TRANSCRIPT OF PROCEEDINGS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

OPEN

BLOOD PRODUCTS ADVISORY COMMITTEE

SIXTY-FIFTH MEETING

OPEN SESSION

VOLUME I

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Pages 1 thru 324

Silver Spring, Maryland
March 16, 2000

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

SIXTY-FIFTH MEETING

OPEN SESSION - VOLUME I

Thursday, March 16, 2000

8:00 a.m.

Kennedy Ballroom
Holiday Inn Silver Spring
8777 Georgia Avenue
Silver Spring, Maryland

MILLER REPORTING COMPANY, INC.
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Executive Secretary

Linda A. Smallwood, Ph.D.

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

2 DR. SMALLWOOD: Good morning, and welcome to the
3 65th meeting of the Blood Products Advisory Committee of the
4 Food and Drug Administration. I am Linda Smallwood, the
5 Executive Secretary, and at this time I will read the
6 meeting statement that will affect the proceedings of this
7 meeting. This announcement is made a part of the record at
8 this meeting of the Blood Products Advisory Committee on
9 March 16th and 17th, 2000.
10 Pursuant to the authority granted under the
11 committee charter, the Director of FDA's Center for
12 Biologics Evaluation and Research has appointed Dr. Jonathan
13 Allan as a temporary voting member for the discussions on
14 donor deferral issues relating to xenotransplantation. In
15 addition, the Senior Associate Commissioner, Food and Drug
16 Administration, has appointed Drs. Valerie Ng and Carmelita
17 Tuazon as temporary voting members for the discussions on
18 indeterminate HIV Western blots with only non-viral bands.
19 A general waiver of applicability has been
20 approved by the agency to permit Dr. Paul Schmidt to
21 participate fully in any general matters discussion. To
22 determine if any conflicts of interest existed, the agency
23 reviewed the submitted agenda and all relevant financial
24 interests reported by the leading participants.
25 In regards to FDA's invited guests, the FDA has

1 determined that the services of these guests are essential.
2 There are reported interests which are being made public to
3 allow meeting participants to objectively evaluate any
4 participation and/or comments made by the participants. The
5 interests are as follows:

6 Dr. Harvey Alter is employed by the National
7 Institutes of Health in the Department of Transfusion
8 Medicine.

9 Dr. Michael Busch is employed by a blood bank. He
10 uses Genetics Systems products in his testing lab that
11 performs Western blots. In addition, he has received
12 Federal funding for research on Nucleic Acid Testing.

13 Dr. Louisa Chapman is an employee of the Centers
14 for Disease Control in the Division of Viral and Rickettsial
15 Disease. She reported unpaid speaking with Novartis. Dr.
16 Chapman also reported research collaborations with Circe and
17 past collaborations with Novartis.

18 Dr. Andrew Conrad is employed by the National
19 Genetic Institute. Dr. Nishioka is employed by the Japanese
20 Red Cross Blood Center. Dr. Susan Stramer is employed by
21 the American Red Cross. Dr. Charles Watson is employed by
22 Aventis Behring, formerly Centeon.

23 In the event that the discussions involve other
24 products or firms that are already on the agenda, for which
25 FDA's participants have a financial interest, the

1 participants are aware of the need to exclude themselves
2 from such involvement and their exclusion will be noted for
3 the public record.
4 With respect to all other meeting participants, we
5 ask in the interest of fairness that you state your name,
6 affiliation and address, and any kind of previous financial
7 involvement with any firm whose products you wish to comment
8 upon.
9 A copy of the waiver addressed in this
10 announcement is available by written request under the
11 Freedom of Information Act.
12 At this time I would like to take the opportunity
13 to introduce to you the members of the Blood Products
14 Advisory Committee. We have additional new members to our
15 committee, and so I would like to just welcome them at this
16 time, and as I call your name, for all members, would you
17 please raise your hand?
18 Our Chairman, Dr. Blaine Hollinger. One of our
19 new members, Dr. Mary Chamberland. Another new member, Dr.
20 Michael Fitzpatrick. Mr. Terry Rice, a new member. One of
21 our temporary voting members, Dr. Ng. Our non-voting
22 consumer representative, Dr. Katherine Knowles; excuse me,
23 Ms. Katherine Knowles. Our non-voting industry
24 representative, Dr. Toby Simon.
25 To my far right, Dr. Jeanne Linden. Dr. Paul

1 McCurdy. Dr. David Stroncek. One of our new members, Dr.
2 Paul Schmidt; thank you, Dr. Schmidt. Dr. Mark Mitchell.
3 Dr. Marion Koerper. And Dr. John Boyle.
4 We also have some members that are absent today.
5 They are Dr. Norig Ellison; Dr. Richard Kagan; Dr. Daniel
6 McGee, who is a new member; Dr. Ohene-Frempong; and Dr.
7 Sherri Stuver, who is a new member.
8 Dr. Gail Macik just arrived. Would you raise your
9 hand, Dr. Macik, please? Thank you.
10 These are the members of the Blood Products
11 Advisory Committee that will be serving us for this meeting.
12 At this time I would like to call on Dr. Epstein to welcome
13 our new members.
14 DR. EPSTEIN: Thank you very much, Dr. Smallwood.
15 I just would like to welcome the new members of our
16 committee on behalf of the Center for Biologics Evaluation
17 and Research, and I would just like to say that we consider
18 the deliberations of this committee to be of very high level
19 importance to the decision-making that we are engaged in
20 within the FDA's blood program. The matters that we bring
21 before you are often weighty in terms of public health, as
22 well as having large economic impacts, and we very much
23 appreciate the work that you do in reading all the mountains
24 of material that we send you and in listening attentively to
25 the debates that we have.

1 You have been read the rules of the road, and you
2 know that all of our policy discussions are done openly in
3 public. There is no smoke-filled room. And so it is very
4 important that all views be heard. Toward this end, we go
5 to great lengths to invite people who have data that needs
6 to be considered, as well as to provide opportunity in open
7 public hearing for opinions to be expressed by all concerned
8 parties.
9 So, again, I thank you in advance for the effort
10 that you will expend on our behalf, and welcome you either
11 as new members or temporary voting members and also guests
12 of our committee today. Thank you, again.
13 DR. SMALLWOOD: Thank you, Dr. Epstein.
14 Before we move quickly to follow the agenda, I
15 would like to make the following announcement and just an
16 administrative note. The announcement is as follows:
17 Farmer and FDA are co-sponsoring an error and
18 accident reporting workshop for manufacturers of biological
19 products on March 31st, 2000, at the D.C. Renaissance Hotel
20 in Washington, D.C. The target audience for this workshop
21 includes manufacturers of vaccines, therapeutics,
22 allergenics, in vitro diagnostics, and plasma derivatives.
23 The focus of this workshop does not include blood banks or
24 source plasma collection centers. Registration information
25 is available through Farmer's web site at the following:

1 farmer.org/meetings. farmer.org/meetings.
2 I would also like to remind everyone, when you are
3 speaking, to please speak directly into the mike, and for
4 those individuals that are speaking from the floor, please
5 announce your name and your affiliation. And please be
6 mindful of the time limitations that we have set. We will
7 try to be flexible but we do need to keep the meeting
8 moving.
9 Thank you, and at this time I will turn the
10 proceedings of this meeting over to the chairperson, Dr.
11 Blaine Hollinger. Dr. Hollinger?
12 DR. HOLLINGER: Thank you, Dr. Smallwood. Yes, on
13 the microphones, you do have to turn them on and off when
14 you want to speak.
15 I do want to also welcome the new members here,
16 and my condolences to the old members here. I thought I was
17 supposed to be off this committee about a couple of months
18 ago, but you are going to have to put up with me at least
19 for another few meetings.
20 This is a very important committee, and I think
21 the important thing is that the committee is actually for
22 advice only; recommendations may or may not be taken by the
23 FDA. But it is important to share your feelings about the
24 important matters that come before this committee.
25 So, with that in mind, we do have a very full

1 agenda for today, so I think we will start out, as we always
2 do, with some committee updates. The first one will be on
3 Bacterial Contamination of Platelets, by Dr. Chiang Syin.
4 DR. SYIN: Thank you, Mr. Chairman.
5 I guess I have the honors to draw the first blood
6 this morning. I will take the opportunity to summarize the
7 FDA Workshop on Bacterial Contamination of Platelets which
8 was held on September 24th last year. In your package you
9 will find a copy of Dr. Edward Snyder's closing remarks
10 highlighting the issues raised in this workshop and a 1995
11 NIH/FDA Conference with a similar but broader theme on
12 Microbial Contamination of Blood Components.
13 The objectives of this workshop could be briefly
14 summarized as to obtain current information on bacterial
15 contamination of platelets, and to encourage research and
16 development efforts to minimize transfusion risk. There are
17 several reasons that prompted us to set up this workshop.
18 As you will remember, the 1995 conference, in an
19 effort to address microbial contamination problems in blood
20 products, called for the following actions: improved
21 surveillance; further investigation into novel screening and
22 detection methods; and judicious use of blood components.
23 As an agency concerned about public health, we
24 were eager to find out what had happened over the last four
25 years and what we have to do to further reduce the

1 transfusion risk associated with bacterial contamination.

2 The reasons that we limited the scope of the
3 workshop to only platelets, there is a rising trend since
4 1976 that the contribution of bacterial contamination to
5 transfusion fatalities reported to FDA has increased to
6 about 10 percent of all cases from 1990 to 1998, and
7 platelets were implicated more frequently than red blood
8 cells by a ratio of 2 to 1.

9 Several other factors also contributed to our
10 consideration, for example, the current practice of using
11 pooled platelets from random donors, which may increase the
12 chance of contamination significantly; and platelets, unlike
13 the red blood cells stored under refrigeration, are stored
14 at 22 degrees Celsius up to five days.

15 This workshop itself was divided into three major
16 scientific sessions to showcase the advances in
17 surveillance, detection methods, and prevention measures
18 over the last four years.

19 As you can see on this slide, Dr. Mo Blajchman of
20 McMaster University in Canada opened the first session by
21 reviewing the prevalence data from several prospective
22 studies conducted in the last decade. The rate of
23 contamination of platelets, in the range of 1 in 2,000 to
24 3,000 units, is far greater than that found for red blood
25 cells.

1 Due to the limitation of time today, I will not
2 discuss the data presented by these surveillance programs,
3 but there is a clear message that bacterial contamination
4 remains a significant problem for platelets.
5 Dr. Len Friedman opened the second session with a
6 presentation of all the factors that may play a role in the
7 development of a detection test, such as sensitivity should
8 be high, but what is the minimum requirement? The current
9 dating period for platelets is only five days, is an
10 important consideration for any test requiring a long period
11 of time to complete, such as bacterial culture or automated
12 culture system.
13 The factors like testing facility: Where should a
14 test be performed? At blood centers or transfusion
15 services? And test complexity should be considered as well,
16 especially with the test, which requires sophisticated
17 equipment, substantial training and skill of the test
18 handlers. And, finally but not least, cost could be a major
19 factor dictating the success of any new test.
20 This table lists many different tests that have
21 been developed for the detection of bacteria in blood
22 products. As mentioned earlier, the sensitivity and turn-
23 around time are the critical factors in assessing the
24 applicability of this test.
25 For example, the sensitivity for culture, using a

1 manual or automated system, could be in the range of 1 to 10
2 colony forming units per milliliter. However, a significant
3 amount of time, usually in days, is required, which could be
4 difficult for platelets with a dating period of only five
5 days. On the other hand, certain tests of reasonable
6 sensitivity that only require a short time to get a
7 conclusive result may be useful as a pre-transfusion test.
8 The third session was chaired by Dr. Steven Wagner
9 of ARC, to evaluate the strategies designed to prevent
10 bacteria from contaminating platelets or to inactivate any
11 bacterial pathogens that may have entered the unit of
12 platelets. Carl McDonald of UK evaluated 12 different
13 disinfection techniques, and found the combination of
14 application of isopropyl alcohol followed by iodine tincture
15 to be effective. In a field study of 100 volunteers, this
16 prep reduced skin bacteria from the donor's arm by 99.8
17 percent.
18 The strategy of diverting the first 15 mL of
19 collected blood is currently under investigation. The
20 preliminary results showed a reduction of over 70 percent in
21 contamination from collected units.
22 A presentation by Dr. Blajchman summarized the
23 studies showing that leukoreduction could be effective in
24 removing bacteria from contaminated units.
25 For the inactivation method, Dr. Lily Lin

1 presented data supporting a direct strategy utilizing a
2 photochemical treatment with psoralen S-59 and a long
3 wavelength UV light. The method was shown to be effective
4 in inactivating a wide spectrum of bacteria strains in
5 single donor and pooled platelet concentrates up to five
6 days. This method is currently under Phase III clinical
7 study in Europe and the U.S.

8 The conclusions of the workshop were drawn from
9 several major points that emerged from this workshop. This
10 could be summarized as follows:

11 First of all, bacterial contamination is a
12 significant problem for platelets, more so with wider
13 acceptance of NAT testing for viral markers. Second, we
14 need to strengthen current surveillance efforts, possibly by
15 making reporting mandatory and harmonizing the collection
16 and testing protocols from different programs.

17 Third, we also need to reduce transfusion risks.
18 Measures such as better skin disinfection that could be
19 readily validated should be adopted. Implementation of
20 testing for microbial detection should be considered,
21 concurrent with an extended dating period to seven days.
22 And the last point is, we need further evaluation and
23 development of novel detection and inactivation methods.

24 As a follow-up on this workshop, FDA has taken
25 several actions. The first action taken is, within a month

1 the Office of Blood Research and Review established the
2 Bacterial, Rickettsial, and Parasitic Agents staff within
3 the Division of Emerging and Transfusion Transmitted
4 Diseases. A research program for the detection of bacterial
5 contaminants in blood is currently underway.
6 Second, in the same month the PHS Bacterial
7 Contamination Working Group, or the so-called BWG, was
8 created under the directive of Dr. Jay Epstein to address
9 the scientific and regulatory issues raised in the workshop.
10 BWG is currently chaired by Dr. Jong Lee and myself, and its
11 members include scientists from NIH, CDC, ARC, and FDA.
12 Several topics, including evaluation of isopropyl
13 alcohol/iodine tincture, diversion of initial blood
14 collection, and extended dating period are currently under
15 discussion.
16 This concludes my summary. Thank you.
17 DR. HOLLINGER: Any comments at all from the
18 committee, or questions?
19 [No response.]
20 DR. HOLLINGER: Dr. Syin, just a question on the
21 platelets.
22 DR. SYIN: Yes, sir.
23 DR. HOLLINGER: Are they still equally effective
24 at seven days, and so on? Extending the date, does that
25 alter the effectiveness of the platelets as a product?

1 DR. SYIN: That is one major area we need to
2 address before we will adopt any of those policy changes.
3 DR. HOLLINGER: Yes, Dr. Simon?
4 DR. SIMON: That was studied quite some time ago,
5 and they are effective to seven days. That was published,
6 but actually they were allowed--dating was to seven days to
7 a couple of years, and then was pulled back because of the
8 concern about contamination.
9 DR. HOLLINGER: Okay. Thanks, Toby.
10 Okay. Thank you very much. The second update on
11 a workshop is on the Criteria for Safety and Efficacy
12 Evaluation of Oxygen Therapeutics as Red Cell Substitutes,
13 and we are going to have this update by Dr. Paul Aebersold.
14 DR. AEBERSOLD: The first overhead is the most
15 important information I am going to convey to you today,
16 because this is the web address for a transcript of the
17 workshop on Criteria for Safety and Efficacy Evaluation of
18 Oxygen Therapeutics as Red Cell Substitutes, so the entire
19 day and a half is available to read. It is fascinating
20 reading. For the record, it is
21 www.fda.gov/cber/minutes/workshop-min.htm. The second
22 overhead, please.
23 This is a flyer for the workshop, which was
24 jointly sponsored by FDA/CBER, and by the National
25 Institutes of Health, NHLBI, and the United States Army. It

1 was held September 27th and 28th, Workshop on Criteria for
2 Safety and Efficacy Evaluation of Oxygen Therapeutics as Red
3 Cell Substitutes. Next.
4 The agenda--can that be focused a little bit?--the
5 agenda included an update on the current safety status of
6 blood products by Dr. Harvey Klein from NIH; a talk on the
7 safety considerations of various investigational red cell
8 substitutes by Dr. Abdu Alayash of CBER; a discussion of the
9 efficacy evaluation criteria for red blood cell substitutes
10 as oxygen therapeutics by Dr. Toby Silverman of CBER.
11 The second session was presentations by
12 manufacturers who are fairly advanced in their clinical
13 trials, and they included Baxter Healthcare Corporation;
14 Alliance Pharmaceutical Corporation; Biopure Corporation;
15 Hemosol, Inc.; and Northfield Laboratories. Following the
16 prepared remarks by these sponsors of investigational
17 agents, all of those representatives then took the table up
18 front and fielded questions from the panel members.
19 The next slide will show our panel members that we
20 had. Without the affiliations, they were Jeffrey Larson,
21 Stephen Cohn, James Holcroft, Michael Joyner, Margot
22 Kruskall, Paul Ness, Reuven Rabinovici, Richard Weiskopf,
23 and Gus Vlahakes.
24 The structure of the workshop, other that the
25 prepared talks that I just described, the rest of the

1 workshop was structured as panel discussions around
2 questions that the FDA considers on a daily basis. We did
3 not ask any of our panel members to give prepared
4 presentations. It was a very wide open discussion of the
5 questions that we presented to them.
6 And if we could switch to the slides now, I will
7 basically summarize the workshop, if it can be summarized,
8 by discussing the questions. I would like to emphasize that
9 it was not a consensus workshop, the purpose was not to find
10 consensus amongst the panel members on the questions that we
11 asked; and that the update I am giving today, I have assured
12 every sponsor of a blood substitute product that there is no
13 new guidance today. This is merely a summary of the
14 workshop. Next slide, please.
15 We asked several questions about safety.
16 Toxicities and laboratory findings known or thought to be
17 associated with hemoglobin based oxygen carriers, including
18 cardiovascular hemodynamic aberrations, immune cell
19 activation, neurotoxicity, coagulation changes,
20 gastrointestinal changes, free radical generation, decreased
21 host cell resistance to infection. Next slide.
22 And the questions we asked panelists: Are there
23 any potential toxicities which should be added to the list?
24 There were. Myocardial injury, and basically every--liver,
25 kidney, pancreas, every organ system was mentioned, I think.

1 Which of the listed findings is potentially
2 clinically significant? I think that all of them was more
3 or less the consensus.
4 Does the use of oxygen therapeutics affect the
5 incidence, susceptibility to, or the severity of systemic
6 infections? That was discussed. There are some
7 publications that there are interactions between soluble
8 hemoglobin and bacterial endotoxins.
9 What evaluations should be included in the safety
10 component of a clinical trial? I can't summarize a day and
11 a half, obviously, but one of the points that was made by a
12 panel member was that the symptoms that one sees in awake,
13 normal volunteers such as nausea and vomiting, may be a
14 harbinger of more serious adverse events that would occur in
15 stressed patients, surgical patients or trauma patients, and
16 that it might be very important to understand the mechanism
17 of causing nausea, vomiting, etcetera in the awake
18 volunteers to find out what is really going on with these--
19 hemoglobin-based products I think were mentioned in
20 particular, but there also are for fluorochemical-based
21 oxygen carrying therapeutics. Next slide.
22 We basically had a half day devoted to questions
23 in trauma care, and then a second half day, the following
24 morning, was discussion of questions around efficacy and
25 safety in elective surgery. So just in the chronology that

1 we held the workshop, trauma was first.

2 Should mortality be the endpoint of choice for
3 clinical trials in hemorrhagic shock or exsanguinating
4 hemorrhage? Are there any endpoints that could serve as
5 surrogates for mortality, and what would constitute
6 satisfactory validation for such endpoints?

7 It was, just to give you the flavor that this was
8 not a consensus conference, we had statements or views
9 expressed such as the following: that mortality is an
10 unambiguous endpoint. That is pretty clear. Another
11 comment was that mortality may be a misleading endpoint,
12 particularly in patients who have traumatic head injury, and
13 there was basically a call that trauma patients with head
14 injury should be studied separately. Another comment was
15 that mortality is an insensitive measure of benefit. So, to
16 emphasize that we were not a consensus conference, we had a
17 wide discrepancy of views on mortality as an endpoint.

18 As for surrogates for mortality, there was
19 discussion of potential candidates but no agreement that
20 there were really much in the way of validated surrogates
21 for mortality, and of course in a trauma setting where you
22 have your endpoint of mortality available, it is also
23 difficult to want to seek some other endpoint because you
24 have mortality rather immediately available in trauma,
25 certainly within 28 days.

1 Surrogate endpoints are very valuable in
2 situations such as cancer survival, where you have to wait
3 five years to see if people have a relapse. Then a
4 surrogate is very important, to get information earlier, but
5 you have the mortality endpoints almost as fast as you have
6 any other endpoints in trauma.
7 What would constitute validation for such
8 endpoints? Well, they would clearly have to be shown to
9 correlate clinically. The next slide, please.
10 Are there any endpoints that are acceptable in the
11 face of an adverse mortality outcome? If you are not saving
12 lives, if you are costing lives, it was I think difficult
13 for people to come up with a reason why the product might be
14 effective.
15 Could the product have an effect on a serious
16 morbidity that has substantial impact on day-to-day
17 functioning? Yes, it could, perhaps.
18 Are changes in morbidity scores, for example,
19 APACHE, an appropriate measure of morbidity outcomes? And
20 in that regard there were several comments that the APACHE
21 III scoring system is a validated outcome predictor, but on
22 the other hand, more than 50 percent of the predictive value
23 of that APACHE III is due to the Glasgow coma score in the
24 previous 24 hours, and the major component of the Glasgow
25 coma score that gives it this predictive value is the motor

1 component. Next slide.

2 Where blood is not available, should the product
3 be tested in actual acute blood loss situations to
4 demonstrate impact on survival? I think in general that the
5 historical development of blood substitutes, that a lot of
6 the intended use of them would be in situations where blood
7 is not available, such as on a battlefield. And yet when
8 they are being evaluated, they are often being evaluated in
9 major medical institutions where blood is available.

10 So we had two discussions, two questions, and we
11 will get to the next one. One is where blood is not
12 available. One is where blood is available as a comparator.
13 And just as a matter of theoretical possibility, a blood
14 substitute could be less safe than banked blood and
15 inappropriate to use in surgery, for example--this is just a
16 theoretical discussion--and yet might offer a tremendous
17 benefit in situations where there is no blood available. So
18 it could be worse than blood but better than no blood. It
19 could be an intermediate type of product.

20 So these were the questions we asked: To what
21 extent can data generated in an emergency room or operating
22 room setting be extrapolated to the rural setting? And are
23 clinical trials in a rural setting necessary to demonstrate
24 efficacy and safety in settings where there is a delay to
25 definitive care? And are trials in the ambulance setting

1 necessary?

2 There was a rather strong belief expressed that
3 one cannot extrapolate fully from an emergency room setting
4 to a field setting where definite control of bleeding is
5 problematic; that you don't have the same things available
6 in the field as you do in a major urban trauma center. For
7 one thing, you won't have plasma and platelets available.

8 There was an overall, I think, sentiment amongst
9 most panel members that clinical trials to assess the safety
10 of blood substitutes should begin in a more controlled
11 setting of elective surgery; that trauma should probably not
12 be the first indications that are studied because it is very
13 difficult to tease out adverse events in bleeding,
14 traumatized patients from the underlying problems that they
15 are experiencing.

16 But also in that regard there was a sentiment that
17 a safety evaluation could have--one wouldn't need to define
18 the safety parameters of a blood substitute in exquisite
19 statistical detail with a tremendously huge study in
20 elective surgery, before one would be able to have enough
21 sense that it is safe enough to at least proceed to trauma
22 trials. The next slide, please.

23 Where blood is not available, to what extent can
24 efficacy demonstrated in clinical trials of product use in
25 cases of civilian trauma be extrapolated to efficacy and

1 safety in combat trauma? I think that the panel recognized
2 that there are many differences between battlefield care and
3 urban, certainly in major urban centers, "scoop and run"
4 type care where you have typical 20-minute delivery to
5 definitive care, whereas in a battlefield situation the
6 Institute of Medicine held a workshop recently, and four
7 hours was a typical kind of delay to definitive care. So it
8 is not clear that one can extrapolate. Next slide, please.
9 Where blood is available, can clinical equivalents
10 in mortality between an oxygen therapeutic and blood be a
11 basis for licensure? If yes, what lower 95 percent
12 confidence interval for mortality rate would be acceptable?
13 Well, the panelists would not let themselves be
14 suckered into a discussion of trial size. We, of course,
15 when we said what 95 percent confidence interval for
16 mortality would be acceptable, for example if you have a 15
17 percent mortality in trauma patients who need a blood
18 transfusion, what increase in mortality would be acceptable
19 as a confidence interval--not a point estimate, mind you.
20 Let's say the point estimates were identical, 15 percent in
21 a controlled blood group and 15 percent in a blood
22 substitute group, what confidence intervals would the
23 panelists want to see? They would not--they were not about
24 to answer that question of trial size in trauma.
25 I might should point out that Dr. Toby Silverman's

1 talk was the current FDA guidance on efficacy trials with
2 blood substitutes, and that is part of the transcript of
3 this conference.

4 But, in general, could clinical equivalence in
5 mortality be a basis for licensure? I suppose that the
6 committee more or less agreed that in principle the answer
7 for that could be yes, that one wouldn't have to be any
8 better than blood in any way, shape or form; if one were
9 equivalent, that it could certainly be a basis for
10 licensure.

11 Then if we turn to the next slide and try to wrap
12 up in a couple minutes here, elective surgery, should an
13 oxygen therapeutic be evaluated in controlled clinical
14 trials in hemodynamically unstable patients requiring blood,
15 prior to licensure for elective surgery, to ensure that use
16 in surgical patients at the highest risk would not lead to a
17 worse outcome than if blood were used?

18 The genesis of this question is, if one studies
19 hip replacement surgery, where the vast majority of the
20 people are expected to come through stably through the whole
21 surgery and without any major morbidities and minimal,
22 minimal mortality, the panelists had great concern that if
23 FDA were to ask people who were seeking a surgical
24 indication such as hip replacement to study unstable
25 patients, that this was somehow mandating that a sponsor

1 seek an indication. And it is not the FDA's role, the
2 panelists felt, for FDA to tell sponsors of investigational
3 agents what indications they should seek.
4 But that was not the basis for the question. The
5 basis of the question was, since you have so few unstable
6 patients in surgery, how can--yet it happens now and then--
7 before we licensed a product, and if we expected in a
8 surgical setting that there would be very few unstable
9 patients, there would be no statistical power to draw any
10 inferences about how the product behaved in unstable
11 patients.
12 Should we then mandate a study in unstable
13 patients where you know you can find them, such as in
14 trauma, to get a feeling for the safety profile there,
15 knowing that there would be relatively rare cases of
16 unstable patients who are going through elective surgery? I
17 won't say that the panel answered the question, but there
18 was a lot of discussion about that. The next slide.
19 Should an oxygen therapeutic be evaluated in a
20 surgical setting with a high degree of patient risk to
21 assess whether those risks are increased by the use of the
22 product? Let me just go through a few comments by various
23 panel members, that only after evaluation in a controlled
24 clinical setting should the product be evaluated in less
25 controlled circumstances; but of course that evaluation in

1 trauma may be a better model for unstable surgical patients
2 than surgical studies themselves. There was a strong
3 sentiment that unless trauma is studied, an area with great
4 potential use for blood substitutes will not have been
5 studied. The next slide.
6 FDA has proposed that studies be powered for
7 safety as well as efficacy, and that safety endpoints should
8 be defined prospectively. If a sponsor is conducting a
9 single pivotal trial in a stable elective surgery situation,
10 what safety endpoints are most likely to predict adverse
11 events in patients at higher risk? Based on the available
12 safety data, what safety endpoints should be required?
13 There were strong statements from panel members
14 that a surgical study should include a wide range of
15 patients, all ages, and that it was important to look at all
16 different risk factors; that patients, many surgical
17 patients--basically, the study should not be studying
18 Olympic athletes who are going through surgery, but should
19 include older patients who have coexisting and often
20 undiagnosed diseases--diabetes, chronic obstructive
21 pulmonary disease, cardiac ejection fractions less than 25
22 percent, chronic liver disease, etcetera--that these should
23 be included.
24 The last slide, I believe--that was the last
25 slide. Then let me just summarize. During this elective

1 surgery discussion there was discussion of animal models,
2 and it was pointed out that there are stressed animal models
3 available such as a renal model or a spontaneous
4 hypertensive rat model, so that one can actually do your
5 preclinical work in stressed animal models.
6 Just a few comments from the panel members, that
7 it was stated that the product should be as safe as blood
8 because, after all, blood is numerically quite safe; that
9 the traditional number of subjects in drug trials is
10 typically 3,000, and that is not an FDA guidance but that is
11 just a comment from a panel member, and that panel member
12 said that there is a safe alternative to a blood substitute
13 product, and that is banked blood.
14 The product may not be safe in all environments.
15 It would be wise to study the product in all settings where
16 it is likely to be used. The product should be very safe
17 for use in elective surgery, especially where blood is
18 available. The endpoint in elective surgery, reduction or
19 elimination of allogeneic blood usage, one panel member
20 considered that to be a biased endpoint, basically in favor
21 of finding an effect of the product. And, finally, if
22 reduction of allogeneic blood use is the efficacy endpoint
23 for surgery, then investigators should try to include
24 patients with large volume blood loss to test the capacities
25 of the product.

1 So, I know these aren't any answers to the
2 questions, and that was not the intent of the workshop, but
3 it is a fascinating transcript. It was a very interesting
4 meeting, from a discussion from a large panel of experts.
5 Thank you.
6 DR. HOLLINGER: Thank you, Dr. Aebersold.
7 Any questions from the committee? Dr. Stroncek?
8 DR. STRONCEK: I would just like to encourage the
9 FDA to continue to hold--that I believe blood is very safe,
10 and we have worked hard to get it there, and any alternative
11 product should be held to the same high standard. And I
12 concur with the member of your panel who said any blood
13 substitute should be as safe and as effective as blood.
14 I would like to point out that while blood
15 supplies have been adequate, it appears that the demand is
16 starting to outstrip supply and there are shortages of
17 certain blood types. So if people are clever and look hard
18 enough, there may be surgical situations, particularly with
19 people with Rh negative blood or unusual phenotypes for
20 making allo antibodies, that they could really try a blood
21 substitute as a situation where people don't have blood
22 available.
23 DR. HOLLINGER: Yes, Dr. Fitzpatrick?
24 DR. FITZPATRICK: Well, I would just like to ask
25 what is going to become of the conference? Is there going

1 to be a summary document or a revised guidance, as was
2 discussed?
3 DR. AEBERSOLD: I think the answer to that is yes,
4 but I do not want to right here say any timetables.
5 DR. FITZPATRICK: Can you tell me which, whether
6 it is going to be a publication of a summary document, or is
7 it going to be a revised guidance?
8 DR. AEBERSOLD: It is our hope to have new
9 guidance. Since the transcript is available, I mean, a
10 summary is nice but the transcript is available on the web,
11 so everything that everybody said is there, and I think our
12 job is to try to pull together our understanding of that
13 workshop and incorporate that into a revised guidance, if we
14 need to revise our current guidance. And, as I said, our
15 current guidance is part of that workshop transcript.
16 DR. HOLLINGER: It sounds like it was a very
17 difficult workshop, particularly, I mean, a lot of questions
18 it sounds like were raised on the issues of safety and
19 efficacy but not much resolution it sounds like was found in
20 which way to proceed at this time. A difficult, difficult
21 situation.
22 DR. AEBERSOLD: Okay. Thank you.
23 DR. HOLLINGER: Thank you. The next workshop
24 update is on implementation of universal leukoreduction, a
25 very important issue that has been discussed at this

1 committee in the past. This will be discussed for us today
2 by Dr. Jong-Hoon Lee.
3 DR. LEE: Thank you, Mr. Chairman. I do not have
4 slides, in contrast to other speakers, so that should give
5 you a break in straining your eyes to read small print. I
6 would like to just take a few minutes to summarize our
7 recent Workshop on Universal Leukocyte Reduction, more
8 specifically the implementation of universal leukocyte
9 reduction.
10 The FDA sponsored a public workshop entitled
11 "Implementation of Universal Leukocyte Reduction" on
12 December 10, 1999 in Bethesda, Maryland on the NIH campus.
13 The workshop was intended to stimulate public discussion on
14 how best implement pre-storage leukoreduction as a routine
15 step, that is, universal leukocyte reduction in the
16 manufacturing of whole blood, red blood cells, and platelets
17 for human transfusion.
18 The FDA anticipated that the ideas and experiences
19 exchanged at the workshop may serve as a source of
20 information for the blood industry in planning for universal
21 leukocyte reduction, that is, industry providing guidance to
22 industry, as well as assisting the agency in formulating
23 regulatory recommendations. Speakers included
24 representatives from the academic community, the device
25 industry, the FDA, and the blood industry, who presented

1 information and opinions on the following major topics or
2 issues:
3 Firstly, the current use of leukocyte reduced
4 blood products in the United States; secondly, how
5 aggressively and according to what time frame pre-storage
6 leukoreduction should be recognized as a new blood
7 manufacturing standard in the United States; and, thirdly,
8 the experiences to date in the U.S. with respect to
9 implementing leukoreduction as a routine blood manufacturing
10 step.
11 An open panel discussion included critique of the
12 proposals to and by the FDA in formulating new regulatory
13 recommendations. As intended, the discussion focused on the
14 implementation of universal leukocyte reduction.
15 Scientific, clinical and economic aspects of universal
16 leukocyte reduction were discussed only to the extent
17 necessary to support a discussion about implementation
18 issues.
19 The following opinions emerged as the major points
20 to consider in drafting a future CBER guidance document on
21 universal leukocyte reduction. Point number one: Blood
22 centers should design their own specific implementation
23 plans within a general framework established by the FDA.
24 Point number two: Two years may be optimal as the FDA
25 recommendation on the time limit to full implementation of

1 universal leukocyte reduction.

2 Point number three: The current FDA
3 recommendations on quality control testing should be updated
4 to provide a higher level of assurance that blood
5 manufacturing complies with established leukoreduction
6 standards. And, point number four: A CBER guidance
7 document on leukocyte reduction to which applicants may
8 self-certify conformance in obtaining a licensure, in other
9 words, a pilot self-certification licensing program to be
10 substituted in lieu of the conventional license application
11 process, should facilitate the shipment of leukoreduced
12 blood across State lines without compromising public health.

13 Further, these opinions recognized that the
14 implementation of universal leukocyte reduction will, first,
15 contain the current haphazard use of bedside filtration and,
16 second, increase the demand for single donor platelets at
17 the expense of pooled random donor platelets recovered from
18 whole blood donations, unless pre-storage pooling of random
19 donor platelets is co-recognized as acceptable blood GMP.

20 Leukocyte reduction is increasingly being regarded
21 as blood GMP rather than as the practice of medicine, as it
22 was once recognized when leukocyte reduced blood components
23 were initially introduced. Insufficient reimbursement, not
24 necessarily excessive cost, remains as the primary obstacle
25 against the rapid implementation of universal leukocyte

1 reduction as a new blood GMP standard.

2 Efforts are ongoing at the DHHS level to
3 coordinate the issuance of new regulatory recommendations
4 about universal leukocyte reduction by the FDA with the
5 related activities at the Health Care Financing
6 Administration, so that the implementation of universal
7 leukocyte reduction indeed enhances the overall quality and
8 ability of patient transfusion support, as intended by the
9 FDA, without introducing indirect adverse effects.

10 I might add that the participants at the
11 Implementation of Universal Leukocyte Reduction Workshop of
12 course consisted largely of those members of the transfusion
13 community that supported universal leukocyte reduction, and
14 I might add that the points that emerged as the major
15 consensus points reflect those that are already in favor of
16 the policy.

17 Subsequent to the workshop, however, there has
18 been what appears to be a barrage--it may be an
19 overestimation, or over-representation by the few--but
20 nonetheless a series of written, formal written
21 communications, e-mail communications, phone communications
22 against the policy, as well. The activity post-workshop
23 underscores the basic controversy behind the policy, but
24 this does not change the FDA position in favor of moving
25 ahead with implementation, but does indeed complicate the

1 decisions discussed at the workshop, that is, the optimal
2 timing to implementation.
3 I think I will reserve my comments to that, and
4 entertain any questions if there are any.
5 DR. HOLLINGER: Yes, Dr. Simon?
6 DR. SIMON: I don't know if you are at liberty to
7 answer this, but at this point do you anticipate that there
8 will be formal rule-making, that is, will be regulations
9 which will make it required that all red cells be leukocyte
10 reduced, and all platelets?
11 DR. LEE: I anticipate that there will be first a
12 guidance document, and the experience under the guidance
13 document will probably dictate whether we move to formal
14 rule-making.
15 DR. HOLLINGER: Can you elaborate a little bit
16 more on, you said you had a lot of e-mails and other things
17 coming in. Where were these emanating from, primarily? I
18 mean from blood banks or from outside interests or things of
19 that nature. And what sort of were the substance of them?
20 DR. LEE: The originators of the communications
21 against the policy consisted primarily of academic
22 transfusion medicine specialists, and the overall number is
23 unclear because all of the communications appeared very
24 similar with each other.
25 DR. HOLLINGER: Sort of like "write to your

1 Senator" or something like that, huh?
2 DR. LEE: Presumably the numbers are still large
3 behind those communications. And the issue primarily
4 consisted of the fact that not all patients require
5 leukoreduced blood, and that this still remains best as the
6 practice of medicine rather than as blood manufacturing, and
7 therefore that FDA should probably not move forward as
8 rapidly as we intend to.
9 DR. HOLLINGER: Yes? David Stroncek.
10 DR. STRONCEK: Again, I would like to encourage
11 the FDA to move rapidly, you know. And one good thing about
12 academics is, we have a lot of bright minds. One bad thing
13 is, you hear every opinion across the spectrum.
14 And as an advocate of universal leukocyte
15 reduction, I think the current situation is very difficult
16 in that there is all kinds of different bags, and as we move
17 in an academic setting to go to all universal leukocyte
18 reduction, as we try new machines, there are bags available
19 with filters and without, and all that makes things very
20 costly. And it is costly for physicians and nurses and
21 staff in blood banks to sort out who gets the leukocyte
22 reduced blood, who doesn't. So I think if we move forward,
23 these economic--the price will go down, and it will not be
24 such an economic barrier, and it will be easier for all of
25 us.

1 DR. HOLLINGER: Dr. Epstein
2 DR. EPSTEIN: Yes, just a few comments. First of
3 all, this was a mass mail campaign in that we received
4 identical letters from numerous correspondents. On the
5 other hand, we certainly read the comments and are attentive
6 and understand the importance of the issue to those who
7 write in. It is the policy of the agency, however, not to
8 respond to a mass mail campaign, and so there will in all
9 likelihood not be individual responses to those persons who
10 wrote in.
11 The policy issue on universal leukoreduction, of
12 course, has been debated in an open public meeting. For
13 those who were not in attendance in September 1998, it was
14 well recognized by the agency and the discussants that there
15 was a large range of scientific views about the benefits and
16 potential risks of universal leukoreduction above and beyond
17 specific settings where benefits were established. But
18 there was a very strong recommendation by the committee, six
19 votes in favor and three abstentions, whether we should move
20 toward universal leukoreduction on the scientific merit.
21 And let me comment parenthetically that we did not
22 bring to the committee at that time the question whether
23 there was scientific benefit for theoretical reduction of
24 risk from transmissible spongiform encephalopathies. That
25 question still hangs in the air, and we will bring it to a

1 future scientific advisory committee. But, the issue of TSE
2 notwithstanding, it was the strongly held view of at least
3 one advisory committee on that occasion that overall the
4 aggregate benefits warranted moving toward universal
5 leukoreduction, leaving the FDA with the question of how
6 fast should we move and how do we address the implementation
7 issues, which are formidable.

8 Blood centers have to create adequate facilities
9 in which to do leukofiltration or leukoreduction by other
10 means like aphoresis. There is some sense that there is a
11 need for more products on the market, such as leukoreduction
12 filters. There is the issue of moving leukoreduction into
13 the blood center as opposed to the bedside. There is the
14 issue of defining the current scientific standard to define
15 adequate procedures, and product standards for the
16 leukoreduced product. And of course underlying all of that
17 is the unresolved issue of reimbursement.

18 Now, as was made very clear, reimbursement is not
19 FDA's issue per se. On the other hand, the Department of
20 Health and Human Services, of which HCFA is a component, is
21 very mindful of that issue and has been working very
22 aggressively to try to develop a solution whereby the costs
23 can be properly passed through to sources of reimbursement.

24 We think that we need to continue to move in this
25 direction, that it is an appropriate quality standard for

1 the products, indeed for non-leukocyte products. In other
2 words, for products whose effectiveness is based on
3 containing the leukocytes, that the leukocytes are of no
4 benefit otherwise to the product.
5 And I don't think that there is a lot of debate on
6 that point. The point that is being debated is whether the
7 effects of leukocytes are tolerable except in certain
8 patient groups, and so the argument would be that if there
9 no need for them to be there and if they can cause adverse
10 effects, they are better removed.
11 So that is why we feel that the issue has moved
12 into a domain of defining a product standard along the lines
13 of GMP, rather than defining a clinical use standard, which
14 is where the matter is now in the clinical domain. So I
15 think that Dr. Lee correctly states that it remains FDA's
16 point of view that we should move our system toward that
17 end.
18 And I think it is worth commenting that at least
19 one large entity, namely the American Red Cross, has
20 committed itself to move toward universal leukoreduction,
21 suggesting that there are private sector solutions for these
22 implementation issues. Nonetheless, we do want to allow
23 sufficient time and sufficient thought to be applied to the
24 implementation issues so that we can have a smooth
25 transition.

1 So, again, we remain open to input through public
2 statements, correspondence, academic publications and other
3 communication, but those who have written in in the form of
4 a mass mailer should not be expecting individual responses
5 from the agency.
6 DR. HOLLINGER: Thank you, Jay.
7 Yes, Mark? Dr. Mitchell?
8 DR. MITCHELL: Can you tell me what the discussion
9 was about, surrounding the decision to move toward self-
10 certification?
11 DR. LEE: Oh, FDA of course is in favor of that,
12 and in fact a pilot program for self-certification has
13 already been implemented in small pieces, and the FDA's
14 intent was to add the leukoreduction piece to that overall
15 program of self-certification for licensure. How to
16 implement that exactly still remains to be resolved, but it
17 will probably be issued in the form of a guidance entitled
18 specifically as a pilot licensing program on how to self-
19 certify, in other words, a set of criteria, more or less
20 some licensing criteria that are written down in a guidance
21 document to which you simply refer to and self-certify.
22 DR. MITCHELL: My question was, you know, how do
23 you determine whether somebody is--why would you decide that
24 this is an appropriate condition under which groups should
25 self-certify, as opposed to being more tightly regulated?

1 DR. LEE: This is an effort to expedite the
2 ability of blood centers to ship leukoreduced blood
3 components across State lines, in other words, to obtain
4 licensure. And it is FDA's intent to verify correct self-
5 certification at inspections on follow-up.
6 DR. HOLLINGER: I am going to take one more
7 question. Dr. Stroncek?
8 DR. STRONCEK: I am not familiar with this pilot
9 program, but in answer to your question, I would assume that
10 you are talking about very standardized products and systems
11 that are developed to deliver a leukocyte-depleted product.
12 So if the manufacturer is selling you this, and this is what
13 it is supposed to do, and I think if you are a blood bank
14 and FDA comes with criteria, you can say, "Well, you tested
15 so many of these and they perform as the manufacturer said,"
16 then I think that self-licensure would make some sense. Is
17 this what you are proposing?
18 DR. LEE: Yes.
19 DR. EPSTEIN: I just want to put this in context.
20 You know, we have presented to the committee several times a
21 blood action plan which was started in July '97, antedating
22 the leukoreduction question. And one of the concepts of
23 regulatory reinvention that was put forward was that for a
24 well-standardized blood product such as certain blood
25 components, it would be possible to move to a model where we

1 generated monographs that become additional specific product
2 standards in the Code of Federal Regulations, against which
3 a blood establishment could certify compliance and then be
4 licensed on that basis. So this is a regulatory reinvention
5 concept which has already been applied in several pilots.
6 In terms of validating the pilot, we still do pre-
7 approval inspecting, and that is how we will determine
8 whether there was actual compliance against stated self-
9 certification. And only if we find that the industry is
10 able to maintain compliance with standards promulgated in
11 that way, will we move forward to putting forth more
12 licensing protocols on that model. So this wasn't invented
13 for the leukoreduction issue. However, we have recognized
14 that if we can do a pilot program on leukoreduction, it
15 would create the opportunity for entities to become very
16 quickly approved.
17 DR. HOLLINGER: Okay. Thanks, Jay.
18 We are going to move on, then. Thank you, Dr.
19 Lee.
20 DR. LEE: Thank you.
21 DR. HOLLINGER: The next workshop update will be
22 by Dr. Tom Lynch on the workshop on Parvovirus B19.
23 DR. LYNCH: Good morning. Last December the
24 Division of Blood Diseases and Resources at the Heart, Lung
25 and Blood Institute organized a workshop on Parvovirus B19

1 to consider what implications this virus had for transfusion
2 medicine. The organizers of the conference, George Nemo,
3 Luis Barbosa, and Barbara Alving, assembled a panel of
4 medical and scientific experts in this virus and in
5 transfusion medicine to consider a broad range of topics
6 touching on all relevant aspects of Parvovirus B19.
7 In particular, the workshop focused on four
8 questions: the prevalence of virus in blood donations; the
9 frequency with which the virus is transmitted by
10 transfusion; the clinical consequences to the recipients of
11 those transfusions of an infection; and what potential value
12 screening of blood donations for this virus might have. The
13 workshop was not charged with making any formal findings or
14 recommendations. However, there were several areas in which
15 a consensus appeared to emerge.
16 First of all, the infectivity of B19 that may be
17 present in transfusable blood components is not completely
18 understood, nor is the ability of antibodies that might also
19 be present in those components to neutralize the virus fully
20 understood, either. There is, however, little evidence of
21 widespread morbidity associated with the transmission of
22 this virus through transfusion, although the frequency with
23 which such transmissions occur could easily be
24 underestimated because of the asymptomatic nature of most
25 infections and the possibility of misdiagnosing transient

1 anemias and reticulocytopenias.

2 Presently there is insufficient clinical evidence
3 to warrant the introduction of universal testing of blood or
4 transfusable components for this virus, and if testing were
5 to be introduced, it would make more sense to focus such
6 testing on units that are destined for high-risk
7 individuals, such as seronegative pregnant women and the
8 immune compromised patients. And there was a clear call for
9 additional research into the significance of this virus,
10 particularly in the setting of transfusion medicine.

11 Now, despite the focus of this workshop on blood
12 and blood components, I was asked to make some remarks on
13 Nucleic Acid Testing in the context of plasma for further
14 manufacturing. I summarized the recommendations that this
15 committee made last September, that such testing could be
16 introduced as an in-process control over the manufacture of
17 plasma derivatives, and I gave some background into the
18 reasons for that decision.

19 I also took the opportunity to discuss some
20 preliminary thoughts the agency has on how such a test would
21 be adequately validated for the purpose of licensure. As
22 you know, the agency has published guidance on Nucleic Acid
23 Testing of other viruses such as HIV, and we think, with the
24 possible exception of the clinical validation of such
25 testing, most of this guidance should apply to Parvovirus as

1 well.

2 However, a working group within OBRR that has been
3 considering standards for such tests has identified two
4 areas in assay valuation that may need modification in order
5 to be applied effectively to Parvovirus testing, and those
6 are the determination of preclinical sensitivity and
7 specificity. I thought I would share these thoughts with
8 you, as well.

9 In outline, we think that a determination of
10 preclinical specificity of a nucleic acid test for
11 Parvovirus B19 should include two components. One would be
12 the testing of individual donations, randomly selected, for
13 the virus, and confirming any positive results that are
14 obtained during the screening. Confirmation should be by
15 both repeat testing and by a separate, different
16 confirmatory test. The titer of any positive unit so
17 identified should also be determined.

18 The study should then move on to testing in
19 minipools, which we think is the most likely mode of
20 implementation, and that segment should include a total of
21 100,000 plasma donations included in these minipools.
22 Again, any positive test should be confirmed, and a positive
23 result in a minipool should be traced back to an individual
24 unit whose positivity should also be confirmed and titered.

25 The second area is determination of preclinical

1 sensitivity. This might involve the testing of 20 or more
2 known positive donations. The availability of such
3 donations is becoming more and more widespread, so there
4 should be no difficulty in obtaining material for such
5 testing. And, again, a determination of viral titer in
6 these units should be performed.
7 That testing would then move on to the minipool
8 stage. This would be the same 100,000 donations tested in
9 the specificity segment, confirming any positive results,
10 tracing back and confirming the positive units that are
11 responsible for the positive results in the minipool, and
12 determining titers on both the minipool and the individual
13 unit.
14 And, finally, we thought it was important that
15 some objective standard for effectiveness be established,
16 and because the objective of this test is to cap the viral
17 contamination in the manufacturing pool, we thought that
18 such a standard should focus on the manufacturing pool.
19 Tentatively, based on a number of considerations, a viral
20 titer of 10 to the 4th genome equivalents per mL is an
21 initial proposal that we would consider at this time.
22 But I want to caution everyone that the data on
23 which such a number is based has not been confirmed as
24 strictly quantitative. There is an effort going on now, in
25 cooperation with laboratories at CBER and the NIBSC in the

1 United Kingdom, to establish international standards for
2 Parvovirus B19 DNA on which such quantitative tests can be
3 accurately calibrated, and until that is accomplished, a
4 hard number can't be set.
5 I think that is all I have to say. I will take
6 any questions, if there are any.
7 DR. HOLLINGER: Thanks, Tom.
8 Questions for Dr. Lynch? Yes, Dr. Fitzpatrick?
9 DR. FITZPATRICK: Dr. Lynch, what is the current
10 thoughts on what a confirmatory test after a repeat positive
11 is?
12 DR. LYNCH: Well, one good example might be
13 repeating the PCR reaction but with a different set of
14 primers directed to a different segment of the genome. That
15 would satisfy the requirement, for example.
16 DR. HOLLINGER: And, Tom, what again is the
17 prevalence of positive samples in donor population, and the
18 incubation--and the period of time that you find the virus
19 in the blood?
20 DR. LYNCH: Well, that, both numbers vary
21 considerably. The prevalence of a positive reaction would
22 depend on how sensitive the test is, of course. The titers
23 can range from very low to truly astronomical numbers, 10 to
24 the 14th, I have heard. The estimates from screening
25 efforts that have been done so far with large numbers of

1 plasma donations have ranged from a low of 1 in 30,000 to a
2 high of greater than 1 in 1,000.
3 Again, I think this variability has to do with the
4 sensitivity of the testing that these various studies
5 employed, but also the highly cyclical nature of infections
6 in the general population. We would, applying these numbers
7 to the numbers given here, for instance, on a validation
8 study, we would expect a significant number of positives to
9 show up in the minipool segment of this screening, but
10 relatively few in the single donor, random donation section.
11 DR. HOLLINGER: I guess that is really why I
12 asked, because you only had 500.
13 DR. LYNCH: Yes. Bear in mind that specificity
14 testing is really to determine what the frequency of false
15 positives are.
16 DR. HOLLINGER: The other thing is, it also has a
17 fairly short period of time that the virus is in the blood,
18 isn't that correct?
19 DR. LYNCH: Yes, at least at high titers, usually
20 a week or so for the acute viremic phase. However, as more
21 sensitive tests have been brought to bear on clinical
22 samples following acute infections, there are low residual
23 levels of DNA that can be detected six months or more after
24 an acute infection. Those titers are very low, and we
25 frankly don't know whether a reaction like that indicates

1 the presence of infectious virus.
2 DR. HOLLINGER: Or it could, but complex with
3 antibody and therefore not infectious at that point.
4 Yes?
5 MR. GABRINSKI: Nathan Gabrinski, North Dakota.
6 Would there be any point in looking at non--
7 DR. HOLLINGER: Could you just grab one of those
8 microphones there just a minute, and again state your name
9 and--
10 MR. GABRINSKI: Nathan Gabrinski from North
11 Dakota. Just wondering about the clinical significance, to
12 get a handle on the clinical significance of Parvo, whether
13 there would be a way of getting a sense of the number of
14 non-immune fetal hydrops cases that are Parvo positive,
15 because this may be a bigger problem than we realize in the
16 pregnancy situation.
17 DR. LYNCH: I think there is at least preliminary
18 data on that point that does suggest a very high frequency,
19 something like 10 percent of the infections during the
20 second trimester, may end up having severe consequences on
21 the fetus, hydrops fetalis being of course the most dramatic
22 of those.
23 DR. HOLLINGER: Oh, yes, Dr. Stroncek?
24 DR. STRONCEK: Last time you presented this, you
25 talked about when you start to use this for clinical--well,

1 not clinical testing but actually screening out plasma units
2 in pools, that you may ask manufacturers to go back and
3 identify positive units, positive donors?
4 DR. LYNCH: Right. There is an important
5 distinction to make here. Thank you for asking this.
6 The proposal that we made last September did not
7 require, in the ordinary application of the testing, a
8 manufacturer to trace back a positive unit and notify an
9 individual donor. That was one of the threshold questions
10 that this committee addressed. However, because there is a
11 need to confirm a result that you obtain in a minipool as
12 being truly positive or falsely positive, there is a
13 necessity during validation to trace back and identify the
14 positive unit.
15 DR. HOLLINGER: Okay. Thank you. Toby, last
16 question.
17 DR. SIMON: What is the status of your
18 expectations by the agency on industry? Are you
19 anticipating this is now GMP, or is this something you are
20 just investigating?
21 DR. LYNCH: We have not drawn any such conclusion
22 today. We believe that there is a strong internal
23 motivation within the industry to implement such testing,
24 because of the acknowledged transmissions of B19 by some
25 manufactured products derived from pooled plasma.

1 Anticipating that desire to implement this testing, we are
2 trying to establish the regulatory context in which that
3 would be done.
4 DR. SIMON: So as of right now, it is not a
5 requirement, but you are setting up what you would expect to
6 see in terms of validation and--
7 DR. LYNCH: That's correct.
8 DR. SIMON: --when you inspect the facilities.
9 DR. HOLLINGER: Thank you, Dr. Lynch.
10 This completes the committee updates, and we are
11 now going to move on to another topic which is going to be a
12 very interesting, I think, and a lively discussion here on
13 indeterminate HIV Western blots with only non-viral bands.
14 Now, there are several speakers who are already
15 assigned to speak, plus several individuals who have asked
16 to speak during the open public hearing, so I am going to
17 ask the speakers that have been assigned here to try to
18 limit their remarks to about 10 to 12 minutes at the most.
19 So we want you to take your best shot at what information
20 you have so we can get to the meat of the issue on this
21 important topic.
22 And to sort of give us an introduction and
23 background into what we are going to be discussing today and
24 what the issues are, we have asked Dr. Mied to provide this
25 to us. Paul?

1 DR. MIED: Thank you, Dr. Hollinger.

2 Recently, Genetic Systems Corporation of Redmond,
3 Washington submitted to FDA a product license application
4 supplement for their licensed Western blot kit, requesting
5 that serum or plasma samples that show only non-viral bands
6 be reported as negative instead of indeterminate. There are
7 four licensed HIV-1 Western blots currently being
8 manufactured. For consistency, approval of such a change in
9 interpretive criteria for one kit should be carried over as
10 a labeling change for all four Western blot kits.

11 In FDA's response to Genetic Systems regarding
12 this supplement, FDA requested data demonstrating that this
13 revision would not result in a risk of an indeterminate blot
14 from a seroconverting donor being interpreted as a negative
15 blot, that is, indicating the donor is not infected with
16 HIV. Now, in order to address the question of whether to
17 allow a negative interpretation for a Western blot with non-
18 viral bands only is appropriate, the data supporting the
19 scientific argument for the change and the benefit to the
20 donors must be weighed against the concern for a potential
21 public health problem that may result from this change in
22 blot interpretation.

23 In an MMWR of July 21st, 1989 entitled
24 "Interpretation and Use of the Western Blot Assay for
25 Serodiagnosis of Human Immunodeficiency Virus Type 1

1 Infections," the Public Health Service recommended the use
2 of the CDC/ASTPHLD criteria for blot interpretation. These
3 criteria are, for a blot to be interpreted as positive, any
4 two of the following bands must be present: p24, gp41, or
5 gp120/160.
6 The virus specific bands on the HIV-1 Western blot
7 are: p17 and p24, gag or core proteins; p31, the
8 endonuclease component of the polymerase translate; gp41,
9 transmembrane envelope glycoproteins; p51 and p66, reverse
10 transcriptase components of the polymerase gene translate;
11 p55, a precursor of gag or core proteins; gp120, the outer
12 envelope glycoprotein; and gp160, a precursor of the
13 envelope glycoprotein. These are the virus specific bands
14 on the HIV-1 Western blot.
15 And here are the three bands, p24, gp41, and
16 gp120/160, two of which are required for a blot to be
17 interpreted as positive. The presence of any band or bands
18 that fail to meet the criteria for a positive blot results
19 in an indeterminate interpretation, and for a sample to be
20 reported as negative, there must be no bands at all visible
21 on the blot. This includes the absence of any non-viral
22 bands that often appear on Western blots, usually as very
23 narrow bands at defined molecular weights.
24 In most cases, non-viral bands result from the
25 binding of certain antibodies in the individual serum to

1 contaminating cellular proteins on the Western blot strip,
2 and these are byproducts of the production of the whole
3 viral lysate that is used in the manufacture of the strips.
4 Currently, the package inserts for all four licensed Western
5 blots state that the criterion for a negative blot is no
6 bands present or the absence of any band reactivity.
7 Non-viral bands on a Western blot are to some
8 extent kit specific. For the Calypte HIV-1 Western blot
9 kit, the non-viral bands most commonly seen are bands above
10 gp120/160, p70, p7, and p5. For example, here is a non-
11 viral band above gp120/160. And here is a very nice example
12 of a non-viral p70 band on a blot interpreted as
13 indeterminate that is otherwise a clean negative. And here
14 are some typical p7 or p5 non-viral bands.
15 For the Bio-Rad Novapath HIV-1 Immunoblot, the
16 non-viral bands are a thin p110, a p90, and occasionally p70
17 or p40. For the Genetic Systems HIV-1 Western blot, p42 is
18 the most frequent non-viral band. For the Organon HIV-1
19 Western blot kit, they are p70, gp45, and p14.
20 If a repeatedly reactive donation is Western blot
21 indeterminate due to the presence of non-viral bands or
22 viral bands that do not meet the criteria for positive blot
23 interpretation, the donor is deferred indefinitely and is
24 currently not eligible for reentry. The donor is counseled
25 that there is a chance that they are infected with HIV, and

1 that they should receive follow-up testing.

2 Now, if the Western blot pattern is stable for six

3 months, they are reassured that they are almost certainly

4 not infected with HIV-1, but will remain deferred

5 indefinitely because of their test results. Since

6 essentially all HIV-infected persons with initial

7 indeterminate Western blot results will develop detectable

8 HIV antibody within one month, this six month time period

9 may soon be shortened.

10 There is a draft PHS guideline on HIV counseling,

11 testing and referral, that proposes to recommend that

12 persons with an initial indeterminate Western blot result be

13 retested for HIV infection at least one month after the

14 first indeterminate result, and that persons with continued

15 indeterminate Western blot results after one month are

16 highly unlikely to be infected and may be counseled as such.

17 So, in essence, these donors will be told that they are not

18 infected but that they would remain indefinitely deferred

19 from donating blood because their Western blot was

20 interpreted as indeterminate.

21 Now, there is some good news on the horizon for

22 donors that are deferred indefinitely because of

23 indeterminate blots. In June 1996, FDA presented to the

24 Blood Products Advisory Committee a modified algorithm to

25 reenter donors who have an indeterminate HIV-1 Western blot,

1 whether that is due to viral or to non-viral bands. This
2 revised algorithm was based on data that showed that the
3 vast majority of indeterminate patterns do persist, and
4 represent uninfected individuals.

5 By the new HIV reentry algorithm, which was
6 endorsed unanimously by the committee but has yet to be
7 recommended by FDA due to the continued absence of an EIA
8 approved for sensitive detection of HIV-1 group O, donors
9 with indeterminate blots, whether due to viral or non-viral
10 bands, eventually could be reentered if their subsequent
11 sample and then donation are EIA negative, without even
12 running a Western blot.

13 What would be the impact of a change in the
14 interpretation of non-viral band only Western blots from
15 indeterminate to negative?

16 It has been reported that approximately 14 percent
17 of all indeterminate Western blots have non-viral bands
18 only. Since all indeterminates represent about 45 percent
19 of repeatedly reactive samples, if you multiply these two
20 together, approximately 6.3 percent of repeatedly reactive
21 samples are non-viral band only indeterminates. Out of 12
22 million donations nationwide per year, with a repeatedly
23 reactive rate of approximately 0.09 percent, about 700 non-
24 viral band only indeterminate donors per year are currently
25 deferred indefinitely because of their indeterminate blot

1 results.

2 Now, as for all other indeterminate blots, these
3 donors are given a counseling message that there is a chance
4 that they are infected with HIV, and that they should get
5 retested. If Western blots that exhibit non-viral bands
6 only were to be interpreted and reported as negative, the
7 donors could be reentered using the current reentry
8 algorithm, if a subsequent sample is negative on the EIA and
9 on a Western blot.

10 However, it has been reported that due to
11 persistent repeatedly reactive results on the EIA, in
12 reality less than 10 percent of all donors for which reentry
13 is attempted are actually reentered and eligible for future
14 donation. Thus, the major benefit of interpreting the
15 Western blots for these 700 or so donors per year as
16 negative, is that they would receive a counseling message
17 that says they are not infected with HIV, rather than donor
18 reentry in a small number of cases.

19 It should be pointed out that there are some other
20 aspects of this issue that I ought to mention in considering
21 whether a change in interpretation of non-viral band only
22 Western blots is appropriate. In the event of a repeatedly
23 reactive EIA screening test, regardless of the Western blot
24 result, the current donation is discarded, so there would be
25 no danger to a recipient that would result from any change

1 in this blot interpretation policy.

2 Now, in this session we are going to hear
3 statements that reflect the widely held belief that such a
4 change to the policy of interpreting non-viral band only
5 Western blots does not represent a public health concern
6 that the wrong counseling message could be given to the
7 donor or the patient. In this session we will see that
8 early seroconverters routinely exhibit specific viral band
9 patterns such as a p24 band and a weak gp120/160 band, and
10 that these patterns are readily identifiable without
11 confusion due to non-viral bands.

12 We will also hear that non-viral bands, for
13 example p70, should not be required to be reported because
14 no individual exhibiting non-viral bands has been associated
15 with either early seroconversion or detection of different
16 HIV-1 subtypes or any other disease agents. The recent
17 introduction of Nucleic Acid Testing or NAT provides an
18 added layer of safety in the event the donor is a
19 seroconverter with an indeterminate Western blot.

20 Currently the industry estimates that 99 percent
21 of all blood donations in the U.S. are being screened by NAT
22 for HIV-1 RNA using minipool testing of serum from those
23 donations. Small pool sizes, such as 16- and 24-unit pools,
24 are being used, so NAT testing does have the high
25 sensitivity to provide added assurance that a donation from

1 a seroconverter will be interdicted and the appropriate
2 counseling message provided to the individual. I should
3 point out that, as with all available test results, results
4 from NAT testing are of value in counseling, and in fact
5 they are currently being used in determining how to counsel
6 the donor.
7 However, we will also hear concerns this morning
8 that there is a danger of non-viral band only blots being
9 misinterpreted by small volume testing laboratories whose
10 personnel may not be proficient in interpreting Western blot
11 patterns. Specifically, concern exists that a viral band
12 such as a p65 may be misread as a non-viral p70, or an
13 uncharacteristically thin gp41 viral band may be misread as
14 a non-viral p42 band, and as a result the blot
15 misinterpreted as negative.
16 It should be pointed out that the occurrence of
17 blots that exhibit those bands only, without any other bands
18 present, is reportedly extremely rare. This concern
19 regarding possible misinterpretation of blots could be
20 alleviated by focusing on effective training and proficiency
21 testing of new or inexperienced Western blot users.
22 Now, to address this need for training and
23 education in blot testing and interpretation, the Human
24 Retrovirus Testing Committee of the Association of Public
25 Health Laboratories, or APHL, just last week adopted a draft

1 recommendation that states, and I quote: "It is imperative
2 that the National Laboratory Training Network, or NLTN,
3 immediately establish training in the performance and
4 interpretation of Western blots, especially for new or
5 inexperienced laboratorians."
6 An additional concern has been raised that an
7 HIV-1 Western blot for an individual infected with HIV-2
8 that shows viral HIV-2 bands could be misinterpreted as
9 negative. However, blots from individuals infected with
10 HIV-2 usually show both gag and pol bands, and would at
11 least be interpreted as indeterminate on an HIV-1 blot.
12 And so in considering the question of whether to
13 permit HIV-1 Western blots with only non-viral bands to be
14 interpreted as negative, we are faced with a scientific
15 argument and a potential benefit to donors that must be
16 weighed against a potential public health concern. The
17 scientific argument is that individuals with non-viral band
18 only Western blots are not infected with HIV. The benefit
19 to non-viral band only donors would be that they would be
20 counseled that they are not infected with HIV. The public
21 health concern is that indeterminate blots with viral bands
22 may be misinterpreted as negative by new or inexperienced
23 Western blot users, and an incorrect counseling message
24 given to the donor or the patient.
25 A trained individual can readily distinguish a

1 non-viral banding pattern and interpret the blot as
2 negative. However, with the possibility of less experienced
3 individuals misinterpreting the blot, the question is, is it
4 better public health practice to take the conservative
5 approach and counsel the donor that the blot was
6 indeterminate and perform the follow-up testing, or to
7 notify the donor that the test was negative?
8 As I conclude, I would like to mention a possible
9 middle ground approach whereby the counseling message could
10 be stratified based on the band pattern. That is, different
11 counseling messages that reflect the likelihood of
12 infection, along with the recommendation to be retested,
13 could be provided to donors with indeterminate blots with
14 viral bands present and to donors with indeterminate blots
15 with viral bands absent.
16 There are some questions that we have for the
17 committee, Dr. Hollinger, if I could go through those. We
18 will be asking the committee, first of all, should FDA
19 permit indeterminate blots with only non-viral bands to be
20 interpreted as negative?
21 Secondly, if not, should blot interpretations such
22 as "Indeterminate (Viral Bands Present)" and "Indeterminate
23 (Viral Bands Absent)" be reported with distinct counseling
24 messages?
25 And thirdly, of course, does the committee see the

1 need for additional studies?

2 Thank you.

3 DR. HOLLINGER: Thank you very much, Paul.

4 Yes, Toby? Let's limit our questions just

5 specifically to the person speaking here today, because we

6 are going to have lots of other things that may answer some

7 of your questions. But go ahead, Toby.

8 DR. SIMON: Yes. I just always want to clarify

9 that, you are talking about the 12 million blood donations,

10 remember there is 11 million plasma donations, so your

11 number of affected people is greater than the 700.

12 DR. MIED: Yes.

13 DR. HOLLINGER: Dr. Chamberland?

14 DR. CHAMBERLAND: Paul, I just wanted to also

15 clarify or make sure it was clear, although the question and

16 the discussion is largely being framed in the context of the

17 blood donation setting, consideration of blood and plasma

18 donors, in point of fact the question really applies to a

19 much broader population. It is essentially all people that

20 are being tested for HIV in many different settings, ranging

21 from the very low risk setting of blood and plasma donations

22 to much higher risk settings, namely people being tested in

23 anonymous testing and counseling sites, STD clinics,

24 etcetera. So these questions for the committee to consider

25 really extend across all these populations. There really

1 has to be only one interpretation and one counseling
2 message.
3 DR. MIED: That is absolutely correct, Mary.
4 These questions have implications not just in the donor
5 setting but in the diagnostic setting as well, and I should
6 point out that that, the diagnostic setting, is where the
7 focus of concern about possible misinterpretation of blots
8 is, by new or inexperienced users.
9 DR. HOLLINGER: Thanks, Paul.
10 Yes, Dr. Schmidt?
11 DR. SCHMIDT: I am asking for clarification in
12 terminology as it evolves. We have reactive and non-
13 reactive and repeatedly reactive. That is one category of
14 stating things. And then we have positives and negatives
15 and indeterminate, and that is applied to another group of
16 tests. And I think all of this relates to the other
17 terminology, which is that of supplementary versus
18 complementary, and I think we can't really--I think it
19 should be clarified. I notice in your writing you have one
20 term that is "EIA negative" which I think is not allowable,
21 but we need a glossary.
22 DR. MIED: Right. Strictly speaking, in the EIA
23 screening test, the interpretations of the results are
24 reactive or non-reactive. Reactive samples go on to be
25 retested in duplicate. Should one or both of those

1 duplicate retests be reactive in the repeat test, the sample
2 is termed "repeatedly reactive."
3 When you switch over from screening to
4 supplemental tests or additional, more specific tests such
5 as the Western blot, the interpretations of those tests are
6 positive, indeterminate, or negative.
7 DR. SCHMIDT: And supplementary versus
8 confirmatory, please?
9 DR. MIED: We are using them in a similar manner.
10 DR. SCHMIDT: Similar? It means the same thing?
11 DR. MIED: Yes, although we don't use the term
12 "confirmatory." Strictly speaking, we are calling them
13 supplemental tests.
14 DR. SCHMIDT: Okay.
15 DR. HOLLINGER: Thanks, Paul.
16 Yes, Dr. Fitzpatrick?
17 DR. FITZPATRICK: Somebody else may answer this,
18 Paul, but you used two terms, one when you were talking
19 about viral bands being interpreted as non-viral, that it is
20 "extremely rare," and when you talked about the HIV-2
21 appearing as an indeterminate on an HIV-1 blot as "usually
22 small." Is someone going to be able to quantitate those, or
23 is that just an estimate?
24 DR. MIED: I think we will hear some data to that
25 effect. For HIV-2, an HIV-2 infected individual, when you

1 run a Western blot, an HIV-1 Western blot on them, you see
2 several bands, and it is usually a characteristic pattern
3 that can be identified as an HIV-2. Specifically, what you
4 see are several bands in viral band locations, and so the
5 bottom line there is that there is little danger of
6 misinterpreting that blot and calling all of those non-viral
7 and hence interpreting the blot as negative.
8 Your earlier, your first question was regarding
9 the interpretation of viral bands as non-viral. There are
10 some specific examples of concerns that I cited, where a
11 viral band could be misinterpreted as a non-viral, and I am
12 pointing out that anecdotally those patterns that we see,
13 when we see those bands existing by themselves where they
14 could be interpreted as non-viral, those are extremely rare.
15 DR. HOLLINGER: Yes, Mr. Rice?
16 MR. RICE: It seems that the indeterminate bands
17 or the bands that seem to be in prevalence are almost test
18 kit specific. Certain bands seem to show up with certain
19 test kits.
20 DR. MIED: The non-viral bands are, yes.
21 MR. RICE: Would this be just making things more
22 complicated, or something that would be adaptable, that the
23 indeterminates, so long as they are consistent with that
24 particular test kit's performance on constantly showing
25 these indeterminate bands, to be more along the line of

1 considering that a negative test, as opposed to simply
2 saying any test kit period, but be more specific to that
3 particular test kit's unique profile or specificity of
4 showing the same bands coming up?
5 DR. MIED: Yes. Should this change in
6 interpretation generally be adopted, we would need to have
7 specific instructions in each of the package inserts for the
8 four different Western blots, that these are the non-viral
9 bands you typically see with this kit, and they would be
10 different for each of the kits.
11 DR. HOLLINGER: Thank you very much, Paul, for the
12 good summary.
13 We are going to now, the next topic is on data
14 from clinical studies. Mr. Christopher Bentsen from the
15 Genetic Systems Corporation is going to give us a
16 discussion.
17 MR. BENTSEN: Good morning. My name is
18 Christopher Bentsen, and I am the head of Regulatory
19 Affairs, Quality Assurance, and Clinical Affairs for Genetic
20 Systems Corporation, a subsidiary of Bio-Rad Laboratories.
21 Until last year we were formerly a subsidiary of Sanofi
22 Diagnostics Pasteur, a French company.
23 We are located in Redmond, Washington, not Redland
24 as listed in the agenda. Redmond, you might know, is a
25 fairly well known small town in Washington. Our local

1 neighbor is another small company called Microsoft.

2 I want to thank the FDA for allowing us to present
3 our clinical trial data this morning and to discuss the
4 issue of indeterminate Western blot results caused by non-
5 viral bands. As Paul mentioned, Genetic Systems submitted a
6 PLA supplement to the agency on July 8th, 1999, with a
7 request for a change in the criteria of negative Western
8 blot results for the Genetic Systems assay from "no bands
9 present" to "no viral bands present."

10 The Genetic Systems HIV-1 Western blot utilizes
11 the LAI strain of HIV-1 which was originally received from
12 the Institute Pasteur in France. It is also known as LAV.
13 The virus is propagated in an undifferentiated human T-cell
14 line known as CEM, which was tested and shown not to contain
15 HLA Class II antigens. Antibodies to HLA antigens are an
16 important source of non-viral bands.

17 Genetic Systems held a pre-IND meeting with the
18 agency in early 1995 to discuss the proposed Western blot
19 clinical trials to be performed in serum/plasma and dried
20 blood spot samples. Clinical trials were then performed in
21 several well-known blood banks, universities, public health
22 laboratories, in the U.S. in 1996. Western blot testing was
23 performed on prospectively and retrospectively collected
24 samples, but no further follow-up studies of viral or non-
25 viral indeterminate samples were done at that time. Final

1 FDA approval was received in November 13, 1998.

2 This is the quality control section of the Genetic
3 Systems HIV-1 Western blot package insert. The criteria for
4 a positive Western blot is the current APHL/CDC definition.
5 This an actual scanned-in image of the three controls
6 provided in the kit. As you can see, each of the viral
7 bands are clearly demonstrated here in the package inserts
8 for users.

9 This is now a close-up of that same Western blot
10 quality control strip. As you can see here, I think, if you
11 look carefully, there is a negative staining or whited-out
12 area in the middle of the broad gp41 viral band. Paul
13 mentioned that we had a non-viral p42 band. This whited-out
14 area is a convenient marker for where the non-viral p42 band
15 that I will discuss is located, so it lines right up with
16 that.

17 This is the current definition of a negative
18 Western blot for serum/plasma and DBS samples in the Genetic
19 Systems 1 Western blot. As Paul mentioned, the definition
20 is "no bands are present." We have an asterisk in our
21 package insert that states: "Negative dried blood spot
22 specimens frequently exhibit a weakly reactive, plus/minus,
23 fine line migrating within the wide gp41 region. This
24 reactivity is clearly distinguishable from gp41, which is a
25 broad diffuse band. Dried blood spot specimens that are

1 reactive only with this discrete 'p42' band...may be
2 interpreted as negative."
3 The major topic of discussion at our pre-IND
4 meeting with the agency was the presence of these weak p42
5 non-viral bands in most dried blood spot samples. It was
6 known at the time that DBS samples frequently contain non-
7 viral bands in the p42 region, and at the time we believed
8 that these were only seen with DBS samples. We met with the
9 agency because the criteria of "negative" as "no bands" for
10 DBS samples would mean that the majority of repeat reactive
11 DBS samples would have to be called "indeterminate."
12 The p42 band appears to be actin, a cell-
13 associated antigen, or an actin binding protein. It is an
14 integral part of the cell, and co-purifies with the gp41
15 viral antigen. During clinical trials and subsequent PLA
16 review, we demonstrated to the agency that this p42 non-
17 viral band could be clearly distinguishable from gp41, which
18 is a broad diffuse band, in those dried blood spot samples.
19 This allowed for the licensure of the Genetic Systems HIV-1
20 blot with serum/plasma and DBS samples.
21 During the clinical trials, matched serum or
22 matched plasma and DBS samples from the same patients were
23 collected and tested. Equivalent performance between
24 serum/plasma and DBS sample pairs were demonstrated with
25 positive samples such as these AIDS patients. The sample on

1 the left is serum and the sample on the right is DBS, and as
2 you can see, each of the patient pairs, we show equivalent
3 banding patterns. Also note that in this area here you can
4 see the whited-out band where this p42 appears in some
5 samples. I will show you that.
6 We also did matched normal donor serum/plasma and
7 DBS pairs, and when testing was performed on these, the
8 matched DBS sample would very frequently exhibit the faint,
9 narrow, pencil-like non-viral p42, which unfortunately does
10 not show up very well on these photographs, but there is a
11 very fine, thin line right there at the p42. The serum or
12 plasma sample from the same person would not exhibit this
13 band. Samples 10 and 11, and 12 and 13, are matched pairs
14 from different donors.
15 We routinely perform testing with the CDC-provided
16 DBS controls, which consist of high positive, low positive,
17 and negative DBS sample, on each lot of the Genetic Systems
18 HIV-1 Western blot. And maybe here you can see a little bit
19 better this faint, narrow p42 band that appears on the
20 negative control on this DBS sample.
21 Samples 4 and 5 were examples of indeterminate
22 serum samples from our clinical trial. Serum sample 4 is a
23 true indeterminate based on the presence of viral bands at
24 p24, p40, and a very faint 51-55 band. This would be called
25 an indeterminate sample. Sample No. 5 is indeterminate

1 based on the presence of a non-viral p42 right here. This
2 band, if you could see it, is clearly distinguishable from
3 the broad gp41.
4 Okay. I would like to quickly go through our
5 clinical trial data from the different study groups. We did
6 six different study groups in our clinical trial. The first
7 group consists of 153 normal donor samples that were EIA
8 repeatedly reactive. In this group 30 percent were
9 indeterminate using the "no bands" criteria; 27 percent
10 would be indeterminate using the proposed "no viral bands"
11 criteria. The difference was four samples or 2.6 percent.
12 I would like you to keep that number in mind as we go
13 through the various study groups.
14 The next study group contains 61 normal donor
15 samples that were again EIA repeatedly reactive, but this
16 time these were all known to be Western blot indeterminate
17 by another licensed Western blot. Testing with the Genetic
18 Systems blot, 59 percent were indeterminate using the "no
19 bands" and 54 percent would be indeterminate using the "no
20 viral bands" criteria, a change of 5 percent or three
21 samples.
22 The next study group was a normal donor population
23 of 301 samples that were EIA non-reactive. Since these
24 samples were EIA non-reactive, they are not normally
25 subjected to Western blot testing. In this population, 11

1 percent of the samples were indeterminate using the "no
2 bands" criteria, and 8 percent would be indeterminate using
3 the "no viral bands" criteria. The difference, again, was
4 eight samples or 2.7 percent. This is almost the exact same
5 percent change seen in the EIA repeat reactive population.
6 In fact, unless rejected by other EIA testing
7 results or by other reasons from the blood bank, these units
8 of blood are acceptable for transfusion and are being
9 transfused every day.
10 Here is the final study groups to be presented:
11 172 AIDS/ARC patient samples were studied, and there was no
12 change in the interpretation with the two criteria. 177
13 high risk EIA repeat reactives were also studied, and there
14 was no change in the criteria. And then, lastly. 176 high
15 risk EIA non-reactive patients were studied; 16 percent were
16 indeterminate using the "no bands" criteria, 14 percent
17 would be indeterminate using the "no viral bands," again a
18 change of 2 percent.
19 So even in the high risk population, the same
20 percent change was seen in "no viral bands" as in the EIA
21 repeat reactive normal donors and the EIA non-reactive
22 normal donors. Therefore, there does not seem to be a
23 correlation between EIA reactivity and the presence of non-
24 viral bands in the Western blot.
25 This is a summary slide of the 1,102 Western blot

1 samples that we reviewed. Eighteen of the 1,102 were found
2 to contain non-viral bands, or 1.6 percent, and we would ask
3 the criteria move from indeterminate to negative with these
4 samples. Or 18 of 144, or 12 percent of all the
5 indeterminate samples.

6 Here is a summary slide of all the non-viral bands
7 seen in the clinical trial. In these studies we performed
8 in 1996, 14 of the 18 non-viral bands seen in serum and
9 plasma were due to the same non-viral p42 bands seen in DBS
10 samples.

11 As we stated earlier when we originally met with
12 the FDA, we were not aware that non-viral p42 bands would
13 also be seen in serum and plasma samples. In retrospect, I
14 guess this is not surprising, since the prevalence is only 1
15 to 2 percent, that we did not know it at the time. One
16 sample had a p42 and a non-viral p37. Two samples had a
17 non-viral fine line around p31. And one sample had a non-
18 viral band below 120.

19 In order to move my presentation along, I am going
20 to skip these two summary slides. You have heard the same
21 data.

22 And then I apologize, but I have been asked to add
23 another slide that is not in your packet. This is a Western
24 blot of a typical seroconversion panel. This was tested at
25 Sacramento Blood Center during our clinical trials. As you

1 can see here, typically the first bands to appear in early
2 seroconversion with the Genetic Systems HIV-1 Western blot
3 are the viral bands p24, p40, and the gp160. The p24 and
4 gp160 bands are the typical hallmarks of early
5 seroconversion. Other viral bands then appear over time.
6 So from left to right is the time line for samples
7 being drawn on this seroconverter patient. The broad gp41
8 band typically appears later than either gp160 or gp120.
9 Here is the broad gp41 band. We are unaware of any early
10 seroconverter sample or seroconversion series where the gp41
11 is the first viral band to appear. Therefore, it is highly
12 unlikely for a laboratory to misinterpret a seroconversion
13 sample as Western blot negative due to the presence of a
14 non-viral p42 only band.
15 In conclusion, Genetic Systems agrees with the
16 1999 recommendation from APHL that the definition of
17 negative for serum and plasma samples should indicate "no
18 viral bands". The definition of indeterminate should not
19 include the reporting of non-viral bands. Genetic Systems
20 will work with the agency to develop the appropriate
21 definition of non-viral bands in the package insert of the
22 Genetic Systems Western blot, and also assist in laboratory
23 training as required.
24 Thank you.
25 DR. HOLLINGER: Thank you, Mr. Bentsen.

1 Any questions? Yes?

2 DR. FITZPATRICK: The high risk population tests,
3 where there were the two that would be now interpreted as
4 negative, were there follow-up samples on those to know if
5 they were seroconverters or truly negative?

6 MR. BENTSEN: No. At the time in 1996 that we did
7 these studies, these samples were not followed up with
8 additional PCR or other testing. The two non-viral bands
9 were not followed up in any way.

10 DR. FITZPATRICK: Thank you.

11 MR. BENTSEN: But I hope our other presenters will
12 show you the prevalence or the incidence of non-viral bands
13 and their significance.

14 DR. HOLLINGER: I think it was important to show
15 that slide about the seroconversion and what changes over
16 time. On the other hand, if that patient that you have
17 there had a gp42, or had a p42, the band that you are--is it
18 gp42?

19 MR. BENTSEN: No, it is called p42.

20 DR. HOLLINGER: p42, then it would be present in
21 that sample anyway, even in the early stages where there is
22 virus present too, anyway.

23 MR. BENTSEN: Right.

24 DR. HOLLINGER: Yes, please. State your name.

25 MR. GOLDSTEIN: My name is Andrew Goldstein, with

1 Epitope. I was wondering whether you had the opportunity to
2 evaluate your Western blot with monoclonal antibodies, since
3 that is one tool to distinguish viral from non-viral bands.
4 I am particularly interested in the p40, which at least in
5 our blot appears that it could be an intermediate breakdown
6 product of the gag gene product in the Western blot.

7 MR. BENTSEN: Yes. The monoclonal studies were
8 done during the clinical trials in the PLA submission, and
9 our monoclonal p24 antibody reacts with the p40. Our p40 is
10 gag-related. That is p18 and p24 together, and migrates in
11 the p40 region. So that is different than other Western
12 blots. As Paul stated, each of the manufacturers' Western
13 blots are a little bit different, so we would hope that each
14 company would submit clinical trial data and modify their
15 package insert appropriately with the FDA.

16 DR. HOLLINGER: Okay. Thank you.

17 The next topic is the American Red Cross
18 experience with indeterminate blood donors, and Sue Stramer
19 is going to give us that information.

20 DR. STRAMER: Thanks, Blaine. Just to clarify, it
21 is the same topic but just the next presentation.

22 Thank you for the opportunity in letting me share
23 the American Red Cross experience with indeterminate blood
24 donors. All of the committee members and the FDA should
25 have a copy of my presentation with which they can follow

1 along slide-by-slide. I didn't burden you with a lot of
2 pre-reading materials, since I didn't have my materials
3 ready.
4 Okay, just to outline my brief talk, firstly I
5 will define once again, if you haven't heard it enough, what
6 a Western blot indeterminate and non-viral band is, and this
7 is for the blots that the American Red Cross uses, which is
8 the Cambridge BioTech blot which is now distributed by
9 Calypte Biomedical. Next I will go into my favorite area,
10 the regulatory consequences of ignoring non-viral bands.
11 Then the current frequency of indeterminate and
12 non-viral and bands in the Red Cross data set over the last
13 two years, so this is quite a large and extensive data set.
14 And then, lastly, looking at a four-month period of time
15 when we have been using NAT testing in conjunction with
16 Western blot criteria to counsel donors, and to look at how
17 those two tests work side-by-side.
18 I will also show you some seroconverting HIV-1
19 donors, and really contrast to you what viral bands look
20 like, and that viral bands when they appear in real samples
21 are also positive by Nucleic Acid Test, and that is a very
22 important distinction.
23 Firstly, according to the kit we use, an
24 indeterminate result is defined as any bands present, but
25 the pattern does not meet the criteria for positive.

1 Further on in the insert it does define non-viral bands have
2 been observed with certain specimens. These bands are not
3 usually accompanied by any of the major viral bands of
4 diagnostic significance, which we know are p24, the gag;
5 p41, envelope; or gp120/160, also envelope.
6 The non-viral bands appear to be cell-related,
7 with the most common in the molecular weight range of 70 kd
8 or 51 to 55 kd, which are possibly HLA-DR proteins, and
9 possibly 43 kd, which is possibly HLA-ABC. In the Red Cross
10 experience, we don't see these, but we certainly see this
11 one, and that is where a lot of my talk will be focused.
12 The American Public Health Laboratory Association
13 meeting last year broke up into working groups, and one of
14 the working groups was to define criteria for Western blots.
15 And out of that conference report for 1999, this is what
16 that working group published. The interpretation of
17 indeterminate should not include reporting non-viral bands,
18 for example, p70.
19 The rationale for this is that since 1991 no
20 individual exhibiting non-viral banding has been associated
21 with either seroconversion, detection of different HIV
22 subtypes or other disease agents. Only viral bands that are
23 specified in the package insert, ranging from molecular
24 weights p17 to gp160, at least in the Cambridge blot, this
25 is the definition of the viral reading frame where the viral

1 proteins migrate. Those are the only ones that should be
2 reported.
3 To go through a little history of not reporting
4 non-viral bands, even though they are mentioned in the
5 package insert, the Red Cross over a period of time was not
6 reporting non-viral bands since they are non-viral bands.
7 So between the period of time of March 1989 and September
8 1993, a total of 621 samples were reported as negative by
9 Red Cross when there was evidence of a band at p70. These
10 included 460 repeat reactive index donations, being repeat
11 reactive by the test we were then using, the HIV-1 EIA, and
12 they also included--here is the danger zone--161 reentered
13 donors.
14 Those 161 reentered donors, with hundreds of
15 multiple donations over this period of time, 1989 to 1993,
16 four years, resulted in a multimillion dollar recall of
17 otherwise safe products. The only thing wrong with these
18 donors upon reentry was the p70 band. Upon subsequent
19 donations and those products being used for pools of plasma,
20 this again resulted in a very costly recall for Red Cross.
21 none of the reentered donors, with hundreds of subsequent
22 donations over this four-year period of time, demonstrated
23 any evidence of HIV seroconversion.
24 Now to show you some recent data over a two-year
25 period of time. For the Red Cross, this represents the

1 screening of 12.4 million whole blood donations. At a
2 repeat reactive rate on our HIV-1/2 kit of .09 percent, this
3 results in just over 11,000 repeat reactive samples. When
4 those samples are then put onto Western blots, this is the
5 break-out that results. 7.1 percent, or the lowest percent,
6 since we do a low-risk population, are positive. 46.6
7 percent over this last two-year period of time was
8 indeterminate, the largest category. 46.3 percent were
9 negative. So this is the message we give to these donors
10 is, "We don't know what's happening."

11 This now focuses on monthly data from the last
12 year, 1999, and what this shows you, of total number of
13 samples received in my lab for confirmatory testing, that
14 when there are variations in the repeat reactive rate of the
15 test, are problems with false positivity of the EIA. We
16 also see concomitant bounce of the Western blot negative and
17 indeterminate samples. That is, these samples track with
18 the false positives seen in the EIA, whereas the line for
19 confirmed positive, which is the red line, is relatively
20 flat. So this was the number actually that Paul used, 44.5
21 percent indeterminate for the period of 1999.

22 If we break out all the indeterminates from the
23 two-year period I am discussing, which were 5,161
24 indeterminates, we see multiple categories. These first
25 three here, which are really not the point of this

1 discussion, are all viral band indeterminates. You can have
2 multiple viral bands from different gene products, but they
3 don't have enough intensity to call those positives, and in
4 many cases they include just envelope bands only, which are
5 not associated with seroconversion.
6 The majority of the cases of indeterminates, 53
7 percent, represent one viral band only, and in that category
8 the majority or almost 2,000 samples are p24 only, gag only,
9 on Western blots. Alternately, you can have multiple gag
10 bands or multiple viral bands on a blot but it is not
11 positive, and again the most common category here are gag,
12 multiple gag proteins.
13 Another category that now we are moving into the
14 non-viral area, but really that hasn't been discussed today,
15 it isn't the topic of today, is something that we call
16 background. That is when you really can't see what you are
17 reading on the blot because there is some staining that
18 prevents the reading or obscures the reading of a certain
19 reading frame on the blots, and we interpret those as
20 background. And since we can't read under background, FDA
21 has encouraged us to call these indeterminates. So that
22 represents 20 percent of what we blot. And then here we
23 have our 14 percent non-viral category, and the majority,
24 well over the majority, 80 percent represent p70's.
25 Now, to look at this data incorporated with

1 Nucleic Acid Testing or RNA for HIV, this covers the last
2 four months of 1999, in which 2.0 million donations have
3 been screened, representing almost 2,000 repeat reactives,
4 again, a .09 percent repeat reactive rate, and about 45
5 percent indeterminates. All of these samples have also been
6 tested for HIV RNA, over 75 percent of them tested as
7 individual donations because of seroreactivity.
8 Now, of those that are positive, 71, 67 were RNA
9 positive, so those four samples that were RNA negative only
10 had envelope on their Western blots, so didn't have evidence
11 of two gene products. The indeterminate category, of these
12 824 indeterminate samples, there was only one sample that
13 was RNA positive, and that one RNA positive sample had a
14 viral band, a strong p24; it had a strong EIA signal of
15 11.62; and it was also strongly RNA positive, with a signal
16 of 18.23. No negative samples, of the 941 tested, exhibited
17 RNA.
18 Again, if you break these into the various
19 indeterminate patterns, which I won't go through, again the
20 only positive here was the p24. None of the 108 non-viral
21 bands exhibited any RNA reactivity.
22 Now to switch gears a little bit. There are
23 indeterminate samples that do have meaning, and HIV
24 seroconverters do go through an indeterminate stage when
25 they seroconvert. Again, these are data generated with the

1 Cambridge blot. This is viral load on the X axis, and
2 different categories during HIV seroconversion on the X
3 axis. This is the early period of where RNA is the only
4 marker positive, and then we move through seroconversion.
5 But this is the category that I want to focus on
6 here. There were 19 seroconverters who did go through an
7 indeterminate pattern, and their first bleed or their first
8 indeterminate pattern had a very high viral load. But if we
9 look at every single sample in that indeterminate category--
10 again, let me remind you that these are HIV repeat reactive
11 samples that are indeterminate based on viral bands only, no
12 non-viral bands, and are undergoing HIV seroconversion, and
13 that every single one of these samples was HIV-1 RNA
14 positive. But what is interesting here is the concentration
15 of RNA in these samples.
16 Also, well, the way I divided these into their RNA
17 concentrations is to look at p24 antigen reactivity. Of
18 these 41 samples, only 29 were p24 antigen reactive, and
19 those would be the ones that you would expect to have the
20 highest RNA concentration, which they did, a median copy
21 count of 800,000 copies per mL. So as we are doing pooled
22 testing in the blood donor environment, every single one of
23 these samples would be detected. Nineteen were p24 antigen
24 negative, but all of them still were RNA positive.
25 There were, however, four samples that had

1 relatively low viral copies, and therefore 37 of 41 would be
2 predicted to be detected by pooled NAT testing as we are
3 doing in the blood centers. So even at the lowest case,
4 even though we are doing pooling, 90 percent of these
5 indeterminates would be detected by RNA.
6 Just again to show you some blots, these are the
7 ones Paul showed you. Here is high molecular weight non-
8 viral, clearly over the viral reading frame, and now even
9 into the numbers or the part of the blot which you could say
10 is adulterated by putting the numbers on the strip. Here is
11 a p5 and p7 on these two strips, again non-viral, below p17,
12 which is the lowest molecular weight of a viral band. Here
13 is our favorite, p70, very distinct and really has no
14 interference with anything else in a viral area.
15 I just show this blot because it is of interest.
16 This is actually a confirmed positive, but a false positive,
17 a confirmed positive that is based on envelope only. So
18 even though we call some blots positive, there are some
19 number that are false positives.
20 Now, in contrast to all of those, this is a
21 seroconverting individual that the Red Cross had. It was
22 our fifth yield sample from p24 antigen screening. You can
23 see here the seroconversion pattern. As this person
24 developed over a month, really nothing changed other than
25 the development of p17. Certainly there are no non-viral

1 bands. There is high molecular weight glycoprotein,
2 gp120/160, and p24, but nothing else.
3 So, in conclusion, due to the manufacturer's
4 requirements, samples with non-viral bands must be reported
5 as indeterminate. However, non-viral bands are just that,
6 if I may quote Roger Dodd. They do not indicate the
7 presence of any virus, past, present or future. Donors with
8 non-viral bands represent 14 percent of total
9 indeterminates, and are otherwise safe donors, that is, RNA
10 negative.
11 HIV-1 viral loads in seroconverting individuals
12 with viral indeterminate patterns exceed the cutoff of
13 pooled NAT testing, at least in 90 percent of cases, none
14 with non-viral patterns. And, lastly, patterns of non-viral
15 bands do not resemble any patterns seen in HIV-1
16 seroconversion, and really could not be confused, I don't
17 believe, with any pattern of early HIV-1 seroconversion.
18 So, thank you, and again I remind you that non-
19 viral bands are just that.
20 DR. HOLLINGER: Thank you, Sue.
21 Questions for Dr. Stramer?
22 [No response.]
23 DR. HOLLINGER: Sue, just again, all of those 14
24 percent that you talked about would be EIA positive, again,
25 if they were tested in general?

1 DR. STRAMER: You mean if we repeated the sample,
2 or if the donor came in for a follow-up sample?
3 DR. HOLLINGER: Well, not necessarily a follow-up
4 sample, but the samples are all EIA reactive, repeat
5 reactive.
6 DR. STRAMER: Correct, correct.
7 DR. HOLLINGER: And if they came back in again,
8 what percentage of them perhaps are negative?
9 DR. STRAMER: Generally, with most of the tests
10 that we do, with most of the EIAs, persistent EIA and
11 Western blot indeterminates remain as EIA repeat reactive,
12 unless there is--
13 DR. HOLLINGER: And so they would not be accepted
14 as a donor anyway.
15 DR. STRAMER: Exactly, exactly. Right. The EIA
16 is the front line screen.
17 DR. HOLLINGER: Okay. Thank you. Thank you very
18 much, Sue.
19 The next presentation, then, is by Dr. Busch on
20 the significance of HIV indeterminate Western blot results.
21 DR. BUSCH: Thanks, Blaine.
22 DR. HOLLINGER: You look different, Mike, without
23 your running stuff on.
24 DR. BUSCH: I want to present several studies from
25 the REDS group primarily, that sort of broaden the issues a

1 little bit. The first data I want to share is to try to
2 pass on in some more concrete sense the impact of notifying
3 donors of false positive and indeterminate test results, and
4 this is based on a survey that the REDS group did of donors
5 who were notified of abnormal test results.
6 As you have heard, there are maybe 5,000 or so
7 donors notified of indeterminate results for HIV per year in
8 the whole blood sector. If you put all the different false
9 notifications together, there is 100,000 to 200,000 donors
10 annually who are being told that they are reactive,
11 typically deferred from blood donation, with a very mixed
12 message as to the potential for infection.
13 What we did was to do an anonymous mail survey in
14 1997 to donors who were notified during the first six months
15 of that year that they were deferred as a result of
16 reactivity to one or more of the viral markers. These were
17 then returned to the coordinating center and analyzed. The
18 donors were notified 6 to 12 months--were surveyed 6 to 12
19 months after the notification.
20 And for sort of benchmark comparison, we included
21 in this notification survey donors who were told they were
22 confirmed positive for the markers that we have appropriate
23 supplemental tests for; our focus today, the group of
24 indeterminates; and confirmation negative, as well as the
25 surrogate marker reactive donors, anti-core and ALT.

1 We notified a total of about 4,000 donors, or sent
2 surveys, and received information from about, I think,
3 1,300. Of particular interest is, there were 169 donors who
4 were notified of indeterminate test results. About a 35
5 percent overall response rate.
6 The first message to the donors--to you is the
7 issue of how accurately--how the donors responded in terms
8 of comprehension of the notification message. And you can
9 see that overall about 50 percent of the donors felt that
10 the notification process was difficult to understand.
11 And throughout the next series of slides you will
12 note that the group of donors who were notified of
13 indeterminate test results had the highest rate of problems
14 understanding, and persisting anxiety and confusion over the
15 notification message. So in this specific example, 66
16 percent of the donors who received notifications that were
17 called "indeterminate" could not really understand the
18 message which was being communicated.
19 Confusion was kind of a different category. Both
20 at the time of notification and six months after
21 notification the donors were asked as to the level of
22 confusion. Again, you can see a very high rate of about 80
23 to 90 percent of donors, at the time they are being notified
24 of these test results, are confused as to what this means,
25 and even six months later, particularly the indeterminate

1 group, 62 percent of these donors are still confused six
2 months after the notification, even after going into the
3 blood center or seeking clarification through their own
4 physician, follow-up activity.
5 Emotional upset, again, 90 percent of the
6 indeterminate donors are upset emotionally on a subjective
7 grading at the time of notification, and this persists out
8 to six months in half of the donors. So just to convey that
9 this is not an insignificant message being passed on to
10 these blood donors. It really impacts their lives.
11 The response, the recommendations of our group was
12 to try to increase the specificity of the screening assays
13 to minimize the number of false positive screens that drive
14 these notifications, but particularly with respect to
15 confirmatory tests, to improve the accuracy of the
16 confirmatory testing and try to incorporate data in the
17 context of the routine confirmatory testing that can
18 reassure, allow us to really reassure these donors that they
19 are not infected, and minimizing indeterminate results,
20 which is really the focus of today's discussion.
21 I might also mention that some blood centers, in
22 the context of current consent decrees, are actually
23 required to trigger look-back recipient notifications on
24 indeterminate donors, which I think--I feel is completely
25 inappropriate.

1 This is the paper that I distributed. It was a
2 large study from the REDS group that focused on
3 indeterminate donors, a follow-up study that enrolled into
4 follow-up 355 indeterminate donors, and none of these proved
5 to be infected. It is a busy table. The bottom line is,
6 none of these donors were proven to be infected through
7 follow-up testing.
8 This does have an answer to a question Blaine just
9 asked, which is, what proportion of these donors who are
10 reactive and indeterminate on initial screening and are not
11 infected, what percentage persist as EIA reactive on follow-
12 up? And in this analysis 56 percent of the donors who were
13 initially indeterminate on the combi test, when followed up
14 six months or greater after that donation, persisted as
15 indeterminate on the combi test.
16 So, in contrast, if you were screened with the
17 HIV-1 assay and then on retesting downstream with the combi
18 test, only 14 percent were indeterminate. It is really a
19 test change issue. If you keep screening the donors with
20 the exact same assay, a high proportion of false reactives
21 will persist, false reactive on that test. It is really
22 when you switch assays, as you go to a new generation test,
23 that you can exclude a lot of false positives and reenter
24 those donors.
25 One other study I wanted to share because I think

1 it is an important message is, you heard even EIA negative
2 donors have a fair rate of background indeterminate bands,
3 and there is a concern, is this anything of significance?
4 And this was a paper actually that Jay Epstein and Harvey
5 Alter were involved with, that looked at pre- and post-
6 transfusion samples and donor samples from some of the post-
7 transfusion studies that Harvey has conducted.
8 And what they found in this study was that there
9 were 19 donors whose blots were indeterminate, whose blood
10 went into recipients, and when they tested the recipients of
11 these indeterminate Western blots, and these were actually
12 EIA negative units that were transfused, 36 percent of the--
13 I'm sorry--yes, 36 percent of these recipients had
14 indeterminate Western blots. But the recipients that had
15 indeterminate Western blots were different, did not get the
16 blood from the donors who had indeterminate Western blots,
17 and the bands were completely unrelated. So this is just,
18 basically this is background noise in blood donors and
19 recipients. It is not a transmissible phenomenon.
20 Next, I just wanted to share some data that was
21 generated over the last several years, particularly in
22 collaboration with Glen Satten at CDC, Steve Herman at
23 Roche, and people from Boston Biomedica, looking at similar
24 data to what Sue showed us, to the ability of RNA to
25 classify indeterminates as they go through the evolving

1 seroconversion phase and accurately detect seroconverters.

2 We tested 51 BBI seroconversion panels, 439

3 samples, by RNA and by different Western blots, and then we

4 estimated the duration of the different stages of evolving

5 seroconversion and then looked at the probability or the

6 accuracy that RNA could sort these into true positive

7 results as the patterns evolve. And as Sue kind of showed,

8 as you go through seroconversion, you go through an RNA only

9 stage, and then the viremia becomes high enough that antigen

10 can detect it, and then the EIA becomes reactive, and you

11 actually go through a transient phase where the very

12 sensitive current antibody tests are reactive but the

13 Western blot is negative, and then on through the

14 indeterminate, the incomplete positive patterns, and the

15 full positive band pattern.

16 And in this analysis, which is in the handout,

17 specific to this discussion, we had 41 specimens that were

18 from the period of time where the EIA was reactive and the

19 Western blot was indeterminate, indeed all viral band

20 patterns indeterminate, and 100 percent of those samples

21 were RNA positive. In fact, throughout these early stages

22 of evolving antibody seroconversion, viremia is typically

23 quite high titer. As Sue showed, and as we independently

24 demonstrated, during this period in question when the

25 Western blot is indeterminate in an evolving seroconverter,

1 the viral load tends to be very high, averaging over 100,000
2 copies per mL, with only rare samples having viral loads of
3 thousands or so, but all of the samples were viremic.
4 Beyond just sort of modeling the viral load, with
5 Glen Satten we were also able to estimate the duration of
6 each of these stages of evolving seroconversion. And again,
7 specific to this discussion, the period of time during which
8 a donor, a person who is infected is in the seroreactive
9 Western blot indeterminate stage is very brief, particularly
10 now that the Western blot criteria have been, if you will,
11 tightened up by not requiring p31. The new two-band
12 criteria that Paul Mied summarized confirms seroconversion
13 very, very early, so we are left with only an estimated
14 five-day period of time during which a seroconverter would
15 go through an EIA reactive blot indeterminate phase.
16 If you multiply that brief period of time, times
17 the incidence of seroconversion in the blood donor setting,
18 you would estimate that on an annual basis only six donors
19 would be detected in the whole blood screening program
20 during that phase of EIA reactive blot indeterminate who in
21 fact were seroconverting.
22 And then what this slide does is, it expresses
23 that small number of donors who would be going through that
24 transient indeterminate phase over the denominator of the
25 number of donors who were actually found to be

1 indeterminate, and from this analysis we only estimate that
2 theoretically as few as 1 in 300, in fact lower than that,
3 donors who are indeterminate would be predicted to be truly
4 infected, going through seroconversion. So just to
5 emphasize the very low rate of predicted frequency of
6 indeterminates.
7 And finally, just as Sue showed from a separate
8 program, the blood system screening program, I wanted to
9 share our experience with actually incorporating the routine
10 nucleic acid data, the RNA data that we are now generating
11 on line, with the confirmatory serologic data. In our
12 system, during about an eight-month period of time, we
13 screen about 1.1 million donations with the Abbott combi
14 test; 470 were repeatedly reactive; and about 50 percent of
15 these were indeterminate, so a similar proportion.
16 We are using the Epitope Western blot, which has a
17 higher rate of "non-viral" bands, but as you will hear
18 later, what are being called non-viral bands on this
19 particular Western blot are actually not even bands; they
20 are artifact above gp 160 and below p18. So, as a result,
21 on this particular Western blot in our system, of the
22 indeterminates, 75 percent of them are being classified
23 based on non-viral band only grading, even though in truth
24 these aren't even bands per se, these are artifact of
25 transferring the gel onto the paper.

1 But in our system, just to emphasize this, I think
2 we heard from Genetic Systems, they estimate that only 2.5
3 percent of their Western blot indeterminates are non-viral.
4 In the Cambridge system it is about 14 percent. In this
5 assay, 75 percent of indeterminates are non-viral bands. So
6 very assay dependent in terms of the rate of nonspecificity.
7 And then this shows the actual correlation between
8 the Western blot results and the routinely obtained nucleic
9 acid test results, and none of our indeterminates and none
10 of our blot negatives were found to be RNA positive. These
11 were virtually all originally tested on minipool testing.
12 We actually took a representative 100 of these on to
13 individual donation Nucleic Acid Testing, and they were all
14 also confirmed negative.
15 And just for comparison, you can see that 21 of
16 the 22 Western blot positive specimens were detected on
17 routine NAT, on minipool screening, to be RNA positive. The
18 one exception was negative on minipool NAT but was tested on
19 individual donation NAT and was positive for RNA on
20 individual donation Nucleic Acid Testing.
21 And I am not going to go into this, but the same
22 message I think bears true for the HCV data. We now have
23 routine RNA data that is very useful in counseling donors,
24 and although Dr. Mied indicated that these routine NAT data
25 are being used by some blood programs to counsel donors,

1 other programs are less comfortable using the routine NAT
2 data to counsel donors because it is an unlicensed assay
3 under IND.
4 And my hope would be that the committee could
5 voice a strong recommendation that the use of these
6 routinely generated NAT data collected under IND today
7 should be incorporated into the donor notification message,
8 because I think it is very helpful to have that RNA data
9 passed on to the donor to reassure them that they are not
10 infected. Thank you.
11 DR. HOLLINGER: Thank you, Dr. Busch.
12 Questions? Yes, Dr. Linden?
13 DR. LINDEN: Mike, towards the beginning of your
14 talk when you talked about the donor survey, it seemed that
15 the confusion and emotional upset was also quite significant
16 in the donors who were Western blot negative. And unless it
17 could be reentered at some future date because of changes in
18 assay, can you comment more on what would really be
19 accomplished by moving this big group of people from
20 indeterminate to negative? You are still going to tell
21 them, "We have this anomaly, so you can't donate."
22 DR. BUSCH: Yes. I am not sure how much
23 reassurance they will get. The one issue is that that data
24 was obtained before we had RNA data, so these donors were
25 still urged that they needed to, even the negatives were

1 urged to come back, and potential concern over a possible
2 evolving infection and need for retesting.
3 So I think one issue is simply being able to
4 incorporate negative RNA data and strengthen the message
5 that these donors are not infected, certainly the negative
6 group, and I think also the indeterminate group, both the
7 non-virals and the virals. It may give these donors a lot
8 of emotional reassurance and minimize the concern over
9 potential infection themselves, transmission to others, need
10 for follow-up testing.
11 But clearly you are right, until we can reinstate
12 these donors or offer them that ultimate reassurance that
13 they can donate blood again, I think there is a mixed
14 message and that there is going to be confusion and people
15 are going to be upset, both personally and at the blood
16 centers. So I think that is the ultimate goal, will be to
17 develop reentry algorithms that actually can reinstate these
18 false positive donors.
19 DR. HOLLINGER: Thank you, Mike.
20 The last presentation in this section is by Dr.
21 Hearn on the risk of false negatives.
22 DR. HEARN: Thanks. If you will bear with us a
23 minute while we get the presentation done, not only am I
24 going to give you a different perspective or a supplementary
25 perspective but I am going to do it in a different way, so I