if more information needs to be given, where and how should
9 it be provided, and what interviewer techniques would make
10 them most comfortable with the interview process.
11 [Slide.]
12 There are five focus groups that have been held so
13 far, various demographic groups. This was done both using a
14 facilitator who was good at getting people to speak up and
15 address the questions at hand, as well as the Red Cross
16 volunteer who kind of explained the background of the
17 process and provided scientific input.
18 The participants were familiarized with the
19 donation environment and the materials. The questions they
20 were to answer were available on a flip chart, and
21 background and facilitation was provided, as I mentioned.
22 [Slide.]
23 The results, interestingly, recommendations were
24 really pretty consistent between the groups, and we got
25 useful comments and recommendations, and I think on a path

1 toward restructuring some of these questions which hopefully
2 can then be validated again prior to making a permanent
3 change, but I think the main conclusion here is these types
4 of focus groups are doable. They are relatively
5 inexpensive, and I think it is worth considering doing some
6 of this work before implementing new questions.
7 [Slide.]
8 So, some general recommendations that I will end
9 with, the first one is consider establishing programs to
10 attract more behavioral science professionals into the
11 transfusion medicine arena. It is important.
12 Second, establish mechanisms to evaluate the
13 understanding and impact of new questions prior to
14 implementation. It is difficult to do if you are not
15 prepared. One way to prepare would be to have a set of
16 rapid response blood centers where you could get this done,
17 because they have training and some funding to be a rapid
18 response network.
19 REDS has served this role in the lab side, and not
20 necessarily the same centers, but I think a small network of
21 centers could easily do some of the questionnaire work.
22 [Slide.]
23 One comment made to me earlier today was what
24 should we do with the screening process. We should
25 basically take the whole thing apart and put it back

1 together again.

2 That is not exactly what I wrote here, but it's a
3 thought. I think perhaps as we move toward NAT testing, it
4 is an opportunity to look hard at the questions that we are
5 asking, consider streamlining, and asking what we really
6 want to ask in a way that we really need to do it.

7 [Slide.]

8 I think there might be some consideration of
9 asking IOM of another independent sponsorship of a consensus
10 conference for two major issues: establish an agreed
11 rationale for current and future questions including cost
12 considerations, which FDA by law doesn't consider.

13 The second thing is we need mechanisms through
14 which new screening procedures can be evaluated within a
15 regulated blood collection operation, a very difficult
16 issue, and Mary went into that in some detail.

17 [Slide.]

18 Fourth, investigate the feasibility of a
19 standardized, validated national screening questionnaire. I
20 think there are issues where some local options are
21 appropriate, but I think there should be an approval
22 process, so that a handful of regions which decide to ask a
23 question that they feel might be important doesn't snowball
24 the country into asking this at all blood centers. I think
25 that is an unfortunate circumstance if that happens.

1 Fifth, fund research to define specificity and
2 predictive accuracy of key screening questions, a very
3 difficult challenge, but I think it is doable.
4 [Slide.]
5 Finally back to the AIR study, there was a
6 publication in Transfusion in '91, about the major results
7 from the first AIR contract. There is also some additional
8 information like interviewer training materials and some
9 details about their short-track screening for regular
10 donors.
11 I would hope that if it is not currently
12 available, public or the field, that FDA would consider
13 making this available in some form, because I think there is
14 some really good information there.
15 I will stop here. Thank you.
16 DR. HOLLINGER: Thank you.
17 The final presentation, Dr. Bianco, from the New
18 York Blood Center.
19 **New York Blood Center**
20 DR. BIANCO: I think that Alan Williams gave a
21 very nice presentation of several high-level issues related
22 to validation or to donor history questions. What I am
23 going to try to do is to take a somewhat more practical view
24 of medical history.
25 [Slide.]

1 answers, and the more questions we ask, the better.

2 [Slide.]

3 Medical history today is one of several layers of
4 safety, and is a major focus. It has its major focus, one,
5 as Dr. Williams presented very well in diseases for which
6 there are no screening assays; two, in known limitations of
7 the screening assays, windows, HIV-O, CJD.

8 Together with all the pre-donation procedures it
9 improves blood safety, but there are ways by which we can
10 measure the efficacy.

11 [Slide.]

12 If we compare the population prevalence before and
13 after medical history, at least from data that are published
14 from the Public Health system, and from data that we have
15 from our own organizations, there is a substantial
16 contribution to education and medical history, and the
17 knowledge, and all the things that are done to the safety of
18 the donors when we look at this prevalence.

19 We do not have specific studies that will really
20 compare what the prevalence is in the population of donors
21 that show at our door, and we will talk a little bit more
22 about that.

23 [Slide.]

24 We defer donors based on medical history, and we
25 defer donors on questions and activities that have very

1 different meaning for the different donors. It may be
2 questions that require interpretation. It may be questions
3 about risk behavior in which the donor is very uncomfortable
4 with the questions, but one thing that I am very sure is
5 that the interviewer, the historian is as uncomfortable as
6 the donor or more uncomfortable as the donor asking those
7 questions.
8 I see when I go to donate blood the discomfort of
9 the technician that is collecting the blood and asking
10 myself, the boss, these types of questions.
11 [Slide.]
12 Now, donors, despite all that, reveal risk
13 behavior in medical history. If we take a summary of some
14 of our medical history, donors will tell us that they had
15 sex with another man, that they had taken drugs, and the
16 ratios are on the right side of the column that I call
17 Prevalence, so about 1 in 1,100 donors or 1,200 donors told
18 us that they have used drugs in the past, and 1 in the CSW,
19 people that have given money for sex, 1 in 35,000 donors.
20 [Slide.]
21 I put in the charts that you have one set of
22 deferral reasons and numbers. I used this in a presentation
23 that I made at the Donor Suitability Workshop, and I was
24 very concerned with this 23 percent of all deferrals, of all
25 donors that presented being deferred.

1 I did a lot of work in our computers, and that
2 other table was not really real, because included all the
3 test deferrals and all the other reasons for which people in
4 the past would have been in our computer as deferred donors.
5 So, a more accurate figure taken for the year of
6 1998 is that among the study group, among 480,000 donors,
7 62,000 were deferred, about 13 percent of them; 25,000 by
8 something very objective like hemoglobin or blood pressure,
9 but 15,000 by the general questions regarding medication,
10 15,000 about questions on infectious diseases.
11 [Slide.]
12 Other things that donors used to do, but they
13 changed their behavior, was the Confidential Unit Exclusion.
14 Here, we are telling a donor the risk may affect the person
15 that is receiving a unit of blood from you, and if you did
16 any of those things that are listed here, if you did not say
17 that you do it, but you have done it, use this label, and we
18 will not transfuse your blood.
19 But the effectiveness of the process has
20 diminished substantially. Today, very rarely in the last
21 four or five years, we will find an individual that used the
22 self-exclusion and that is positive on an HIV test.
23 [Slide.]
24 It is true that the total numbers got diminished
25 substantially, but this is due probably, and that is a

1 graphic form of the same thing, this is due probably to the
2 changes of characteristics of the donors as revealed in the
3 HIV positive donor studies in which in the early days were
4 mostly males who had sex with males, sophisticated,
5 understanding the crisis of HIV and AIDS, and today, many,
6 about half of them, women, and that really do not
7 understand, about half of them cannot identify clearly what
8 is the risk that led them to become positive for HIV.
9 [Slide.]
10 So, CUE was effective in the eighties. Today,
11 only a small proportion of donors use it, very few are
12 positive, and probably is associated with the changes in the
13 donor population.
14 [Slide.]
15 But even like that, about 0.4 percent of our
16 donors still select CUE, and many of them for the wrong
17 reasons, and who will note it is for the wrong reasons when
18 they do it in the process of giving a directed donation for
19 their child or for a relative, and they will use that label,
20 and then later they will scream why can't you release that
21 unit of blood, it was for my child, and that they did not
22 understand the process.
23 [Slide.]
24 However, there were things that came from the AIR
25 study that were very important, and these encouraged at that

1 time with the memo on April 23, '92, encouraged us to
2 introduce direct questions about behavior to our donors.
3 We were very scared. We have volunteers here. We
4 were afraid that we were going to violate their privacies,
5 we were offending them, but until the process happened, and
6 a substantial number, as we compared between '90 and '91,
7 when we did not ask those questions, and when we started
8 asking direct questions to the donors, that HIV risk
9 questions increased substantially, while other types of
10 deferrals did not increase.
11 [Slide.]
12 More recently, we had a similar experience in
13 small numbers to affect the total donations with a donor
14 base of about 400 in 1,000 donations, but we saw a 12-fold
15 increase in the number of people that were deferred the
16 moment that we asked, not only injection drugs, but snorting
17 cocaine.
18 [Slide.]
19 So, donors reveal risk behavior. Donors who are
20 deferred, but we should say that donors who are referred up
21 front do not donate. We do not have a sample, we do not
22 test those donors.
23 Consequently, we do not know what is the
24 specificity, the sensitivity, the positive predictive value
25 of those questions. We do not know if anybody that we

1 deferred because of a history of hepatitis has actually had
2 hepatitis ever. Certainly, I would like to encourage,
3 together with Dr. Williams, that these studies should be
4 carried out.
5 They are very, very important because of the
6 number of people that are affected, because of the
7 consequences of donor deferral both for the system, for the
8 recipient, we do not have the unit of blood available, and
9 for the donor who is extremely upset. He tried or she tried
10 to do something good, and they were told that because of
11 something like a history of hepatitis or something else,
12 they cannot do something good.
13 [Slide.]
14 What else do we know? That many donors, yes,
15 review risk, but donors who review risk behavior do not
16 present risk to the system. They are deferred, so they are
17 not going to donate.
18 The people that do not change as we add questions,
19 as we change deferral periods, are people who denied risk
20 behaviors even when they have risk behavior. We have to
21 realize that whatever changes we make only affect people
22 that are truthful in their answers, and we know that 1.9
23 percent of the donors from the studies that Dr. Williams
24 mentioned will for some reason, and I don't think that it is
25 a question of lying, but for some reason not be able to come

1 up with the right answer at the right time.

2 [Slide.]

3 However, we continue to add complexity to the

4 system. There are too many questions involving too many

5 events in the life of the donor.

6 The complexity of the questions interferes with

7 the accuracy of the answers.

8 The perception of discrimination, the one-year

9 deferral versus lifetime deferral that Dr. Williams

10 mentioned, and the fact that we have no effective means of

11 validation of those changes.

12 [Slide.]

13 When we talk validation, that scares me working in

14 a blood center. If I go through the process validation

15 documents from 1987, it says that we have to establish

16 documented evidence with a high degree of assurance.

17 [Slide.]

18 We can make medical history more effective. We

19 cannot treat it as a device. We can maintain the know

20 effectiveness of medical history by repeating the REDS

21 surveys at regular intervals, by measuring the prevalence of

22 markers among donors who are not deferred, and we can

23 measure sensitivity and specificity of medical history

24 questions by carrying out studies of deferred donors that

25 include testing for determination of marker prevalence.

1 [Slide.]

2 In my opinion there are many questions in medical
3 history for which my answer is no. One of them is I don't
4 think that all layers of safety carry the same weight, and
5 we cannot treat them in exactly the same way.

6 Medical history is not device. I don't think that
7 all questions should be identical. I think that uniformity,
8 you lose that sensitivity that we have, that we have despite
9 being a very homogeneous country and having the same holder
10 in New York and in San Francisco, people are different, and
11 people respond differently, and I think that locally, we
12 have much more contact with the population, must more
13 sensitivity to the ways they understand the questions.

14 [Slide.]

15 I think that medical history will have to be
16 placed in the context of the technologies that we have,
17 particularly now implementation of NAT, the weight of
18 medical history will decrease for the tests for which we are
19 using NAT.

20 Computer-based interviews were very well discussed
21 by Dr. Williams.

22 [Slide.]

23 Just to end with a few points. I don't think that
24 we can validate medical history because it is not a device,
25 but we can apply validation principles, for instance, for

1 the computer system that we use for medical history.

2 We think that we should change the character of

3 medical history, particularly at NAT implementation, and I

4 think that we could eliminate questions that are better

5 covered by screening technologies, and we could focus on

6 diseases and risks for which we have no screening test. I

7 think we would be much more effective in selecting our donor

8 base.

9 Thank you.

10 DR. HOLLINGER: Thank you, Celso.

11 This concludes the formal presentations. We have

12 one person who has asked to speak in the open public

13 hearing. I think that is Paul Cumming.

14 **Open Public Hearing**

15 DR. CUMMING: My name is Paul Cumming. I work

16 with Dr. Thomas Zook and the staff of the Hocksworth Blood

17 Center under a grant from the National Institutes of Health,

18 and also with Dr. Edward Wallace out of the Center for

19 Management Systems. I am here to report, give the first

20 results from implementation of the Hocksworth's Quality

21 Donor System, which is an automated multimedia donor

22 interviewing system.

23 You heard all of the potential advantages and the

24 reasons why the screening may be important, so I won't bore

25 you with those. In terms of those of you who were at the

1 Donor Suitability Conference, you got pretty much of a full
2 introduction to the system in terms of what it was by Dr.
3 Zook.
4 Basically, the thing that makes it different than
5 the other systems including Turner's study with audio-CASI
6 is it adds color and photographs. The reason for the
7 photographs is as much as the old adage "A picture is worth
8 a thousand words," and so we can emphasize particular parts
9 of the questions.
10 It provides the same confidentiality or the audio
11 confidentiality by putting sound through the earphones. We
12 have a lot of different validation criteria for the system,
13 but the primary one that we are interested in at the moment
14 or had the most discrepancy among or discussion among the
15 staff was the issue of donor acceptability, truthfulness,
16 things we can get from a survey.
17 The results we just got in, I just got the
18 material this Tuesday from the first stuff. We implemented
19 February 22nd, and we are implementing at the Hocksworth
20 Blood Center, and we are doing it slowly to make sure we
21 know what we are doing, and so that we don't do any harm and
22 just good.
23 [Slide.]
24 The questionnaire, I will cover this briefly since
25 I have got three minutes, and you can come back and ask

1 questions. The questionnaire we are using, this is an exit
2 questionnaire, and it attempts to get at whether or not the
3 user of the system sees the presentation as clear, how
4 satisfied they were with the time it took for the interview,
5 were they comfortable with the privacy and the degree to
6 which they were comfortable, do they believe the computer or
7 the nurse interview will generate more honest answers from
8 donors, and some information on their familiarity with
9 computers.
10 That was given to everyone that used the system,
11 that part of it, and I will give you the results on that in
12 a moment. The other part was only completed by repeat
13 donors which were most of the group that we looked at.
14 As Dr. Zook noted in his presentation at the Donor
15 Suitability Conference, a big difference here is that we are
16 comparing the same donor interview with the automated people
17 as with the manual system. It is an identical
18 questionnaire. Basically, the output of the system is that
19 it prints the donor questionnaire and looks very much the
20 same as the one that is used with the manual system.
21 The ones that were asked of all donors is whether
22 or not they prefer the video or they prefer the personal
23 nurse interview, whether it was more understandable or less
24 understandable with the Donor Quality System, the automated
25 system, and what their likelihood of return was, the object

1 being to make sure that we get a maximum number of return
2 donors and don't scare them away.
3 [Slide.]
4 This was a summary provided by Hocksworth staff
5 Tuesday of the questions. I took it this morning and
6 reduced it to some bar charts that I think make it easier to
7 see. In terms of the demographics of the group, they are
8 not, at least from my perspective, atypical of a group in
9 the Midwest of donors. They seem to be in some parts
10 slightly older than what I recall, but that just may be the
11 Hocksworth Blood Center.
12 The respondents were almost all whole blood donors
13 as that is where we decided to start, a few platelet donors.
14 [Slide.]
15 We also collected comments on the bottom of the
16 form, as you saw, 17 of that 28, by the way, got complaining
17 about the length of the interview. The interview is roughly
18 a 10 to 12-minute interview by the computer, mandatory audio
19 for any first-time donor and for most questions for second-
20 time donors.
21 That compares to an interview of three to five
22 with the original system that was approved by FDA for
23 marketing in December of '97 and at your last meeting they
24 commented that we were finally--or they were approving a
25 system which was the Hocksworth system.

1 [Slide.]

2 Again, this is a small sample, very preliminary,
3 but to the best of my knowledge, no one else has ever had
4 any data like this which is so comparable of putting an
5 automated process into an existing system.

6 Across the top, the only program I could find
7 rapidly this morning that would give me some graphics, and
8 hope to get the patterns out of it. You can see as to
9 whether or not the Hocksworth Quality Donor System was
10 clear, very clear to unclear.

11 Generally speaking, something like 87 percent of
12 the donors saw it as very clear, an issue there being that--
13 assuming that the questions the donor asked are right--then,
14 is it clear to the donor, do they understand what the
15 question is, and we were asking that.

16 In general, for the slides you will see--and this
17 group is different than the next set--the 1 and the 2
18 answers are favorable to the Hocksworth system, and the 4
19 and the 5 are unfavorable or, in some cases, in comparison
20 to the nurse system, they refer to that. Three is a neutral
21 response in general.

22 If you look at the time--and I couldn't find
23 anything that would hold these scales the same, so I am
24 going from 100 percent scale to a 60 percent scale--if you
25 look at the time and their satisfaction with it, you will

1 see that the most dissatisfaction, only 40 percent of the
2 donors were satisfied with the time, but it was not as bad
3 as I thought it would be. I thought it would be much worse
4 for that long of an interview. Dr. Zook, on the other hand,
5 didn't think it would bother them. It turns out he was
6 correct.

7 On privacy, the results are what I expected, you
8 know, how comfortable were they, very comfortable, again 87
9 percent of the donors gave it a very comfortable ranking.

10 As to whether or not they would be more truthful
11 with a nurse or a computer, the weight there clearly is into
12 to the 1 and 2 category as opposed to into the 4 and 5
13 category, which is the nurse. Most of the donors said the
14 bulk of them--I have forgotten what the number is--that they
15 would be most truthful with the computer than they would
16 with a nurse.

17 [Slide.]

18 These are the comparative responses, the second
19 part, the repeat donors only. Again, the percentages are at
20 the top. I reversed the axes, I was having trouble finding
21 something that would show things up. Now, you have got the
22 numbers on the bottom and the size of the percentage along
23 the side. But the convention holds.

24 The 1's and the 2's are favorable to the system,
25 and the 5 to something else, the alternative or a manual

1 system, a nurse, and the 1 in this case they prefer the
2 automated system, the 5 they prefer the nurse system, 3
3 being neutral. You can see there that much against the
4 common wisdom of the blood industry, the automated system is
5 at least as preferred or more preferred than the nurse
6 system by these donors, with the larger single number of
7 percentages, something like 32, 33, being ambivalent as to
8 which way it is done, which was somewhat of a surprise, as
9 well.

10 Looking to what they saw as most understandable,
11 another one of these clarity issues, you have to understand
12 the question before you can answer it, most of them again
13 were indifferent. Basically, the 3 there, they said that
14 they didn't see it as either clear or less clear or
15 understandable rather, but you can see, of the people who
16 added opinion, the bulk of them saw the computer as
17 providing a more understandable presentation with only, I
18 think it was 2 percent or something like that, that saw the
19 nurses as providing a better understanding of what the
20 questions were about.

21 As to whether or not they would return, the last
22 slide on the bottom there, you can see that the bulk of them
23 were indifferent essentially, however to the extent they had
24 an opinion, they thought that the computer system would have
25 a favorable impact on their return.

1 What we concluded from that basically was that, in
2 general, repeat donors favor or were neutral toward the
3 automated system as compared with the prior personnel
4 system.
5 DR. HOLLINGER: Thank you
6 Is there anyone else for the public hearing before
7 we turn it over to the committee, anybody else who wants to
8 make a comment?
9 [No response.]
10 DR. HOLLINGER: If not, then, we will close the
11 public session and move into the committee discussions. I
12 will open it up to any comments from the committee.
13 Yes, Dr. Boyle.
14 **Committee Discussion**
15 DR. BOYLE: I am just going to make an
16 observation. I do surveys for a living, and looking at the
17 current state of your screening questionnaire, I think
18 before you mandate anything, people ought to do a lot more
19 research on that questionnaire, a lot more thought about
20 what it is supposed to be accomplishing.
21 I mean one of the issues is are you just trying to
22 scare people away or are you trying to get honest answers.
23 If you are trying to get honest answers, then, there is at
24 least three issues you have to deal with.
25 Number one is attention. If you put 50, 60, 80

1 questions, you lose people's attention, so you have to
2 decide what you are going to focus on. Also, the way you
3 format it is going to be of great interest.
4 Next to the issue of attention, you have got to
5 get to understanding, and some of the work that was being
6 done by the Red Cross was trying to get at what people heard
7 and understood from those questions to decide whether those
8 are good or bad questions, but you have doing this for 20-
9 some or more years, and it is certainly time to do more than
10 five focus groups. You need a lot of cognitive testing to
11 get at that type of stuff.
12 The final issue is the honesty, and I don't know
13 how to tell you to get to honesty. In my personal
14 experience, some people lie on surveys, but an awful lot of
15 people prefer to misunderstand the question, and what you
16 want to do is define the question in such a way that they
17 can understand and answer it, and I think it is striking the
18 fact that if you ask very direct behavioral questions, you
19 get better answers than if you try to fudge around it.
20 So, my only comment to maybe open this thing is
21 before you move forward to decide there needs to be a
22 standard form or what is in that standard form, you need to
23 spend a lot more time because you have defined this
24 screening as one of the main pieces of the safety net, of
25 the multi-tiered safety net, so I would suggest you use the

1 same level of science on that, that you have done on some of
2 the other levels.
3 DR. HOLLINGER: Thank you, John.
4 Jane, would you, since this is why you are here,
5 would you comment about all of this, please, from a
6 behavioral standpoint, or any other comment that you might
7 have?
8 DR. PILIAVIN: First, I have to agree with Dr.
9 Boyle that there is a science to asking questions. One of
10 the presenters earlier was making a distinction between
11 behavioral science--and they didn't say it this way--real
12 science.
13 It is I think in some ways more complex to try to
14 do behavioral science, but certainly doing some very
15 systematic things about the question, and having focus
16 groups is a good start, trying to find out what people
17 actually think the question is asking. You can get some
18 really surprising answers when you actually are honest
19 enough and gutsy enough to ask people what they really think
20 you are doing.
21 A lot of you are familiar with my perspective on
22 the whole donor recruitment process including the screening,
23 and I find it very difficult to separate out this piece of
24 what we do with donors from the whole process that starts
25 with whatever kinds of education people get in general about

1 the health system and then the recruitment process which
2 ends up bringing a certain set of people into the actual
3 donation place.
4 It is obvious from the statistics that are shown
5 of the prevalence of viral markers in donor populations and
6 the prevalence in the total population that however we are
7 doing it, we are doing an excellent job of getting a very,
8 very, very safe group of people.
9 But I think that before you start, well, maybe at
10 the same time you are worrying about the questions per se,
11 you need to be worrying about how the people get to the
12 donation session.
13 If you look the REDS data, there are a number of
14 clues in there, one of which is coercion, another of which
15 is incentives. As a recall the REDS study, reasonable
16 numbers of people who were not truthful at the time of being
17 questioned say that they were either pressured in the
18 recruitment setting or were given what strikes some of us as
19 incentives that are kind of an offer you can't refuse sort
20 of thing, and I think we have to seriously consider those
21 issues along with the issues of what are we asking them,
22 because if you induce someone to come into a situation on a
23 basis that is probably inappropriate, you can hardly then be
24 surprised if they are less than truthful with you because
25 they are there for a reason that is somewhat different from

1 the reason that you want them to be there. So, there is
2 that issue.
3 One of the things that struck me in one of the
4 previous presentations, the one about the post-donation
5 reports just struck me with something that I had never
6 actually thought about before. It was well over half of the
7 actual problem reports were donors who call in and say, oh,
8 you know, I just remembered I got a tattoo or whatever.
9 Do people ever give donors the whole set of
10 questions that they are going to be asked at the time they
11 are being recruited, because what I was sitting her
12 wondering, not as a social scientist, but as a person who
13 used to give blood, what did the donor do when the donor
14 went home, did the donor say, you know, they asked me this
15 question--to their husband or their wife or went back to
16 work and said something to a colleague--they asked me a
17 question about whether I had had my ears pierced, why do you
18 suppose they wanted to know that.
19 Maybe in discussing things with the people in this
20 personal setting, they have come to the realization of why
21 this might be important and they then call the donation
22 center. I think it would be really instructive to find out
23 what the social process is by which donors come to that
24 post-donation report.
25 So, there is a couple of things that I think you

1 need to think about, is how much do donors really know about
2 what they are going to be asked when they get into the
3 setting, and is there some way you can short-circuit those
4 people and have them not show up, so that you don't have to
5 worry about then are they lying in the setting, do they then
6 feel somewhat constrained because everybody is looking at
7 them, and they feel like they can follow through.
8 I also noticed from the reading I did that you
9 sent me in this FDA oversight and remaining issues of
10 safety, the '97 report of the donor survey, that there are
11 specific demographic groups who tend to show up over and
12 over as the ones who are not answering truthfully or are not
13 understanding or are being unwilling to talk to whoever it
14 is that is interviewing them.
15 Those, I offer as three alternative
16 interpretations of why the answer that you get in the survey
17 is different from the answer they gave in the donation
18 setting.
19 I am wondering if that is a clue that there is
20 something different in the donation setting as a social
21 situation as far as the members of these groups are
22 concerned. It was specifically African-American men as I
23 recall who are the ones that tend to show up in that
24 statistic.
25 It was mentioned that there are some political

1 aspects possibly. I think that was referring to men who
2 have sex with men as a group that feels like they are being
3 discriminated against, but it may also be the case that
4 African-American men in this setting, as in most settings,
5 feel that they are being discriminated against in some way.
6 It, of course, is also a group that tends to have
7 on the average less education, so those things may be
8 working together. I am thinking here very much as a social
9 psychologist who thinks about the interaction setting
10 itself.
11 Now, this is where the questions are being asked,
12 but it isn't specifically the questions themselves. Dr.
13 Bianco said he notices his technicians being uncomfortable
14 when they are talking to the boss. Well, of course, they
15 are uncomfortable talking to the boss. I mean that is a
16 status reversal here, it is usually the high status person
17 that is asking questions of the low status person, and so
18 even if you weren't their boss, if you were known to be them
19 as an M.D. in some other setting, they would be
20 uncomfortable.
21 But we also have a great deal of discomfort in
22 this society in interactions in which the status varies,
23 different statuses of people in a conversational setting are
24 different, blacks talking with whites, men talking with
25 women, older people talking with younger people, and I am

1 just wondering if anyone has ever thought about looking at--
2 here, I am reminded, a number of years ago I proposed that a
3 conversational analyst be employed by people to do some
4 research. I have a person in mind actually.

5 A conversational analyst is a person who really
6 sits down and very, very closely analyzes what goes on when
7 people talk to each other from the level of pauses in speech
8 and sideways glances through to everything else that goes on
9 in that situation.

10 I suspect, for example, that when your technician
11 is asking you questions, she usually does not look you in
12 the eye. Is that true?

13 DR. BIANCO: Yes.

14 DR. PILIAVIN: Okay. I suspect that when white
15 interviewers, white female interviewers are talking to black
16 male potential donors, they do not look them in the eye
17 either, because there is a kind of discomfort that we have
18 in this culture in interracial interactions.

19 You can get an awful lot of nonverbal cues from
20 someone when you actually look at them in the face that you
21 don't get by keeping your head buried in your form and
22 writing things down.

23 This, of course, is probably a major issue for
24 untruthfulness in general or the inability of the person who
25 is doing the interview to pick up discomfort that might

1 indicate potential untruthfulness. As long as we are doing
2 things face to face and not doing it with computer-assisted
3 devices, we are going to have to think about the fact that
4 this is a social situation.

5 It is a situation in which two people who don't
6 know each other are having an extremely intimate
7 interaction, and that is bound to extremely uncomfortable,
8 and people tend to do it as quickly as possible to get out
9 of there as fast as they can. This is why it is probably
10 good that the computer takes longer.

11 So, all of these things argue for a close
12 evaluation of what is actually going on in the situation. I
13 think it is probably more important than the actual wording
14 of the questions although, as I said, I think that is
15 something that needs looking at.

16 So, if we are going to stay with these kinds of
17 interactions that are nurse on potential donor, we need,
18 first of all, to study what goes on there. Once we know a
19 little better what goes on there, although I think if you
20 just think about it a little bit, you have a pretty good
21 idea right now what goes on there, a little bit of
22 sensitivity training to how you do this in a way that is
23 best designed to pick up people's discomforts rather than
24 try to avoid them, because the discomforts are teaching you
25 something, again, nondiscriminatory ways of dealing with

1 people who are different from you, that that is really
2 critical.
3 Another thing I picked up from one of the
4 presentations before is the privacy issue. I have never yet
5 been in a blood donation center--and I have given blood in
6 lots of different places in various countries in the world--
7 and never found one yet that I thought was sufficiently
8 private except in Poland, and that was a long time ago.
9 In Poland, they actually have a doctor sit and
10 talk to you in a private room. I don't know why Poland did
11 that, but it is really my only experience, and particularly
12 on mobile drives where I believe 80 percent of the blood
13 used to come from--maybe still does--cramped quarters, not
14 even partitions most places, in high schools, kids sitting
15 cheek by jowl with other kids, and you have all of these
16 kinds of issues just confounded in mobile drives.
17 I guess that was kind of a stream of
18 consciousness, and it is at this point all I have to say,
19 but I will sit and listen to the rest of it. I will
20 probably think of something else.
21 DR. HOLLINGER: Thank you, Jane.
22 Other comments? Yes, Dr. Fitzpatrick.
23 DR. FITZPATRICK: We have used standardized donor
24 forms in DoD since Vietnam, and it is not essentially the
25 questions in our setting that creates the errors. It is the

1 skill of the interviewer and the person asking the question
2 or the skill of the person asking the donor to explain the
3 yes answer to the question that was supposed to get a no
4 answer, and I think that is a big part of the equation that
5 is left out here.
6 I have observed people in a fair number of donor
7 centers in the military over the past 24 years, and the
8 interviewer has a conflicting goal. Their goal is to
9 collect as much blood as possible, but also to maintain the
10 safety of the blood supply by screening out the donors that
11 should be screened out.
12 So, depending on the skill of the interviewer and
13 the integrity and sometimes you might say integrity or
14 purpose of the screener, if you get a quick answer from the
15 donor that meets your need in getting them to donate blood,
16 you may not pursue that answer further, and I think in a
17 number of the cases where I have reviewed accident reports,
18 and a donor has been accepted that should have been
19 deferred, some additional questioning by the screener would
20 have deferred the donor.
21 They just didn't understand completely why that
22 question was important or why they should provide more
23 information or why the time frame was important, why is it
24 important that your tattoo was within the past year, you
25 know, they got a tattoo, they can't remember exactly when,

1 that sort of thing.

2 So, I think as we move forward, those are the two
3 parts of the equation. One is simplifying the questions,
4 and I agree with everything that was just said, we need to
5 know what the donors think about the question when they read
6 it and what they think we are actually asking, and the other
7 is to look at our screeners and our interviewers, so that
8 their purpose in life is the correct one and they are asking
9 the right questions to find out why the donor answered it
10 that way.

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

12 DR. NELSON: I can't remember all the data from
13 the REDS and the other study when they have looked at donors
14 who had markers that might have been screened out, but it
15 would be interesting to see in what setting they gave blood.

16 Alan, is that part of it in terms of a blood drive
17 at a church with large numbers of other people or individual
18 donors? My wife has the job of recruiting donors for the
19 church, and I have heard her talk to people over the phone,
20 and she doesn't read the questions that they are going to be
21 asked, I will tell you. She tries to get--and I am not sure
22 how she thinks about whether or not they might have had a
23 risk or not--but I can see where different donors, the
24 process of recruiting even before you get to the blood bank,
25 that they may be very different.

1 I wonder, have you looked at that, is that part of
2 the equation?
3 DR. WILLIAMS: The data are available in the
4 questionnaire in terms of both the site the blood was
5 collected and what motivated the donor to come to the blood
6 bank in the first place, but we haven't look at it in that
7 context. It is something that could be done.
8 DR. HOLLINGER: Yes, Dr. Mitchell.
9 DR. MITCHELL: In the REDS study, it did show that
10 a lot of people who did not defer themselves that should
11 have were black and latino men, and I have done recruiting
12 and actually blood drives targeted at black and latino men.
13 I think that one of the reasons is sort of that
14 people aren't as truthful is because of the social
15 pressures, you know, we talked about the job location.
16 Another, I think is that people need to understand why you
17 are asking those questions, and it is not clear, but I think
18 that also the cultural sensitivity, as has been said before,
19 about the interviewer plays a big part in that.
20 There are a lot of questions, for example, about
21 people from African countries, and so on. My experience is
22 that people don't mind if they understand why you are asking
23 those questions and if you know sort of in advance that
24 there is an issue, that people don't feel badly, but if you
25 are there at a site, and, you know, people want to give once

1 they have made that commitment to come, people want to give.

2 At times we talked about having a donor pool, a

3 low-risk donor pool, and sort of developing a low-risk donor

4 pool, and I think that that would be the best way to go, and

5 do it in such a way that you might say that these people are

6 preferred donors, but not to exclude others who don't fit a

7 certain profile.

8 I also had a technical question. One is about the

9 snorting of cocaine and the risk factors associated with

10 that, and what is an ISU.

11 DR. HOLLINGER: Well, question about cocaine I

12 think was primarily put in because of some studies that

13 suggested that there may be an association with transmission

14 based on the fact that the nasal membranes are quite

15 avascular and on using either a tube or a dollar bill, or

16 whatever is used for snorting the cocaine, goes and usually

17 passes into a person's nose, and then is passed on to the

18 next person. There is often blood around that tube.

19 In fact, there are some interesting aspects of

20 that alone. Often, women are at the bottom of the chain

21 when that is done, and so they are much more likely to be at

22 risk because it usually goes from the males, if there is a

23 group of people doing this, often passes from the males who

24 maybe will snort the cocaine, passed to the next person, and

25 then finally to the women at the end of the chain, so there

1 are some even enhanced risks with that group, so there is a
2 little subtlety, but that was really why that question was
3 asked.
4 DR. MITCHELL: Is that a theoretical?
5 DR. HOLLINGER: No, the data that Dr. Catalina in
6 the NIH blood center, published in The New England Journal
7 of Medicine a couple of years ago I guess it was, maybe
8 three years now, looked at that and suggested that there
9 were some data.
10 Now, there have been some other studies that have
11 not supported that, and so that is an important issue is
12 whether it really is or not, but when you think about it
13 epidemiologically, I think it makes some real sense, and you
14 talk to the patients who do it, I think it would make some
15 sense.
16 DR. PILIAVIN: He asked another question, which is
17 what is ISU, and I was wondering that, too.
18 DR. WILLIAMS: I am not sure exactly what
19 materials the committee was sent, but we may be responsible
20 for that. In the 1998 donor survey, we separated out
21 injecting drug use in terms of other illegal use from
22 injecting steroid use, and we now commonly refer to steroid
23 injection as ISU.
24 DR. HOLLINGER: We thought it was Iowa State
25 University, but we weren't sure about that. That is why you

1 got no answers to it.

2 Corey.

3 MR. DUBIN: I think from our perspective we have
4 always conceptualized the donor pool, at least our
5 experience since we came to the table is that the donor pool
6 in this country has never really been tapped to its greatest
7 degree, so every time we seem to get in trouble, we seem to
8 either want to relax the regulations or figure out why we
9 can't get more out of the people we are getting it out of
10 already.

11 In our own discussions internally, we like keep
12 banging our head against the wall because we wonder if we
13 are just naive, more naive than we understand, or if people
14 just don't seem to get it or what drives the equation.

15 We have said this here many times, and we are
16 going to keep saying it, I think, because I think there is
17 something to be said. The administration and the Congress I
18 think can be used to our advantage, the majority leader,
19 speaker, President, in ways that President Carter attacked
20 energy in the 1970s, when he went to the nation.

21 I thought it was interesting when we had that
22 weather-related shortage of blood in the Northeast. On the
23 cover of USA Today, I believe it was the next day or a
24 couple of days later showed all these farmers in Iowa with
25 their arms out, rolling their sleeves up.

1 There was a message there, at least we saw a
2 message there, but that message only got communicated to
3 those farmers in Iowa in a critical situation, and it seems
4 to me we need to start reconceptualizing what the donor pool
5 is in this country, because I don't think we have begun to
6 tap what is really out there.
7 Every time we hear in this committee, and the ones
8 that have been around a long time have seen this, you know,
9 sometimes you hear out of us this is deja vu, every time we
10 hear we have got a back-up on standards or we are going to
11 change something because we have got a problem, to us it is
12 the same old problem, why do we keep going back to (a) risky
13 populations, or (b) the same people we are taking it from
14 now.
15 How much analysis can we do on drawing blood out
16 of people we have already drawn blood, when there is all
17 kinds of people in this country we are not touching? I
18 don't think that is necessarily, I am not saying it is FDA's
19 responsibility, because clearly it is not, but clearly, the
20 government in a broader construction of that, i.e., the
21 administration and the Congress, could be brought to bear,
22 and I think the cover of USA Today was a very good example
23 of that.
24 The second part we would raise, which is FDA, is
25 we do think MSM is a problem, and we think it is a problem

1 for two reasons. One, obviously, it is discriminatory, and
2 from our perspective, either equally as important or more,
3 it is not getting the job done because it is too narrow,
4 because it is about a population, and it is not specifically
5 listing the risk behaviors that are associated with the
6 transmission of AIDS or any other pathogen, so people are
7 getting through that shouldn't if the policy was targeted on
8 risk behavior, and we have been making that point for some
9 time, as well.
10 DR. HOLLINGER: Dr. Bianco.
11 DR. BIANCO: Corey, I agree with the two things
12 that you have said, but I have a challenge for you. The
13 best experience that we have in recruitment is when we can
14 link a donor with a recipient, when we have a picture of a
15 baby or we have a mother that said my life was saved because
16 I received blood that was given to me by the community is
17 when things happen.
18 Your community could help tremendously our ability
19 to recruit donors.
20 MR. DUBIN: I think it is very interesting. For
21 four years I have been sitting in this chair talking, and
22 nobody has approached us until right now. Nobody has
23 approached us and said--we have even told people we would be
24 glad to help, and again it is the same point, what is in
25 this equation that we are missing, because there is clearly

1 something we don't understand, because we are prepared to do
2 that obviously.
3 There is no real effort in doing that for us. We
4 do benefit intensely from the nation's blood supply, but
5 what is missing, and I don't have any answer. Clearly, on
6 one level, Celso, we would be glad to help, we have offered
7 many times, but I really think that donating blood has to be
8 put back in the equation as a part of good citizenship, and
9 we ought to do some good thinking about how to convince
10 families rather than convince individual donors to keep
11 coming back, how do we convince families that X amount of
12 time here, the family ought to go down to the local blood
13 bank.
14 Are there social engineering techniques we can use
15 there? I don't know, but we certainly feel like we just
16 keep focus on the same crew, and sometimes that is a risky
17 crew, and we get real nervous when that happens.
18 DR. HOLLINGER: Jane, I would like to ask a
19 question. Dr. Fitzpatrick and Dr. Mitchell brought up some
20 very important questions also, ideas about that the
21 explanations of why things are not done or not given.
22 I mean I could perceive of groups of donors,
23 potential donors first coming in with an informed individual
24 explaining to them all the questions, why they are being
25 asked, what they mean, and so on, might probably give you a

1 pretty good donor population if that were done.

2 But how do you go about doing something like that,

3 is it possible, is it just daydreaming or what, can you

4 comment? Then, any other comments you have, please.

5 DR. PILIAVIN: Well, one of the things that some

6 donor centers do a little, but I never understood why more

7 donor centers don't do it more, is using committed regular

8 donors to do some of their recruitment, and it certainly

9 would be relatively easy to program such people who have

10 answered these questions multi, multi-times themselves and

11 understand why they are being asked, to be those kinds of

12 educators and ambassadors to new donors, and they would be

13 free, just like they are free when they come and give blood,

14 they would be free to do this.

15 I even think that people like me, who gave many

16 gallons of blood and then can't anymore for health reasons,

17 would be an idea population for this because we are feeling

18 bad that we can't do it anymore, we were hooked on this

19 activity, and so there is that.

20 I also think that we are in a climate now, at

21 least I perceive it this way being on a college campus,

22 where college students are starting to get excited about the

23 idea of volunteering and doing things for the community. It

24 has gotten to be kind of the thing to do, I mean let's not

25 be cynical about it, I hope it is really something that

1 these kids will keep doing.

2 But giving blood is volunteering, and I don't
3 think this general ethos about volunteering has included
4 blood donation as one of those things they have talked
5 about. They are always talking about going down to the
6 local food pantry or soup kitchen or helping with the
7 homeless, reading to children, tutoring children, all of
8 these things that are one on one person kinds of things,
9 because I think they think that is what appeals to these
10 kids, but I think there could be something involved in
11 orientations on college campuses.

12 Also, and I wrote this in my book nine years ago
13 or whenever that book came out, we really need to think
14 about including discussions of blood donations and uses of
15 blood in health curriculums as young as grade school with
16 children. I mean we are teaching children things about
17 health all along the line including sex education, and so
18 on.

19 I don't see any reason why units couldn't be put
20 together that have blood donation as part of a general
21 discussion of community health, but that, of course, is a
22 very long-range project and would involve huge
23 organizational and governmental cooperation, which I just
24 find unlikely in this day and age.

25 DR. HOLLINGER: Marion.

1 DR. KOERPER: Something you said sort of struck a
2 bell with me in terms of getting to want to come and donate
3 without the sense of coercion, or, you know, everybody else
4 at work is doing it, so I had better go do it, too, or they
5 will think that I am doing something I shouldn't do.
6 When we are trying to recruit patients for various
7 studies that we have ongoing, we actually send out a letter
8 and a copy of the consent form, and say if you are
9 interested, call us back, so that it is not like they are
10 sitting in the room with the doctor, and I say, gee, would
11 you like to participate, and they feel like how can I say no
12 to my child's doctor.
13 I don't know how you would come up with a list of
14 potential donors although, for instance, my son's high
15 school does have a donor day at high school, and my son's
16 college does, so one might have a list of students or what
17 have you, but rather than that initial contact being another
18 person, the church member, for instance, for whom it is hard
19 to say no, to send out a letter of explanation and a copy of
20 all those questions, because you said people may not really
21 understand the questions, but if they could read them in
22 advance, so send a letter explaining the reasons for
23 donating, but who shouldn't donate, and the questionnaire or
24 the questions with why these questions are important, and
25 then inviting people, if they would like to donate, to call

1 to make an appointment, have a number for them to call.

2 DR. PILIAVIN: Of course, the reason that coercion

3 is used is because it works, but I think young people are

4 where the idealism is, and we keep seeing all these danger

5 signals about the baby boom generation who have been the

6 blood donors are aging, and we are going to need to replace

7 them. Well, the boomer babies are here, that is the young

8 people now. These are the boomer's babies.

9 So, we have got the echo boom is what the

10 demographers call it. it is not quite as big as the first

11 boom, but it is pretty big. It seems to be to me the time

12 to do this kind of intensive education at the high school

13 and college level partly because if you establish a habit at

14 that age, it is likely to stick.

15 We all know that is the problem with cigarettes,

16 right? I mean you start it young, that is when you have got

17 trouble. I happen to be hopeful that positive habits can

18 work the same way.

19 I am afraid I really have to go. I have got a

20 plane at 7 o'clock out of National, and there is a van that

21 leaves at 5:30 that will take me to the Metro, and then I

22 will get there.

23 DR. HOLLINGER: Thank you for your comments,

24 appreciate your coming.

25 DR. PILIAVIN: Thank you.

1 DR. HOLLINGER: Corey?

2 MR. DUBIN: I think we have to reinfuse, kind of
3 get away from the cynicism that won't work, look, folks, we
4 got the Speaker of the House, Newt Gingrich, to back us in
5 legislation that we passed the Congress unanimously. We
6 were able to do that.

7 Everybody said you have got to be kidding, that is
8 not possible. I think those things can be done, and in some
9 of our discussions with some of the Republican leadership
10 who we were working with on the legislation, we raised this
11 issue, you know, because we were there, we had time with
12 them - John McCain, Porter Goss, some very influential
13 Republicans, Democrats, as well.

14 We got a positive response from them. Some of
15 them told us they had never been approached. We again felt
16 like are we missing something, is something going on that we
17 don't know about. I mean I wonder if the blood bank in
18 Illinois where Hastert is from, the new speaker, has ever
19 approached him or if Porter in Chicago has ever been
20 approached or Barbara Boxer or, you know, Lois Capps in
21 California, who I guarantee would do it because I know Lois.

22 I mean I think there is ways that we have got to
23 kind of reinvigorate this thing, because the negative side
24 is, like I said before and I am going to say it again, we
25 get very nervous when you all start looking at the risky

1 people, because we have been down this path once already,
2 and we are still in some ways partly the canaries of the
3 blood supply, but as we move into recombinant, you have got
4 the immune deficient people who are hanging out there and
5 the alpha-1 people, and they are the ones even at more risk
6 now than we are, and we don't want to see a repeat
7 performance.

8 If we are talking to a Senator McCain or Senator
9 Leahy, and we raise this issue, they say, sure, but we have
10 never been approached, what does that mean, what is missing?

11 DR. HOLLINGER: I take it, Corey, you would feel
12 that with the new tests coming down the line, the NAT
13 technology and other things, it doesn't sound like you would
14 be willing to have many of these questions removed from the
15 system that are currently being asked.

16 Is that correct or incorrect? Do you think that
17 there is a possibility that these questions can be removed
18 as not being very helpful with the new technology that is
19 there, it is really picking up additional risks?

20 MR. DUBIN: You have to separate derivative. You
21 know, in terms of our area, I mean certainly as recombinant
22 technology becomes more and more on line, but for people who
23 are still using human plasma derivative products, I think
24 the GAO summed it up, the viral inactivation technologies
25 work, the tests work, but there is serious GMP problems out

1 there, and there are serious problems in the operation of
2 the system.
3 We ratchet up the system nice and tight,
4 absolutely, we are a lot safer than we have been, and the
5 technology is there, but you have got to have a system where
6 people are meeting GMP and the tests and the technologies
7 being applied are being done and applied correctly with the
8 kind of in-service training that is needed for it to work.
9 DR. HOLLINGER: Mark.
10 DR. MITCHELL: I have a couple of things. One is
11 that I still think that it is important not to have a
12 national standardized format because I think that there are
13 so many variables locally, I mean from language to culture
14 and understanding of the questions. I think that there
15 should be national guidelines, but not a requirement for
16 that.
17 Another question I have I guess is about CJD, if
18 it is going to be taken out, if it is no longer going to be
19 a deferral, then, why ask questions about it.
20 DR. HOLLINGER: There are some reasons. Go ahead,
21 Jay.
22 DR. EPSTEIN: We do still defer donors either for
23 CJD or CJD risk including classic CJD risk. It is just that
24 we do not now routinely and automatically withdraw plasma
25 derivatives, so we have limited the conditions under which

1 there is a derivative withdrawal. We do still screen the
2 donors and retrieve components if they were donated when we
3 get post-donation information.

4 DR. HOLLINGER: Gail.

5 DR. MACIK: I just wanted to comment the same as
6 far as what you are going to do with our questionnaire. I
7 do believe there has to be mandated questions to be asked,
8 but then leave it to the regions to decide how they ask the
9 question. So, you want to make sure that all the same
10 things are asked, that you put it in the right language, in
11 the right culture, and in that case, if somebody walks in,
12 you offer them do you want to speak with someone, do you
13 want to watch a video, do you want to use a computer screen,
14 so that they feel comfortable with whatever media they pick,
15 because a grandmother who has never seen a computer doesn't
16 like to sit in front of a computer and try to figure out
17 what button to push. She is going to be more likely wanting
18 to talk to a real person.

19 So, I think it comes down to, yes, mandating what
20 has to be asked, but not how you ask it, and then have
21 individual areas think of who they are serving, are you
22 primarily urban, are you primarily rural, are you from the
23 country of Texas. You know, there is various things that
24 you have to think about when you put these together.

25 Then, also, to get into how do you recruit people.

1 There has to be a civic duty that comes up and getting
2 people to come forward, but I think better effort at
3 educating before they show up, putting out quick little
4 snippets even on television, you know, if they get
5 repeatedly in front of them like, you know, if you have a
6 tattoo, it might do this, so you want to be careful when you
7 donate your blood or just things that you wouldn't otherwise
8 think about, ear piercing, you know, and things like this
9 that you wouldn't necessarily think about, but you made all
10 the effort to get over to the blood bank after being cajoled
11 by your neighbor or church group, and then you are going to
12 be thrown out because you had your ears pierced and you
13 can't remember if it was nine months ago or it was six
14 months ago or whatever.
15 You know, there needs to be just kind of some
16 thinking about this, and I would go a little bit with Corey,
17 really trying to get a defined donating group probably makes
18 more sense than really relying on the blast of civic duty
19 going out and trying to get donors that come together as a
20 group.
21 DR. HOLLINGER: Dr. Fitzpatrick.
22 DR. FITZPATRICK: Even though we use a standard
23 form in DoD, I wouldn't advocate a national standard form.
24 I agree with Corey and Dr. Bianco that different communities
25 need different things, and our form is designed differently

1 from, say, from the Red Cross form, because our population
2 is different, and we try to make the questions understood.
3 I am not sure we do so well with that, but we try.
4 Then, for the need, you know, in times of national
5 emergency or national disaster, the population responds very
6 well, and we have never had a problem with a blood shortage
7 during a period of a national disaster or emergency, but we
8 do need to target increasing the number and the supply, and
9 so maybe if we reduce the number of questions or eliminate
10 questions, we may affect the fact that we have a very safe
11 population.
12 We showed by the statistics that our donor
13 population is different from the general population. If we
14 eliminate the questions, we may invite many of those people
15 back because as time goes on, it won't be so well known that
16 you shouldn't donate if you have done those things or had
17 your ears pierced or tattoo or whatever, and now we become a
18 screener by testing, and we increase the expense of the
19 product by doing that instead of screening out those donors
20 before we take all the effort to draw the blood, test them,
21 and put it on the shelf.
22 DR. HOLLINGER: Just a question for one of the
23 blood banking people here. Are the questions in most blood
24 banks shorter for repeat donors or are they exactly the
25 same?

1 DR. BIANCO: Exactly the same.

2 DR. HOLLINGER: Exactly the same. Okay.

3 DR. BIANCO: And 80 percent of the donors in the
4 majority of the centers in the country are repeat donors,
5 so, Corey, there is a core donor population. The problem
6 that we have is that it is not enough, and that population
7 is aging.

8 DR. HOLLINGER: John.

9 DR. BOYLE: I have learned a lot since I began by
10 just criticizing the questionnaire. All I would like to say
11 is that once again, I don't know what the purpose of the
12 screening is or the questionnaire is. You could have a lot
13 of different purposes.

14 But if I went to a federal agency and described a
15 survey that I was going to do, that was going to be on
16 sensitive topics, however, we were going to do the
17 interviewing in person, under conditions that were less than
18 private, that we were going to let different regions--we
19 will give them the same list of topics, but they can ask the
20 questions differently, we are not going to train the
21 interviewers or we are going to let them be trained locally,
22 and we are not going to deal with the issues of how they
23 interact with people of different social caliber or various
24 things, and yet I was going to come back and say I had some
25 kind of standardized result or at least I had some sense of

1 what I was bringing back and that it was relatively uniform,
2 I certainly wouldn't get that contract.
3 So, the only question that I would pose is when we
4 think of the things that we want to do that we may be
5 limited, and once again I don't know how limited we are in
6 terms of the privacy, but clearly if you ask sensitive
7 questions under non-private conditions, the likelihood that
8 you are going to get really valid responses from those
9 people who are doing the things that are less usual is
10 questionable.
11 Similarly, with all the nicks of we want to do it
12 our own way, you know, probably what needs to be thought
13 through is what is the purpose of the screening phase and
14 then how best can it be done, but right now I can just
15 describe it as extraordinary.
16 DR. HOLLINGER: Yes, Jeanne.
17 DR. LINDEN: I just wanted to bring up the issue
18 of repeat donors. I know Dr. McCurdy has in previous
19 meetings talked about the fact if we could just get the
20 donors that we have to come back more often--I agree it is
21 an aging group and we do need to expand the donor base, but
22 if we could get people to donate twice a year instead of
23 once, then, we would have a lot better blood supply, and it
24 is people who have been prescreened.
25 I would think that if we could do something about

1 the questionnaire process that recognizes that they are
2 former donors and looks at changes from the previous, and
3 not every single "ever" question all over again, and that
4 just gives them some recognition, it's like, gee, you have
5 been here before, and we are going to treat you in a special
6 way, would be a little bit positive in giving them a more
7 beneficial experience.

8 The other problem with that, though, is I know
9 that a lot of people don't donate more frequently simply
10 because it isn't convenient for them. My O-negative husband
11 is the perfect example. He will donate when it is
12 convenient, otherwise, forget it.

13 Just as an example, the blood collection agency in
14 our area does the recruitment from 300 miles away, and
15 people have no clue of geography. I talked to somebody the
16 other night who tried to get us to go to a bloodmobile that
17 was two counties away.

18 I think that the blood banks can do a better job
19 with perhaps more local involvement for recruitment to make
20 things convenient for people, and there is lots of different
21 aspects to this, but we need to make it a more positive
22 experience for people, and then we can maybe retain them to
23 come back a second time.

24 I think the questionnaire is part of that, but
25 there are other aspects, as well.

1 DR. HOLLINGER: Captain Gustafson.

2 CPT GUSTAFSON: I will correct something on the
3 abbreviated donor history. We have approved it for
4 primarily serial plasma donations when the donor comes back
5 as many times as twice a week, and they will be asked. The
6 high-risk questions are all asked orally, but some of the
7 other things as has your history changed or has anything
8 happened since you were in last, have you seen a doctor,
9 those types of questions that might tell the screener that
10 they should delve a little bit deeper into it.

11 Also, for autologous donations when the donor is
12 giving maybe for a surgery that is planned in a month or
13 two, and they give repeated donations, and those are given.

14 I think there is one or two blood centers who have
15 been approved for an abbreviated donor history form,
16 otherwise, I don't know if they actually use it. There is
17 the issue with the allogeneic blood donor, that they only
18 give once every eight weeks, so the span of time, then,
19 between donations is greater, but we do have some donations
20 now that are approved for the abbreviated history form.

21 DR. HOLLINGER: Dr. McCurdy.

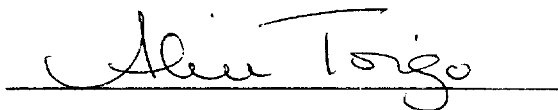
22 DR. McCURDY: It seems to me that what we are
23 hearing about it that there are a lot of different things
24 and a lot of different opinions about how blood donors
25 should or are or are not recruited, and I suspect that what

1 may be needed is a relatively innovative start-from-scratch
2 look at the whole process to see where we are going.
3 I think that although only 20 percent or less of
4 donors are first-time donors, of those that are left, as
5 Jeanne said, the vast majority of them donate once a year,
6 and if you could get them to donate a second time, you might
7 have an awful lot more blood or at least half of them to
8 donate a second time.
9 We are drawing blood now pretty much the way we
10 did 15, 20, 30, 40 years ago. Most of it is on mobiles.
11 Mobile is relatively easy as far as the recruiting staff is
12 concerned, it is relatively expensive as far as the
13 collecting staff is concerned.
14 A few blood centers have moved toward fixed sites
15 that are open periodically. They may have staff that rotate
16 from one fixed site to another, but I think there are a lot
17 of things that could be looked at in relatively basic and
18 innovative fashion, and I think that if somebody were to
19 come up with a well-planned, careful study, I think the
20 NHLBI would be happy to discuss what might be done further
21 to understand better what we are doing and how.
22 DR. HOLLINGER: We are at 5:30. Does anybody else
23 have any particular burning questions? Yes, Paul.
24 DR. McCURDY: One other thing. There was a rather
25 extensive study done in the late seventies by Alvin Drake

1 from MIT as to why donors who were donating stopped
2 donating, and there were a number of reasons, but they all
3 boil down to essentially what Corey said earlier today,
4 nobody asked me.
5 DR. HOLLINGER: Just to remind the committee and
6 others who are going to come tomorrow, the session will
7 start at 8:00 tomorrow. It will be an update first on tick-
8 borne diseases workshop, then, there will be a session on
9 IGIV, and then a session again, a reintroduction of
10 inadvertent contamination of plasma pools for fractionation
11 with the probability of completing this at 2:30 or 3 o'clock
12 tomorrow afternoon.
13 We will see you all then at 8 o'clock in the
14 morning.
15 [Whereupon, at 5:35 p.m., the proceedings were
16 recessed, to resume at 8:00 a.m., Friday, March 26, 1999.]

C E R T I F I C A T E

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



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