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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

69TH MEETING

OPEN SESSION

Thursday, June 14, 2001

8:30 a.m.

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

2 DR. SMALLWOOD: Good morning, and welcome
3 to the 69th meeting of the Blood Products Advisory
4 Committee. I am Linda Smallwood, the Executive
5 Secretary of the committee, and at this time I will
6 read the conflict of interest statement for the two
7 days that this committee will be meeting.

8 The following announcement is made part of
9 the public record, to preclude the appearance of a
10 conflict of interest at this meeting.

11 Pursuant to the authority granted under
12 the committee charter, the Director of the FDA
13 Center for Biologics Evaluation and Research has
14 appointed Dr. Paul McCurdy as a temporary voting
15 member. In addition, the Senior Associate
16 Commissioner of FDA has appointed Drs. Patricia
17 Charache and Michael Wilson as temporary voting
18 members.

19 To determine if any conflicts of interest
20 existed, the agency reviewed the submitted agenda
21 and all relevant financial interests reported by
22 the meeting participants. As a result of this
23 review, the following disclosures are being made:

24 In accordance with Title 18, United States
25 Code, Section 208, Dr. Paul McCurdy has been

1 granted a general matters waiver with permission to
2 participate fully in the committee discussions.
3 Also, Drs. Kenrad Nelson and Paul Schmidt had
4 waivers previously approved by the agency that are
5 applicable for this meeting.
6 Dr. Raymond Koff has been granted a
7 written appearance determination, in accordance
8 with Title 5, United States Code, Section 2635.502,
9 which permits him to participate fully in the
10 committee discussions.
11 The following participants have
12 associations with firms that could be affected by
13 the committee discussions: Drs. Boyle,
14 Chamberland, Fitzpatrick, Kagan, Koerper, Knowles,
15 Linden, Macik, Nelson, Schmidt, and Simon.
16 However, in accordance with our own statute, it has
17 been determined that a waiver, an appearance
18 determination, or an exclusion is not warranted for
19 these deliberations.
20 With regards to FDA's invited guests, the
21 agency has determined that the services of these
22 guests are essential. There are reported interests
23 which are being made public to allow meeting
24 participants to objectively evaluate any
25 presentation and/or comments made by the

1 participants.

2 Related to the discussions on reentry for
3 donors deferred because of HIV or HCV NAT or
4 serologic test results, Dr. Michael Busch reported
5 he is employed by the Blood Centers of the Pacific.
6 Dr. Susan Galel reported that she is employed by
7 the Stanford Blood Center; she also evaluates
8 AmpliScreen assays for use in blood donor
9 screening. Dr. Susan Stramer reported she is
10 employed by the American Red Cross, National
11 Confirmation Testing Laboratory.

12 For the discussions on uniform donor
13 history questionnaire, Dr. Joy Friday is employed
14 by the American Association of Blood Banks. Dr.
15 Sharon Orton is employed by the American Red Cross.

16 For the discussions on transfusion-related
17 acute lung injury, Dr. Mark Popofsky is employed by
18 the Haemonetics Corporation. Dr. Patricia Kopko
19 has a grant with the National Blood Foundation on
20 HLP Class 2 antibodies and white blood cell
21 activation with transfusion-related acute lung
22 injury.

23 For the discussions on leukoreduction
24 filtration failures, Dr. Thomas Bork is employed by
25 the Canadian Blood Service. Dr. Rebecca Haley is

1 employed by the American Red Cross. Ms. Sherrie
2 Jennings is employed by the Gulf Coast Blood
3 Center. Ms. Linda Ford is employed by the Oklahoma
4 Blood Institute.
5 In the event that the discussions involve
6 other products or firms not already on the agenda
7 for which FDA participants have a financial
8 interest, the participants are aware of the need to
9 exclude themselves from such involvement, and their
10 exclusion will be noted for the public record.
11 With respect to all other meeting
12 participants, we ask in the interest of fairness
13 that you state your name, affiliation, and address,
14 and any current or previous financial involvement
15 with any firm whose products you wish to comment
16 upon.
17 Copies of waivers and the appearance
18 determination addressed in this announcement are
19 available by written request under the Freedom of
20 Information Act.
21 At this time I would like to quickly
22 introduce you to the members of the Blood Products
23 Advisory and our special consultants.
24 The committee chair is Dr. Kenrad Nelson.
25 When I call your name, would you please raise your

1 hand? Thank you. Seated next to him is Dr.
2 Sherrie Stuver; Dr. David Stroncek; Dr. Gail Macik;
3 our special consultant from the Center for Devices
4 and Radiological Health, Dr. Michael Wilson; Dr.
5 Paul McCurdy; Dr. Daniel McGee; Dr. Blaine
6 Hollinger; Ms. Kathy Knowles; Dr. Toby Simon.
7 My far left, Dr. Michael Fitzpatrick; Dr.
8 Jeanne Linden; Mr. Terry Rice; Dr. Paul Schmidt;
9 Dr. Mary Chamberland; Dr. John Boyle; Dr. Marion
10 Koerper; and Dr. Raymond Koff.
11 Again, I would just like to emphasize that
12 when you are speaking, to please state your name
13 and your affiliation, and please try to adhere to
14 the time frames. We have a very packed agenda
15 today, but we hope to get through this, with your
16 cooperation.
17 At this time I will turn over the
18 proceedings of this meeting to the chairman, Dr.
19 Kenrad Nelson.
20 DR. NELSON: Well, thank you, Dr.
21 Smallwood. The first item on the agenda are some
22 committee updates, and Dr. Nightingale told me that
23 he's not feeling well, and will be back in a few
24 minutes, hopefully. So we'll start with Dr. Elliot
25 Cowan, who will talk about current thinking on

1 clinical trial design and performance standards for
2 approval of rapid HIV tests.
3 DR. COWAN: Thank you, and good morning.
4 So much for having an extra five minutes.
5 This morning I briefly wanted to give you
6 an update on--oops, that is the wrong presentation.
7 I don't want to talk about CLIA until this
8 afternoon. There should be a file labeled
9 "update". There we go.
10 I wanted to give you an update on clinical
11 trial design and performance standards for approval
12 of rapid HIV tests. The purpose of this update is
13 to review the standards that CBER is recommending
14 for the performance of rapid HIV tests and
15 standards for clinical trial design.
16 By way of history, on June 15th of last
17 year we presented to you performance standards for
18 the approval of rapid HIV tests, and those
19 standards are 98 percent as the lower bound of the
20 one-sided 95 percent confidence interval for both
21 sensitivity and specificity. Subsequently, we
22 presented to you on September 15th of last year
23 revised clinical trial recommendations for the
24 approval of rapid HIV tests.
25 Just to review what those recommendations

1 are, for sensitivity studies it would consist of a
2 series of confirmed positive specimens, a minimum
3 of 500 specimens. We are recommending 1,000. And
4 these would be fresh specimens for each specimen
5 type, so that if a claim was made for serum, for
6 plasma, for finger stick blood, for venous blood,
7 there should be 500 specimens as a minimum for
8 each. We are recommending 1,000.
9 This has to do with performing a study
10 which is of sufficient power to be meaningful. A
11 manufacturer may perform a study which consist of
12 any size, as long as it is more than 500, but
13 should realize that if the performance standards of
14 98 percent as the lower bound of the 95 percent
15 confidence interval are not met, that that study
16 may have to be repeated.
17 Secondly, for sensitivity there would be
18 prospective testing of high-risk individuals. I'll
19 give details on that when I talk about specificity.
20 Worldwide confirmed positive specimens
21 should be examined, a minimum of 200, and in this
22 case repository specimens are appropriate. The
23 reason that we're asking for fresh specimens for
24 the confirmed positives and for other studies is
25 that this is looking at the intended use specimens.

1 And finally for sensitivity studies,
2 analytical sensitivity should be examined by
3 looking at 10 seroconversion panels and three low-
4 titer panels.
5 For specificity, we are recommending
6 prospective testing of low-risk individuals, a
7 minimum of 500. Again, 1,000 are recommended.
8 Again, fresh specimens for each specimen type.
9 Prospective testing of high-risk individuals, again
10 a minimum of 500, 1,000 recommended, of fresh
11 specimens for each type.
12 The negative individuals, negative
13 specimens from this study would be applied to the
14 specificity calculations, and any positive
15 specimens from this high-risk population study
16 would be applied toward the sensitivity
17 calculations.
18 Preclinical studies for specificity would
19 consist of 200 specimens from individuals with
20 unrelated medical conditions and 100 specimens with
21 interfering substances.
22 Finally, the updated information that I
23 can give you is that we are in the process of
24 writing a guidance document which is entitled
25 "Guidance for Industry on Clinical Trial Design and

1 Performance Standards for Approval of Rapid Tests
2 for HIV Antibody for Use as an Aid in Diagnosis,"
3 and again, that document is in preparation.
4 Thank you very much.
5 DR. NELSON: Questions?
6 What did you mean by "interfering
7 substances"? Is there a number that--
8 DR. COWAN: Interfering substances would
9 consist of things like high bilirubin, high
10 hemoglobin, triglycerides, things like that.
11 Medical conditions, of course, would be HTLV,
12 hepatitis, syphilis, other things like that, flu
13 vaccines.
14 DR. NELSON: Thank you.
15 I guess the next item on the agenda, Dr.
16 Smallwood will describe some proposed FDA
17 scientific workshops.
18 DR. SMALLWOOD: I'm just going to make a
19 brief announcement that we have two workshops that
20 are in process now. A workshop on "Best Practices:
21 Reducing Medical Errors" is scheduled for November
22 8th and 9th, 2001. It will be held in Mazur
23 Auditorium, the NIH Clinical Center on the NIH
24 campus. The second will be a workshop on nucleic
25 acid testing scheduled for December 4th and 5th,

1 2001, at the Lister Hill Auditorium, National
2 Library of Medicine, also at the NIH campus.
3 There will be further public notification
4 concerning these meetings. There will be a Federal
5 Register announcement, and there will also be
6 brochures sent out so that individuals may be able
7 to register. Thank you.

8 **REENTRY FOR DONORS DEFERRED BECASUE OF HIV OR HCV**
9 **NAT OR SEROLOGIC TEST RESULTS**

10 DR. NELSON: The first topic today is
11 Reentry for Donors Deferred Because Of HIV Or HCV
12 Nucleic Acid Testing Or Serologic Test Results, and
13 Dr. Paul Mied will give an introduction and
14 background.
15 DR. MIED: Thank you, Dr. Nelson.
16 Each year an estimated 14,000 donors are
17 deferred from donating blood for an indefinite
18 period because of a repeatedly reactive EIA result
19 and a negative or indeterminate supplemental test
20 for antibodies to HIV or HCV. In addition to these
21 indefinite serological deferrals, the
22 implementation of pooled sample NAT, or nucleic
23 acid testing, for HIV RNA and HCV RNA has resulted
24 in deferrals of several hundred donors due to
25 potentially false positive NAT test results each

1 year.

2 In anticipation of licensure of the first
3 pooled sample NAT method for HIV RNA and HCV RNA,
4 FDA is developing guidance for industry on
5 implementation of NAT testing. This guidance will
6 address all aspects of donor testing, product
7 management, and donor management, and it will
8 include algorithms for testing discussed at the
9 March 2001 Blood Products Advisory Committee
10 meeting, and also algorithms for donor reentry to
11 be discussed at this meeting.

12 At the March 2001 meeting of the Blood
13 Products Advisory Committee, FDA proposed uniform
14 algorithms for management of whole blood and source
15 plasma donations tested by pooled sample NAT. Now,
16 the focus of that FDA proposal was the action that
17 should be taken in the event of discrepant test
18 results, such as when a master pool is reactive but
19 individual donations are nonreactive.

20 The data presented at the March BPAC
21 session showed that in each discrepant case it was
22 the master pool that was falsely positive due to
23 contamination either during specimen handling or
24 during the assay run, and that false negatives on
25 individual donations have not been seen in the

1 studies performed using various NAT methods under
2 IND.
3 In response to FDA's questions, the
4 committee vote in each case was that the NAT result
5 on individual donations should be considered the
6 definitive test result, and that units could be
7 released in each case. This outcome really makes
8 the uniform NAT testing algorithms relatively
9 simple.
10 This algorithm that goes directly from
11 testing the master pool to testing individual
12 donations may be more applicable to the screening
13 of whole blood than source plasma, although it
14 could be used for either at the discretion of the
15 blood establishment. This algorithm recommends the
16 release of all units when all individual donations
17 are nonreactive on the NAT test.
18 Since false positive NAT results have been
19 known to occur, this NAT testing algorithm also
20 includes a recommendation that donors deferred
21 because of a positive NAT result on their
22 individual donations be considered eligible for
23 reentry, whether the discriminatory NAT, which is
24 essentially the same NAT test for the individual
25 viruses, was subsequently positive or negative, as

1 long as the initial NAT positive result was not
2 confirmed by a positive result on a supplemental
3 NAT test. Now, a supplemental NAT is a validated
4 confirmatory gene-based test that is either the
5 same NAT method used with a different set of
6 primers or a different NAT technology.
7 This alternative algorithm would be more
8 likely to be used by source plasma establishments
9 with large pool sizes, say of 512 or 1,200
10 donations, who usually perform a deconstruction of
11 the master pool, testing archived or freshly pooled
12 subpools to identify the reactive individual
13 donation. This algorithm recommends the release of
14 all units when subpools or individual donations are
15 nonreactive on the NAT test, and it also includes a
16 recommendation that donors deferred because of a
17 positive NAT result on their individual donation be
18 considered eligible for reentry.
19 Some of these donors, deferred on the
20 basis of the result of NAT testing, as well as
21 those deferred on the basis of the results of
22 serologic testing for HIV and HCV antibodies that
23 is being performed concurrently with NAT, may be
24 uninfected and could be made eligible to donate
25 blood or plasma again. However, many donors

1 currently deferred because of serologic HIV test
2 results remain deferred, because only some blood
3 establishments are attempting to reenter donors due
4 to the complexity of the current HIV reentry
5 algorithm and concerns about inappropriately
6 reentering a donor because the correct tests were
7 not performed.
8 The current FDA recommendations for
9 reentry of blood donors deferred because of a
10 repeatedly reactive test for antibodies to HIV were
11 outlined in the memorandum to blood establishments
12 of April 3, 1992. The current recommendations
13 state that reentry may be attempted when the
14 donor's initial repeatedly reactive sample is
15 negative on a licensed HIV-1 Western Blot or IFA.
16 If the original repeatedly reactive test
17 was an HIV-2 test, that is either a single virus or
18 a combination HIV-1/2 test, to exclude the
19 possibility of HIV-2 infection, the initial sample
20 that is negative on a licensed HIV-1 supplemental
21 test should be tested by a second different
22 licensed HIV-2 EIA and must be negative. Then a
23 follow-up sample should be obtained at least six
24 months later and tested by the original EIA; a
25 whole viral lysate EIA, if the original repeatedly

1 reactive test was not a whole viral lysate-based
2 test; a licensed HIV-1 Western Blot or IFA; and a
3 second different HIV-2 test, if the original
4 repeatedly reactive EIA was an HIV-2 test.
5 All these tests must be negative for
6 reentry of the donor. That's the currently
7 recommended procedure for donor reentry for HIV.
8 The current FDA recommendations for
9 reentry of blood donors deferred because of a
10 repeatedly reactive test for antibodies to HCV were
11 outlined in the memorandum to blood establishments
12 of August 5, 1993. The donor should be reevaluated
13 by testing a follow-up sample collected after a
14 minimum time period of six months following the
15 index donation.
16 That follow-up sample should be tested for
17 anti-HCV using a licensed multi-antigen screening
18 EIA, and if it's nonreactive, tested using a
19 licensed multi-antigen supplemental test. If the
20 supplemental test is negative, the donor may be
21 reentered. However, many donors remain deferred
22 because the use of the recently licensed RIBA-3
23 supplemental test as part of this previously
24 published FDA reentry algorithm has not been widely
25 implemented.

1 The goal of this BPAC session is to
2 outline suitable criteria for reentry of donors
3 deferred because of HIV or HCV NAT or serologic
4 test results. Today, FDA is proposing two new
5 reentry algorithms based on the combined use of NAT
6 and serologic testing for consideration by the
7 committee and for public comment, one for donors
8 deferred because of HIV test results and a second
9 for donors deferred because of HCV test results.
10 FDA's proposal for HIV reentry is
11 summarized in the next two slides. There are
12 several options that we will discuss in this
13 proposal. Donors are placed into three groups
14 based on their screening test results.
15 FDA's current thinking is to propose that
16 Group 2 donors may be considered for reentry.
17 These are donors who have NAT positive results but
18 they are seronegative. The NAT positive result has
19 not been confirmed by a positive result on a
20 supplemental NAT. If a supplemental NAT is done,
21 it must be negative.
22 FDA will be asking the committee whether
23 it is useful to consider for reentry donors in
24 Group 1, donors with both a positive but
25 unconfirmed NAT and a repeatedly reactive screening

1 test for anti-HIV-1/2 that is also unconfirmed,
2 that is, indeterminate or negative on a
3 supplemental test.
4 The issue here is that within this group
5 of donors, the number who may be eligible to
6 reenter is expected to be very small. It's
7 estimated at, say, 100 donors per year, and Sue
8 Stramer will have a lot more to say about this a
9 little later, so that considering this group of
10 donors for reentry may not be cost-effective or
11 yield-effective for the blood establishment.
12 Additionally, FDA proposes in Group 3 that
13 these donors may be considered for reentry. These
14 are donors with negative NAT who have a repeatedly
15 reactive screening test for HIV antibody, but
16 negative or indeterminate HIV-1 Western Blot or IFA
17 results on the initial sample. Now, Group 3
18 actually consists of three subsets of donors:
19 those with Western Blot results that are
20 indeterminate with viral bands present;
21 indeterminate with non-viral bands only; and
22 negative.
23 Another question that FDA will be asking
24 is whether possible reentry should apply to the
25 subset of donors in Group 3 who have indeterminate

1 Western Blots with viral bands present. The issue
2 here is whether follow-up studies on donors whose
3 blots are indeterminate but have viral bands show
4 that they are actually not infected with HIV.
5 Now, data presented on Western Blot
6 indeterminates at the June 1996 BPAC meeting led to
7 a conclusion by the committee that the rate of HIV
8 infection in persons with an indeterminate Western
9 Blot is extremely low, and that reentry could be
10 attempted for that group of donors as a whole. The
11 rationale behind the current FDA proposal is that
12 negative results of NAT testing on a follow-up
13 sample are a sufficient basis to negate concerns
14 over an indeterminate Western Blot containing viral
15 bands, provided of course that a suitable screening
16 test for antibodies to HIV also is negative on
17 follow-up testing of the donor.
18 Now, there is of course, in accordance
19 with current FDA recommendations, a fourth group of
20 donors not shown on this slide who would be
21 eligible for reentry: those with a repeatedly
22 reactive result on an HIV-1 p24 antigen test, and
23 with an indeterminate, that is, an invalid or non-
24 neutralized result on the neutralization test.
25 Some sponsors with NAT testing methods under IND

1 are currently attempting to obtain data to
2 demonstrate that their NAT method for HIV RNA, when
3 licensed, will be able to replace screening for
4 HIV-1 p24 antigen.
5 As long as antigen testing has not been
6 replaced by a particular licensed NAT method and
7 continues to be performed concurrently with NAT and
8 antibody testing, this group of donors would
9 continue to be eligible for reentry, as is
10 currently the case, if after eight weeks, at least
11 eight weeks, the p24 antigen EIA and all other
12 screening tests on the follow-up sample are
13 negative. Reentry for HIV-1 p24 antigen would
14 dovetail nicely into this FDA reentry proposal, but
15 it has been omitted from these slides for
16 simplicity.
17 FDA proposes, for all three groups of
18 donors deferred because of NAT or HIV antibody test
19 results, that a follow-up sample be taken after a
20 minimum time period of eight weeks for follow-up
21 testing of the donors by both HIV NAT and serology
22 follow-up testing. This slide shows the four
23 possible outcomes of the NAT and serology follow-up
24 testing.
25 If that follow-up sample is HIV NAT

1 positive, whether it is also EIA repeatedly
2 reactive or negative, the donor should be
3 permanently deferred.
4 If both the NAT and EIA tests on the
5 follow-up sample are negative, FDA proposes that
6 the donor may be reentered, that is, would be
7 eligible to donate again. FDA proposes that the
8 donor may be reentered, and that donation taken at
9 a later date would then be tested using the usual
10 battery of screening tests. Thus, two NAT tests
11 and two EIA tests would be performed and must be
12 negative before a unit from that donor could be
13 used.
14 Performing follow-up testing first on a
15 sample from the donor, before a donation is taken,
16 may prevent a potentially contaminated unit from
17 being drawn and placed in the quarantined inventory
18 of the blood establishment. Now, the argument can
19 be made that you don't make blood safer by
20 reentering donors, so you have to be doubly sure,
21 and testing a sample and then a donation would
22 provide an additional level of assurance in
23 reentering the donor.
24 On the other hand, a possibility to
25 consider here is whether a donation, not just a

1 sample, may be taken on this second visit and used
2 if all tests are negative. We will hear comments
3 today that a second visit by the donor just to give
4 a sample is unnecessary, and adds complexity for
5 the donor and for the blood establishment, who
6 would have to manually handle and track the testing
7 of the sample off-line, separate from a
8 computerized system, and that the donor should be
9 allowed to donate a unit at that time. We would
10 welcome comments from the committee on this point.
11 But the main issue at this stage is
12 whether an eight-week follow-up period encompasses
13 the pre-seroconversion window period for HIV with
14 sufficient confidence that negative serology rules
15 out HIV infection. In the absence of evidence for
16 seroconversion, the negative NAT on follow-up
17 testing would be taken as evidence that any prior
18 positive but unconfirmed NAT result was an error.
19 Now, several specific concerns regarding
20 HIV-2 Group O and HIV-1 Group M variants need to be
21 addressed at this point, so let me go back one
22 slide.
23 For donors in both Group 1 and Group 3, if
24 the index donation was repeatedly reactive on an
25 HIV-1, HIV-2 combi EIA, and if the HIV-1 Western

1 Blot or IFA performed on the initial sample is
2 indeterminate or negative, current FDA
3 recommendations are that testing for possible HIV-2
4 infection be carried out. These donors would only
5 be considered for reentry in Groups 1 or 2 if that
6 second, different licensed HIV-2 EIA is negative,
7 or if it's repeatedly reactive, if the optional
8 HIV-2 supplemental test is not positive, that is,
9 indeterminate or negative.
10 In June 1996, the Blood Products Advisory
11 Committee voted that an HIV reentry algorithm
12 proposed by FDA was acceptable. This algorithm
13 would allow reentry of donors with an indeterminate
14 Western Blot if, after six months, two EIA tests,
15 one on a sample and the second on a donation, were
16 negative.
17 It was considered permissible to run an
18 EIA test on the follow-up sample and then on the
19 donation that is the EIA test that is currently in
20 use at the blood establishment. It does not have
21 to be the original EIA that was run on the index
22 donation.
23 In 1995, two cases of confirmed HIV-1
24 Group O infection were identified in the United
25 States. Studies showed that some licensed HIV

1 screening tests have reduced sensitivity for Group
2 O, and the concern was expressed at the June 1996
3 BPAC meeting that a donor with an HIV-1 Group O
4 infection who is identified by a repeatedly
5 reactive test on the index donation and is then
6 deferred for six months, could then provide a
7 follow-up sample that is negative and a subsequent
8 donation that is negative because the blood
9 establishment has changed to using a different EIA
10 that is not as sensitive for Group O as was the
11 screening test that was used on the index donation.
12 That donor could then be reentered and could
13 transmit the infection.
14 As a result of this concern, FDA decided
15 to place the issuance of guidance containing the
16 approved reentry algorithm on hold until test kits
17 are licensed that are labeled with a claim of
18 sensitivity for Group O.
19 Now, to alleviate this concern about Group
20 O and also HIV-1 variants, in the current algorithm
21 for reentry FDA would like to stipulate that the
22 testing on the follow-up sample from the donor
23 include a licensed HIV NAT method that is labeled
24 sensitive for HIV-1 Group O and HIV-1 Group M
25 variants. In addition, the anti-HIV-1/2 EIA test

1 performed on the follow-up sample should be the
2 original EIA for HIV-1 and HIV-2 that was run on
3 the index donation, or an alternate EIA that is
4 also an HIV-2 test and is labeled sensitive for
5 HIV-1 Group O.
6 Now, the last question on HIV reentry
7 addresses the case in which follow-up testing by
8 HIV NAT is negative but there is a persistent HIV
9 antibody EIA repeatedly reactive result. An option
10 to consider is whether the donor can be further
11 tested by Western Blot, and if the Western Blot
12 test result is negative or if an indeterminate blot
13 pattern has not progressed, such as one with non-
14 viral bands only, can the donor be treated de novo
15 as a member of Group 3 and reconsidered for entry
16 after a second waiting period of eight weeks?
17 Many blood establishments would like to
18 continue to follow up such donors. However, if a
19 significant percentage of them actually prove to be
20 infected, concern has been raised about their
21 continuing to visit the donor setting for follow-
22 up.
23 FDA's proposal and proposed options for
24 HCV reentry are summarized in the next slides.
25 Similar to the reentry options for HIV, donors are

1 grouped according to their screening test results.
2 Again, FDA proposes that reentry be considered for
3 donors in Groups 2 and 3, donors who are positive
4 on NAT but negative on HCV serology and vice-versa,
5 with the reactive test being unconfirmed by
6 supplemental NAT or RIBA in either case. FDA seeks
7 advice from the committee on several options that
8 are included in this proposal.
9 We will ask whether it is useful to
10 attempt reentry for Group 1 donors, that is, donors
11 with NAT positive not confirmed positive by a
12 positive result on a supplemental NAT, if one was
13 performed; HCV antibody EIA repeatedly reactive;
14 RIBA indeterminate or negative results. Now, the
15 issue here is similar to that for HIV reentry,
16 namely, whether it is practical to consider for
17 reentry the small number of donors who are
18 screening test reactive both on NAT and serology.
19 The next question addresses whether Group
20 3 donors who are NAT negative and HCV EIA
21 repeatedly reactive for antibody should include
22 those with an indeterminate RIBA. Now, the
23 pertinent data that we will see in this session
24 will address the prevalence of HCV infection in
25 RIBA-indeterminate donors.

1 FDA's current thinking is to give the
2 blood establishment the option of following up with
3 an HCV NAT test at any time up to six months after
4 the index donation, for example, eight weeks later,
5 due to concerns about intermitted HCV viremia
6 resulting in a possible true negative NAT on later
7 follow-up testing. Current research indicates that
8 detectible viremia may be intermittent and may also
9 be resolved in about 20 percent of cases--and we'll
10 hear a lot more about that this morning, too--in
11 about 20 percent of cases of HCV infection, so that
12 we might expect a follow-up NAT for an infected
13 individual to occasionally be a true negative.
14 This preliminary follow-up NAT, this
15 preliminary one, could be made a recommendation
16 rather than an option, to add an extra measure of
17 safety. This HCV NAT would be performed for
18 purposes of donor counseling, and if it's positive,
19 to exclude the possibility of reentry. If that
20 optional NAT test is negative or if it is not done,
21 the donor would be followed up with HCV NAT and HCV
22 antibody EIA after an appropriate period of time to
23 quality for reentry.
24 FDA proposes for all three groups of
25 donors deferred because of NAT or HCV antibody test

1 results, that a follow-up sample be taken after a
2 minimum time period of six months for follow-up
3 testing of the donor by both HCV NAT and HCV
4 antibody EIA. And again, we would welcome comments
5 from the committee regarding whether a donation,
6 not just a sample, could be taken during this
7 second visit by the donor and used if all tests are
8 negative.

9 This slide shows the four possible
10 outcomes of the HCV NAT and HCV serology follow-up
11 testing. If that follow-up sample is NAT positive,
12 the donor should be permanently deferred. If both
13 NAT and EIA tests on the follow-up sample are
14 negative, FDA proposes that the donor may be
15 reentered, that is, would be eligible to donate
16 again.

17 FDA is also asking if waiting at least six
18 months after the index donation is an adequate
19 period of time. The current published FDA
20 recommendation that I showed before on HCV reentry
21 is that a minimum time period of six months elapse
22 between the index donation and the follow-up
23 sample. But the answer to this question really
24 depends on data which shows whether a six-month
25 follow-up period encompasses with sufficient

1 confidence the pre-seroconversion window period for
2 HCV.
3 In the last question, FDA will ask whether
4 a donor with negative NAT but with a persistent HCV
5 antibody EIA repeatedly reactive result, may at the
6 option of the blood establishment be reconsidered
7 for reentry in a second cycle of testing, provided
8 that an appropriate RIBA test is negative.
9 The presentations in this session are
10 intended to focus on the data the committee will
11 need to address these questions. Dr. Michael Busch
12 will present a scientific overview, including data
13 for both HIV and HCV on time to viremia and on the
14 duration of the viremic pre-seroconversion window
15 period; evidence for and against transient viremia
16 in the eclipse phase; and immunosilent infections.
17 Dr. Susan Stramer and Dr. Susan Galel will present
18 data obtained under IND from screening and follow-
19 up studies using the Gen-Probe and Roche NAT
20 testing systems, respectively.
21 Thank you.
22 DR. NELSON: Thank you very much, Dr.
23 Mied.
24 Questions from the committee? Yes, John?
25 DR. BOYLE: I have a couple of questions

1 for clarification purposes. First, although your
2 algorithms are different for plasma and blood, the
3 questions posed to the committee are for both. Is
4 that correct?
5 DR. MIED: Yes, that's correct.
6 DR. BOYLE: Okay. Second question. Are
7 donors under the new, the proposed thing, are the
8 donors informed of their positive test after the
9 first positive test, or only after the confirmatory
10 test?
11 DR. MIED: In serology testing, they are
12 informed after the result of the confirmatory test.
13 That's a PHS recommendation, that results not be
14 provided until the supplemental test is performed.
15 For NAT testing under IND, the story is a
16 little bit different. Sometimes the question of
17 whether that was a false positive is resolved right
18 away, before the donor is even informed that his
19 result was positive the first time around.
20 DR. BOYLE: Last question. Since the
21 intent of this change is not to directly improve
22 blood safety, is the goal of the change to increase
23 the number of units of blood that are available, or
24 is it to reassure donors who have initially tested
25 positive that they are now negative?

1 DR. MIED: It's both, but primarily the
2 latter. I talked initially about 14,000 donors per
3 year deferred just because of serology test
4 results, and many of those are not infected, and
5 the message to them is very troubling.
6 DR. BOYLE: Thank you.
7 DR. NELSON: Yes, Toby?
8 DR. SIMON: I just wanted to clarify that
9 when you were asked the question about the
10 reentries being different for blood and plasma,
11 they are the same, aren't they?
12 DR. MIED: They would be the same, yes.
13 DR. SIMON: Thanks. Right. And just in
14 terms of also responding from industry, in terms of
15 what is told donors, it is somewhat different in
16 the plasma industry because the donors come to
17 donate twice a week, so that the time they come
18 after they've had a positive serology, they
19 obviously can't donate, so they have to be told
20 something.
21 With whole blood and pheresis donors, you
22 have several weeks, so you have time to get the
23 confirmatory results, but we often don't in the
24 plasma industry.
25 DR. NELSON: By a supplemental NAT, that

1 just means a NAT with a different methodology than
2 the original NAT screening? Because they're not
3 licensed yet. Or what do you mean by a
4 supplemental NAT?
5 DR. MIED: We mean, by a supplemental NAT,
6 a NAT method that has been validated to work on
7 individual donations, and some of the IND holders
8 are doing this. But a supplemental NAT can be the
9 same NAT method as the one that was used
10 originally, but with a different set of primers and
11 probes, or it can be an entirely different NAT
12 technology.
13 DR. NELSON: If the probes are different,
14 it's a different test, I think. But it has to be
15 licensed and be known to be sensitive.
16 DR. MIED: Well, it would be part of the
17 licensure, yes, that they could perform a
18 supplemental NAT that they validate.
19 DR. NELSON: Right, so theoretically,
20 maybe not actually but theoretically, if the
21 primers were different it could be a viral variant
22 that the supplemental NAT was not as sensitive to
23 as the original NAT, right?
24 DR. MIED: Yes. From the data we've seen,
25 and it is limited data so far, under IND the

1 testing that has been done on viral barriers has
2 turned out pretty well. The NAT methods are
3 working well with HIV-1 Group M variants, as well
4 as HIV-1 Group O.
5 DR. NELSON: Other questions? Okay, thank
6 you, Dr. Mied. It was a clear presentation of some
7 fairly complex algorithms.
8 The next speaker is Dr. Michael Busch from
9 Blood Centers of the Pacific, who will tell us
10 about window periods.
11 DR. BUSCH: Thanks, Kenrad. Yes, I want
12 to first applaud FDA for not only entertaining
13 reentries for NAT reactive donors but most
14 important, as Paul summarized, for allowing the NAT
15 data and the implementation of NAT to allow a major
16 advance, I think, in the counseling and
17 reinstatement of seroreactive donors, which
18 numerically the false positive seroreactors are
19 dramatically greater than the number of NAT
20 reactors.
21 I want to just start out here with just a
22 couple of slides, sort of summarizing the general
23 patterns that we're all very familiar with for HIV
24 and HCV, and then the rest of the talk is sort of
25 an update of a recent talk I developed that looks

1 at the more oddball kinds of findings that we have
2 seen and sort of puts them into a broad context of
3 different stages of infection.
4 But in general what we understand for HIV
5 is that within typically several weeks of exposure,
6 during which there may be a period we call the
7 eclipse phase, during which one can't detect virus
8 in the plasma but the person has been exposed and
9 is incubating the virus, probably in lymphoid
10 tissue, that is followed by a very brisk ramp-up
11 phase viremia with a rapid doubling time of 21
12 hours, that eventuates in a peak viremia that is
13 actually controlled by the seroconversion, by the
14 cellular and human immune responses, and one
15 typically stabilizes the viral load at a so-called
16 set point. And virtually 100 percent, 100 percent
17 of people who become infected with HIV and ramp-up
18 the viremia remain persistently infected. Of
19 course, with the current HAART therapy, many of
20 these people can be driven to NAT negative and yet
21 remain infected.
22 This also shows then the typical timing
23 between the detection of RNA about 5 to 10 days
24 before one can detect p24 antigen, and then usually
25 about five days later the contemporary, very

1 sensitive antibody tests we use in blood screening
2 become reactive. The Western Blot typically
3 becomes indeterminate several days later and then
4 positive within typically two or three weeks of
5 seroconversion.
6 With HCV it's quite a different pattern of
7 primary infection. Again, we seem to have a brief
8 period following an infectious exposure when one
9 can detect the virus, and then that's followed by a
10 very brisk ramp-up phase, even more rapid than HIV,
11 a doubling time of about 17 hours, and of course
12 you've seen a lot of data on this ramp-up phase
13 from these viruses as we've talked historically
14 about the relative value of different contexts of
15 nucleic acid testing, minipool or single donation,
16 or p24 antigen versus RNA.
17 But for today's talk what is most
18 important is that for HCV, unlike HIV, we typically
19 have this very high titer, prolonged plateau phase
20 viremia prior to seroconversion. So for unclear
21 reasons, the virus can persist in the liver and
22 replicate at extraordinarily high levels, and yet
23 have no evidence of either ALT elevation,
24 suggesting a cellular immune response, or antibody
25 seroconversion, for often two months or more.

1 Now, this slide shows the sort of general
2 paradigm, which is a stable, high-titer plateau
3 phase, but what I'll be emphasizing in the further
4 talks is the observation more recently of somewhat
5 more complex patterns of viremia. So as we've gone
6 through this and thought about it and studied these
7 different infections more and tried to understand
8 the infectivity during different stages of
9 transfusion-transmitted viral infections, we've
10 come to sort of further classify infection into a
11 more complex series of phases. I'll talk about
12 each of these.
13 The pre-ramp-up viremia phenomenon is
14 something that we've only uncovered in the last
15 year or so by testing back plasma donor panels and
16 finding very low-level intermittent viremia prior
17 to the ramp-up phase. We talked about the ramp-up
18 phase and the plateau or peak viremia, plateau for
19 HCV, peak viremia for HIV.
20 Another point that we've observed, and
21 I'll illustrate, is that at the time of
22 seroconversion some individuals show much, a very
23 dramatic fluctuation in viral load. And
24 occasionally we'll see people, particularly with
25 HCV, go RNA negative intermittently around the time

1 of seroconversion, and then some of these people
2 will eventually clear the viremia and establish a
3 resolution, a presumed complete eradication of the
4 infection with HCV. But the major of the people
5 for HCV, about 80 percent, and 100 percent of HIV
6 people, become persistent carriers with varying
7 viral load set points.
8 Two other phenomena that have been
9 observed with HCV, not to my knowledge--well,
10 there's a few cases with HIV--are the immunosilent
11 carrier, people who become viremic and remain so
12 and yet fail to seroconvert, and another phenomenon
13 of what we call transient viremia without
14 seroconversion, meaning people in whom viremia has
15 been detected and presumptively confirmed with
16 alternative sources of that original donation, or
17 even in some cases separate follow-up samples, and
18 yet subsequently the viremia is no longer detected
19 and the people fail to seroconvert. And obviously
20 these phenomena become very important to
21 considerations about a conservative reentry
22 strategy.
23 The pre-ramp-up viremia is a phenomenon
24 that we have uncovered, again, by testing back on
25 these plasma donor panels, and I'll illustrate some

1 examples. It's a very low level, usually only
2 detectible by individual donation NAT, so it may
3 not be that relevant to this discussion because,
4 again, we are screening with pooled NAT; often
5 intermittent, meaning that it's not a consistent
6 low-level viremia but disappears, and we've used
7 the term "blips" of viremia to describe this.
8 Usually the levels are so low that they can only be
9 detected by the very high sensitivity individual
10 donation NAT, and typically are below the level of
11 the quantitative assay, so we can't even get a
12 definitive viral load with the quantitative viral
13 load assays.
14 We don't know what these represent. We've
15 confirmed them with multiple assays and on multiple
16 aliquots. In some cases the hypothesis is that
17 they may represent the inoculum itself, or a very
18 early focal replication of the virus in lymphoid
19 tissue or liver, that seeds a little bit of virus
20 into the blood intermittently but precedes the
21 ramp-up phase.
22 And it's also possible that some of these
23 may represent individuals who have had repeated
24 exposures, and that these are actually independent
25 of what eventuates as the full infection; these are

1 an abortive replication phenomenon due to
2 independent exposures in the preceding weeks or
3 months. The preferred hypothesis, I think, is that
4 these represent a very early phase of viral
5 replication, prior to the ramp-up extensive
6 dissemination.
7 One question is, can these occur
8 transiently and not eventuate in a full ramp-up
9 viremia? We've only discovered them by testing
10 back from cases that did eventually become
11 unequivocally infected, but studies are underway
12 now to understand whether these may occur in very
13 high-risk populations in the absence of definitive
14 infection.
15 Another critical question is, is this
16 infectious? And I'll show you a summary slide of a
17 study going on now that is asking that question.
18 And there are also studies looking more carefully
19 at the kinetics and sequencing of the virus to
20 better understand this.
21 Now, this just illustrates a panel for HIV
22 that demonstrated this so-called "blip" pre-ramp-up
23 viremia. These are the serial bleed dates. This
24 is a panel from Alpha Bioclinical Partners. This
25 day zero is the day on which the first definitive

1 RNA positive result was detected, actually by
2 minipool NAT, and you can see that that was
3 confirmed and quantifiable by a quantitative PCR
4 assay, and that over the subsequent weeks this
5 person demonstrated the typical rapid ramp-up
6 viremia followed by seroconversion, and then the
7 viral load down-modulated.
8 Now, all of the prior bleeds from this
9 donor three weeks preceding were negative by
10 quantitative RNA, but when we tested them by
11 replicate high sensitivity qualitative RNA,
12 basically NAT screening assays, what was detected
13 was the first sample at 21 days prior, 1 of 10
14 replicates was found reactive. The next sample a
15 few days later, seven of eight replicate high-
16 sensitivity PCR assays were positive. And then
17 this person was negative consistently for two or
18 three weeks, and then we get into the ramp-up
19 phase.
20 And it's this phenomenon that again has
21 been confirmed on multiple replicates in several
22 laboratories. It's the observation that we're
23 trying to understand. In HIV we've seen this in 6
24 out of 18 panels that had serial samples extending
25 back, and in each case it tended to occur almost

1 exactly three weeks before ramp-up, two to three
2 weeks, suggesting that it's very consistent in
3 timing with the exposure to ramp-up viremia
4 phenomenon. So we're hypothesizing that this is
5 again an early replication phase that seeds the
6 plasma, but then the virus disappears into the
7 eclipse phase and replicates in lymphoid tissue
8 before it explodes.

9 With HCV we've actually seen this in a
10 different pattern. Again, this is now testing back
11 on a panel of what we would call a NAT converter.
12 So this donor was found to be viremic by pooled NAT
13 at this time point, and you can see the downstream
14 samples show the typical sort of plateau phase, 10
15 to the 7th copies per mL viremia.

16 When we tested back to better define the
17 ramp-up phase, we as expected found a few samples
18 immediately prior to the pooled positive that had
19 viremia and could be quantified, and these are the
20 kind of data that I've showed previously with
21 respect to the ramp-up phase dynamics. But what
22 was surprising, and I think important, is that in
23 addition as we tested back over several months of
24 preceding samples, we detected a low-level viremia.

25 And what these graphs are representing is

1 the percentage of replicates by the high-
2 sensitivity HCV TMA assay that were found to be
3 reactive. And what we found in this case was that
4 two months prior to ramp-up, this person had a
5 brief period over a week where two sequential
6 donations were detected, three out of four reps, by
7 TMA, and these were also confirmed by high-
8 sensitivity PCR assay.
9 Then the donor went negative, and then
10 again had a week of intermittent low-level viremia,
11 again non-quantifiable but detected by replicate
12 TMA and PCR, then negative, and then a low
13 positive, then negative. So it's almost as if
14 you're getting some biological fluctuating
15 replication.
16 We've seen this in about half of the HCV
17 panels, this pre-ramp-up viremia phenomenon, and
18 believe it's real and are trying to understand it.
19 And in collaboration with Harvey Alter, we're
20 actually now approved and are proceeding with some
21 chimp transmission studies using these pre-ramp-up
22 type samples, actually beginning with samples that
23 precede the blips, infusing large volumes, 50 mL,
24 from each of 10 donors into a chimp.
25 And then if that does not transmit, then

1 we'll proceed to the valley between the blip and
2 the ramp-up phase and determine whether there is
3 infectivity in this phase. And then finally we'll
4 go to the blips themselves and answer the question
5 as to whether the viremia, this very low-level
6 viremia detected in this phase, can transmit.
7 So then after that sort of unexpected
8 finding and data related to the blip viremia, we do
9 into the ramp-up phase. Now, there's extensive
10 data that I think demonstrates that this ramp-up
11 viremia, even the very lowest level viral loads, as
12 low as 10 or 50 copies per mL, are infectious, and
13 so our data really would support that all of the
14 ramp-up phase is infectious.
15 The plateau phase, we've talked about this
16 prolonged high-titer viremia in HCV that precedes
17 seroconversion. I'll show you some data on minor
18 fluctuations in viral load, in some cases more
19 dramatic than others. With HIV and HBV we don't
20 see that prolonged plateau pre-seroconversion, but
21 rather a rapid transition to a peak viremia that
22 then down-modulates with seroconversion, probably
23 as a result of immune control and clearance of the
24 virus.
25 Then we have a phase that I alluded to,

1 the peri-seroconversion phase, that as the immune
2 system kicks in, we will not infrequently see
3 fairly dramatic down-modulation of viral load, in
4 some cases in HCV even clearance or eradication of
5 infection. Now, in most cases this is a smooth
6 drop and it sort of stabilizes into a steady state
7 viremia, but some cases, as I'll show, show very
8 dramatic fluctuation, including some examples where
9 we've seen intermittent negative individual
10 donation and minipool NAT.
11 One slide I felt was necessary to present,
12 it's an older slide but it's an important sort of
13 point to be clear on. These are data on the time
14 from exposure to seroconversion that historically
15 have been used in a variety of studies, such as the
16 Shriber study, to estimate the duration of the pre-
17 seroconversion window period, and again we're
18 talking here about time from the exposure.
19 And the data that's available on this is
20 fairly limited because it only is valid if you have
21 an unequivocal point source of exposure, such as a
22 transfusion or a needle stick accident, and then
23 you have serial samples to assess time to
24 seroconversion. But, given that, with HIV and HCV
25 really the best data we have for HIV comes from a

1 CDC compilation of needle stick accidents that
2 eventuated in infection, and for which there were
3 serial samples tested by antibody as these patients
4 were monitored for evidence of infection.
5 That analysis, which Glen Satton
6 conducted, yielded a point estimate of 46 days from
7 exposure to seroconversion. This was cases that
8 were accrued during the late '80s and very early
9 '90s with early generation antibody tests, so we
10 think this is probably out-of-date.
11 Unfortunately, many of these cases, there
12 are no stored samples to go back and test the
13 samples. These were cases that just were exposed
14 and they were being tested at their hospital, and
15 the samples weren't being saved but the data was
16 what was contributed to this analysis that CDC
17 conducted.
18 Now, one disturbing thing here is that
19 there were some examples that took about six months
20 to seroconvert. There were two examples like that
21 in this analysis. Now, in both of those cases--in
22 one of those cases there were serial samples
23 available to go back and test. In both cases, the
24 patients, these health care workers, became
25 symptomatic about a week prior to serocoversion and

1 actually had a detectible viremic sample preceding
2 antibody.
3 In one of the cases, and in another
4 published case of a delayed HIV seroconversion,
5 there were samples available that could be tested
6 back, and all of the samples except for the samples
7 collected just before seroconversion were negative
8 for RNA and antigen, suggesting that these rare
9 delayed cases are really prolonged eclipse phase
10 infections where there is no viremia, the virus is
11 sort of hiding out in the lymphoid or mucosal
12 lymphoid tissues, and then only after a very
13 delayed period does the virus disseminate and does
14 one detect virus in the plasma and then
15 seroconversion.
16 This is important because when we're
17 talking about time to reentry for NAT, these donors
18 have to have been detected initially by that index
19 donation as NAT reactive. So I don't think that
20 these rare cases of delayed seroconversion for HIV
21 are necessarily relevant to the discussion today.
22 For HCV we have data actually from more
23 than this, but 46 cases that were compiled that
24 indicated 70 days on average from exposure to
25 seroconversion, with an outlier of 128 days.

1 Now, for HIV, in all of the cases that I'm
2 familiar with, in plasma donor panels or in the
3 yield cases detected through screening either the
4 whole blood or plasma sector, once a donor is
5 picked up as viremic, their subsequent evolution of
6 patterns is very consistent, with the progressive
7 ramp-up to the peak to the down-modulation and
8 seroconversion within several weeks of infection.
9 So with HIV we have not observed what I'll talk
10 about later, transient viremias or immunosilent
11 carriers that we have seen for HCV.
12 For HCV, we see again this rapid
13 transition to high-titer viremia. Interestingly, a
14 fair number of the HCV cases will show a small
15 fluctuation in viral load early following the peak
16 viremia, the entering the plateau phase, and this
17 is some kind of interaction between the virus and
18 the host that then establishes this steady state.
19 In terms of the duration of that plateau
20 phase, this is data from one study that we've
21 conducted looking at transfusion cases, where we
22 know the date of exposure and then we've tested
23 serial weekly samples and can define the day where
24 we detect RNA, which is typically within the first
25 one to two weeks following exposure, and we can

1 follow these samples and detect ALT and then
2 finally antibody seroconversion.
3 And the next slide summarizes data from 30
4 cases that we studied in the transfusion
5 transmitted viruses cohort, a Kappel and Meyer
6 analysis of time from the exposure event,
7 transfusion, to first detected RNA, to ALT, and to
8 antibody. And you can see here that RNA is
9 detected on average about 12 days, often the very
10 first available sample post-exposure. ALT
11 elevation occurs about 50 days, probably reflecting
12 cellular immune response. And the antibody tests
13 kick in about 70 days post-exposure, again with an
14 outlier of about 130 days.
15 Now, as Paul mentioned, in HCV about 20
16 percent of people who get exposed and go through a
17 viremic phase resolve the viremia. And this is
18 data from a study that Ken was involved with, the
19 alive cohort, Dave Thomas's group, where they
20 studied a series of injection drug users who
21 seroconverted, about 100 cases.
22 And they tested the samples prior to
23 seroconversion and downstream, and they were able
24 to sort these cases into about 80 percent that
25 became persistent carriers versus those who

1 resolved the viremia. And what we see here is that
2 in the cases that resolved the viremia and
3 eventually became RNA negative, consistently so
4 over many, many years of follow-up, these
5 individuals show this fluctuating viral load around
6 the time that they're resolving the viremia.
7 In addition, even the cases that became
8 persistent carriers, 12 percent of those cases at
9 the time of serocoversion had an isolated negative
10 RNA result, pointing out that around the time of
11 that important interaction of the host immune
12 system with the virus, the viral load can fluctuate
13 dramatically. In some cases the immune system is
14 successful in eradicating the virus, but even in
15 those who become persistent carriers there can be
16 transient negative results at the time of
17 seroconversion.
18 This is a case that was discovered in the
19 NAT screening of whole blood donors in Florida, in
20 a donor who was detected at this time point zero by
21 the TMA assay. Prior donations were negative for
22 antibodies and ALT. There was no residual sample
23 to go back and test.
24 This index sample then was strongly
25 positive by the TMA assay, detected by pool testing

1 and individual. Now, you see the TMA test, which
2 doesn't have a very broad dynamic range, seems to
3 be strongly positive throughout this period until
4 it goes negative actually at the time of
5 seroconversion. The bleed before seroconversion
6 and then at the time of seroconversion, the TMA
7 result was negative.
8 In addition, when we tried to quantify
9 viral load, the viral load showed much more
10 dramatic fluctuations, going below limit of
11 detection on several samples during this phase.
12 Now, there were ALT spikes corresponding to this,
13 suggesting that the cellular immune response was
14 probably controlling the virus, but it just
15 illustrates how one can get dramatic fluctuations
16 in viral load, including negative minipool and
17 individual donation NAT results at times around the
18 time of seroconversion.
19 Now, finally to just touch on these two
20 other phenomena, the so-called immunosilent
21 carriers and transient infections, this again is
22 defined as persistent viremia, the absence of
23 seroconversion. There have been case reports for
24 all three viruses, rare case reports for HIV, I
25 think a total world literature of about five cases

1 who developed AIDS and never developed antibody.
2 They tend to develop AIDS very quickly because
3 their immune response to the virus doesn't control
4 viremia.
5 With HCV we'll show you some examples, and
6 they are again rare but clearly do occur. Again,
7 in some cases for HCV, there's been two examples
8 published, one from France and one from the Red
9 Cross here, where donors who have these persistent
10 non-seroconverting infections have been documented
11 to transmit infections. In this case from France,
12 they transmitted to multiple recipients over a
13 series of years, so these clearly can be
14 infectious.
15 Now, the other phenomenon of transient
16 viremia, it has to be confirmed on alternate sample
17 sources or with follow-up sampling, and preferable
18 with serotyping and to confirm that this is real,
19 because this is very similar, obviously, to a
20 contamination event. So the only way that we
21 become confident that this is real, is really with
22 confirmatory data from other samples, and
23 preferably follow-up samples with genotyping both
24 of the virus and of the patient sample to confirm
25 that this is not a contamination.

1 Now, these have been observed. I'll show
2 you an example, and Sue may talk later about her
3 case, but we really don't know how frequent these
4 are. We suspect they are extremely rare. Whether
5 they represent blips that don't eventuate into full
6 infections is unclear, but there are studies going
7 on now to try to better define whether this is
8 happening at any frequency.
9 This is a slide that Sue will show later,
10 that illustrates both these immunosilent and blip,
11 transient infections. This is data from 25 Red
12 Cross NAT yield cases over the last two years, and
13 these are the cases that were HCV confirmed, RNA
14 positive on the original donation, and enrolled
15 into follow-up.
16 And the red here shows the time to
17 seroconversion. This is quite consistent with
18 around a 40- to 60-day time to seroconversion in
19 the vast majority of these NAT positive cases who
20 were followed prospectively.
21 But what I want to call your attention to
22 first are these bottom two cases, examples of
23 immunosilent infections detected at day zero as NAT
24 positive, having serial samples that remain NAT
25 reactive and antibody negative, in one case out to

1 a year, this is 350 days, in another case out over
2 600 days remained viremic and seronegative. Now,
3 these are not a problem in terms of reinstatement
4 because NAT is a part of the reentry algorithm, so
5 these donors would be detected as persistently NAT
6 positive.
7 More disturbing are two other examples
8 that Sue has, one of which, particularly important,
9 the donor was found to be NAT positive both on the
10 donation serum and plasma NAT tube and the plasma
11 component itself, with at least one follow-up
12 sample. And this donor then on subsequent bleeds
13 remained NAT negative and antibody negative, so
14 this is a phenomenon of transient infection in the
15 absence of follow-up seroconversion that we really
16 need to better understand biologically, and I think
17 needs to be recognized as we entertain
18 reinstatement.
19 Finally, after people seroconvert, now it
20 becomes a brief discussion about the issues
21 relevant to reentry of seroreactive donors, and how
22 good is the negative NAT results for verifying that
23 these donors can be confidently reinstated? Post-
24 seroconversion, again, most people who have
25 confirmed seroreactivity become chronic carriers,

1 and others though, in the case of HCV they do
2 appear to resolve infection.
3 With HCV we've talked about the fact that
4 20 percent of people become NAT negative despite
5 persistent confirmed positivity. Now, one question
6 is whether these people are infectious and whether
7 one would be comfortable reinstating, or using
8 liver or other tissues in transplant settings from
9 confirmed antibody positive but non-viremic HCV
10 cases.
11 Just some brief data from the blood
12 systems screening program, for HIV first. In our
13 program, through a period of the first nine months
14 or so--I should have updated this--but for 511
15 donors who were EIA repeat reactive, they sorted
16 out into 22 confirmed antibody positive, 249
17 indeterminate, and 199 negative.
18 Now, in our studies, none of these donors
19 who were indeterminate or negative were confirmed
20 positive through routine NAT screening. We also
21 tested a representative group of these by
22 individual donation NAT, and again, none of them
23 proved to be viremic by individual donation NAT, so
24 strongly supporting the recommendations by FDA that
25 we consider reentering these donors with non-

1 confirmed serology and negative NAT results, these
2 donors down here.
3 Now, this illustrates a point that we'll
4 see with HCV, as well, that of the 22 confirmed
5 Western Blot positive donors, 21 of them were
6 detected by the minipool NAT as viremic. One was
7 not, but when that one case was tested by
8 individual donation NAT, it was found to be
9 reactive, so this donor was infected but just had a
10 low viral load.
11 With HIV, we and others have done
12 historical large studies of indeterminate donors.
13 Now, in the past these studies were quite involved
14 because we had to get these donors back and do
15 nucleic acid testing to rule out infection. Now,
16 these numbers are huge because we are routinely
17 getting nucleic acid test results on every
18 donation, so we can really counsel and reassure
19 these donors at the get-go. I'm not going to go
20 into this, but the bottom line is, we studied these
21 355 donors extensively by PCR and serologic tests,
22 and none of these donors proved to be infected.
23 Now, in terms of HCV, as I summarized, the
24 observation of rate of viremia among seropositive
25 donors, about 80 percent, turns out to be true in a

1 whole variety of cohorts. Not only among the large
2 numbers of blood donors who we have obtained
3 routine NAT data on do we consistently see
4 approximately 80 percent persistence, 20 percent
5 clearance, but one sees the same thing in studies
6 of injection drug users, in AIDS patients, again
7 strongly suggesting that this really may represent
8 eradication of infection, and may even represent
9 immunity to reinfection. Many of these injection
10 drug users continue to be exposed, and yet we see
11 these patients, once they've cleared the viremia,
12 never become recurrent viremic, or only rarely so.
13 So this suggested these people may not be
14 infectious, and indeed there was a study published
15 several years ago, a review of HCV data correlating
16 infectiousness with PCR results, over 2,000 people
17 who were exposed to anti-HCV positive sources, and
18 overall in this study there were 148 transmissions
19 associated with the subset of these confirmed
20 antibody positive donors that were viremic.
21 The transmission rates varied dramatically
22 from the seropositive sources relative to the type
23 of exposure, so about 6 percent perinatal, 6
24 percent needle stick, about 80 percent
25 transmissions with solid organs, and about 90

1 percent of the donations that were transfused that
2 were antibody positive and RNA positive,
3 transmitted. Now, in this study sort of the key
4 bottom line was that they did not observe any
5 transmissions from 874 cases that were confirmed
6 antibody positive but RNA negative, suggesting
7 again that these people who are antibody positive,
8 RNA negative, have truly eradicated and are not
9 infectious.
10 But we have recently done some studies
11 with Ev Operskalski in the REDS group, looking back
12 at samples from the TTVs, donation samples from the
13 repository. These were confirmed positive samples.
14 I think there were about 90 confirmed positive
15 donation samples for which we knew the recipient
16 outcome by testing the downstream samples. Overall
17 there was about an 80 percent infection rate in
18 these recipients.
19 But this shows the rate of infection
20 relative to the donation RNA status, and you can
21 see that there were 15 samples that were RNA
22 negative by a quantitative RNA assay with about a
23 2,000 copy sensitivity, comparable to minipool NAT,
24 and we did see six transmissions from these 15
25 cases. So this is just to emphasize that

1 personally I don't believe we can be comfortable
2 ever reinstating a donor who is RIBA positive and
3 RNA negative. Although the evidence would support
4 that most of these people have eradicated the
5 infection and are probably not infectious, I think
6 there are other evidences that some of these people
7 may have low-level infection and could transmit.
8 With HCV, again you'll see much more data
9 from Susan Stramer and Susan Galel from the two
10 major screening programs from the Blood Systems
11 Group, data correlating again the RIBA pattern with
12 the NAT results. And we had here 849 RIBA
13 positives. Of those, 80 percent were viremic.
14 Interestingly, when we tested these samples or a
15 subset of these that were negative by pooled NAT,
16 by individual donation NAT about 5 percent of them
17 were low-level viremic by individual donation NAT,
18 so again arguing that we cannot consider
19 reinstatement of confirmed RIBA positive but pooled
20 NAT negative donors.
21 In our studies we did find a small
22 fraction, 6 percent of the indeterminate RIBA
23 results, were confirmed by NAT results. Half of
24 these were actually indeterminate because of the
25 SOD band reactivity, so this is a control band.

1 They had multiple HCV bands and would have been
2 positive, were it not for this control band
3 reactivity. The others had the usual sort of
4 indeterminate high-risk bands of c22 or c33.
5 So there is a small fraction of
6 indeterminates that are viremic, but these would
7 usually be detected by RNA. And certainly on
8 serial follow-ups, I think if you are negative by
9 RNA and EIA negative, that reinstatement of these
10 donors would seem appropriate, and we haven't
11 detected any donors who were RIBA negative and
12 infected.
13 So in terms of the data that I reviewed
14 and summarized in the FDA algorithms, for donors
15 that are NAT reactive, that are not confirmed by
16 supplemental NAT and EIA nonreactive, I am
17 comfortable with the FDA recommendations that those
18 donors be considered for reinstatement if they are
19 nonreactive on NAT and EIA at least eight weeks
20 out.
21 With respect to HCV, I think the data on
22 the intermitted viremia around the time of
23 seroconversion and the rare observations of
24 immunosilent and transient infections justifies the
25 FDA position of a six-month wait, and I think also

1 supports their recommendation that there be an
2 interval sample prior to an allowed donation; that
3 you have to test a sample out six months
4 independent of a donation, and then the donor
5 should come back and can donate again, at which
6 point again all the tests will be repeated.
7 To me it's a little bit easier to
8 discriminate the recommendations for the NAT-
9 reactive, EIA-nonreactive relative to the opposite,
10 the much more common EIA-reactive, NAT-nonreactive
11 donations. Again, if the supplemental tests are
12 positive even for HCV, where we think people do
13 eradicate, I don't think reinstatement should be a
14 consideration. If the supplemental tests are
15 negative or indeterminate, I think reinstatement is
16 appropriate.
17 Personally, I would tend to recommend
18 going for the six months here, even for HIV,
19 because I think these donors, giving them six
20 months to clear that false positive serologic
21 reactivity is useful. If you bring them back too
22 quickly, they may have a persistent nonspecific
23 reactivity, maybe even in the same lot of reagents,
24 that would result in a nonspecific EIA again, and
25 then you'd be back at step one. So I personally

1 think that a six-month deferral for both viruses
2 for reinstating the EIA false reactives may be more
3 appropriate.
4 Thank you.
5 DR. NELSON: Thank you very much, Mike.
6 Questions? John?
7 DR. BOYLE: Just one question on your
8 comfort level for the reinstatement. Do you have
9 any difference in that comfort level between plasma
10 donors and blood donors?
11 DR. BUSCH: Well, I think there is a
12 practical reality. I don't know for a fact, but I
13 personally would be surprised if the plasma
14 industry is considering or would likely consider
15 active reinstatement. Their programs tend to be
16 much higher throughput, and once a donor is
17 problematic, it's sort of not the setting where
18 they are going to go back, and for reassurance of
19 the donor purposes, liability concerns, etcetera.
20 So I don't think the plasma donor reinstatement
21 programs are a serious consideration, although I
22 don't know for sure.
23 And there is certainly evidence that there
24 is a slightly higher incidence rate. There is
25 certainly a higher yield of these NAT tests in the

1 plasma donor sector. On the other side of the
2 coin, they have on the back end extensive
3 inactivation techniques that would eradicate. So I
4 don't really think there is a justification for a
5 differential policy.
6 DR. NELSON: Mike, in those, the panels
7 that you saw these blips for hepatitis C in these
8 frequent--I guess these were plasma donors, were
9 any of these drug users or people who would also
10 have frequent exposure during that period, or do
11 you know that?
12 DR. BUSCH: Right. We don't have
13 interview data on any of these donors. These
14 panels are anonymized with respect to the donation
15 IDs. There are studies that I know the CDC and the
16 REDS group are trying to initiate in collaboration
17 with the plasma industry, that would begin to do
18 interviews of these viremic donors, but at this
19 point we don't have evidence of risk behavior.
20 Although we know in the whole blood sector, and I
21 think you've even done historical studies, that the
22 vast majority of these HCV viremic donors and
23 antibody positive donors, that parenteral drug
24 exposure is the major risk.
25 DR. NELSON: It might be interesting to do

1 genotyping studies of the viruses during the--

2 DR. BUSCH: Right.

3 DR. NELSON: --to see if it's the--

4 DR. BUSCH: Right, to compare with the--

5 the problem is, the viral loads are so low that

6 we've had a lot of difficulty getting those data.

7 DR. STRONCEK: What about HIV p24 antigen

8 testing? Does that add any value for the bulk of

9 NAT and antibody testing?

10 DR. BUSCH: No, in my opinion there is no

11 additional value, that every sample that has ever

12 been detected as antigenomic and real is readily

13 detectible by the pooled NAT systems.

14 DR. NELSON: Paul?

15 DR, SCHMIDT: Looking back at the donors

16 of somebody who gave blood--who received blood

17 about five years ago, let's say, or within the

18 limits of what we know about NAT testing, and the

19 patient is HCV positive, and looking back at the

20 donors who may have cleared, if they're both NAT

21 and serologically negative, does this rule them

22 out? This is a different approach to what you have

23 presented here, I think.

24 DR. BUSCH: Right. No, you may have

25 gotten a pre-handout that I sent in that included

1 that approach of trying to use either recipient
2 outcome or donor lookback transmission data to
3 understand better the infectivity question.
4 Unfortunately, there has not been a real
5 good, I think, either national or international
6 effort to compile data on reported cases of
7 transfusion infection, and then going back to the
8 prior donations and understanding whether those
9 donors are infected. We are beginning to see some
10 really nice data from Japan and several European
11 countries where they have established comprehensive
12 repositories. Every donation has 2 or 3 mLs of
13 plasma saved.
14 And in a recent paper that will be coming
15 out soon in "Transfusion" from Japan, they had
16 about 95 cases of presumed HCV transmission from
17 blood transfusion, where they had recipients who
18 had HCV, no other risk factors. Most of them even
19 had documented seroconversion. Every single
20 donation sample was negative for HCV RNA, and the
21 donors were negative on follow-up.
22 So in Japan it looks as if virtually all
23 of these cases are really not transfusion at all.
24 They are community independent infections. With
25 HBV, though, they have found documented

1 transmissions, including a couple of cases with HBV
2 where the donation aliquot tested HBV DNA positive
3 from one of these donors implicated. On follow-up,
4 the donors were negative, so suggesting with HBV
5 that there may be transient viremias that don't
6 persist in the donors and yet may have transmitted
7 the virus to the recipients.
8 DR. FITZPATRICK: On the slide where you
9 talked, from Operskalski, where you're looking at
10 the 15 minipool positive, were there single donor--
11 DR. BUSCH: No, those were 15
12 serologically confirmed positive donations that
13 were negative by quantitative PCR, with a 2,000
14 copy sensitivity.
15 DR. FITZPATRICK: Okay.
16 DR. BUSCH: Yes, we did have, on some of
17 those we had enough volume for high sensitivity
18 TMA, for example, and on some of them we did detect
19 the virus, on some we didn't, the caveat being that
20 these samples are 25 years old, from the freezer,
21 so the viral load could have been artifactually
22 suppressed.
23 DR. FITZPATRICK: Okay. Thanks.
24 DR. NELSON: Yes, Blaine?
25 DR. HOLLINGER: I think, Mike, on some of

1 the things like the needle stick where you're
2 looking at the window period, you know, you can't
3 really exclude that these are not reinfected or
4 infected at a later period of time, particularly in
5 the needle stick patient. You don't have subtypes
6 that you can go back to, to look at the index case
7 to see if they really acquired that.
8 And then to make assumptions that there is
9 a long period there where they may be infectious
10 but you can't detect it, I think it may be wrong.
11 I can tell you from the TTV study, that patients
12 that we thought acquired their infection from blood
13 donations, now looking back it, we probably think
14 that many of them clearly acquired the infection
15 outside the blood transfusion. So just because
16 they got a blood transfusion didn't mean that they
17 acquired their infection from that transfusion. So
18 I think one has to be careful about those kinds of
19 statements.
20 DR. NELSON: Okay. Thanks. Next will be
21 Dr. Sue Stramer from the Red Cross.
22 DR. STRAMER: These colors are lovely. Do
23 I have a pointer?
24 Thank you. There will be some redundancy
25 between Mike's talk and mine, but that's actually

1 good because it supports the data that Dr. Busch
2 has just reviewed.
3 I can't read this. I just want to give a
4 NAT talk to update where we are with NAT programs
5 in the United States. What this slide shows you,
6 for two years of NAT testing, the various programs
7 under INDs and their current pool sizes that are
8 being done, including data that I just recently got
9 from Canadian Blood Services.
10 So this shows you the number of donations
11 screened over that two-year program, the number of
12 yield cases that we've had for HIV, and the number
13 of yield cases that we've had for HCV. Of the
14 seven, eight HIV cases here, two were also detected
15 by p24 antigen, again addressing the insensitivity
16 of p24 antigen relative to pooled NAT.
17 If you pool all of those data together and
18 just at bottom line say, "Where are we since we
19 implemented the NAT INDs," these are the data.
20 Over 29 million donations screened in two years,
21 with 113 HCV yield samples identified, for an
22 overall frequency of 1 in about 260,000, and this
23 number has been amazingly consistent over that two
24 year period of time.
25 For HIV, fewer donations but still a

1 startling 26 million plus donations that have been
2 screened and pooled, with eight positive for HIV
3 NAT, including two that were p24 antigen positive,
4 for a yield combining the two markers of HIV
5 infection of greater than 1 in 3 million, so
6 relatively low yield but the numbers are fairly
7 consistent, and certainly of a higher yield with
8 pooled NAT than they are with p24 antigen.
9 The next three slides are not meant as a
10 reading test, and unfortunately, the committee has
11 eensy-weensy copies of my slides, but for anyone
12 who does want a copy of my slides, the committee or
13 otherwise, I can e-mail them to you if you give me
14 your e-mail address or write me an e-mail.
15 But, anyway, this is the Red Cross
16 algorithm, and I will dwell on Red Cross data, for
17 two reasons: one, I am from Red Cross; and, two,
18 it's the largest consolidated data set that we
19 have. So firstly I just want to go through the
20 algorithm that we've been using under IND.
21 Once we have a NAT reactive donation, the
22 donor is deferred. As discussed by Paul Mied,
23 discriminatory TMA testing is done, since we use
24 the Gen-Probe system, but at the same time we also
25 send a sample for supplemental NAT testing. The

1 supplemental NAT test we use is the PCR test at
2 National Genetics Institute, which has been
3 validated for all HIV-1 subtypes and is ultra-
4 sensitive, actually more sensitive than the
5 screening test we use.
6 Any NAT reactive donor is enrolled into a
7 follow-up study. There are basically three types
8 of follow-up studies, broadly, two. One is if you
9 are a discriminated positive donor and one if you
10 are non-discriminated, because for non-
11 discriminated donors we have to understand the
12 nature of the multiplex activity relative to
13 negativity and discriminatory testing.
14 So if you discriminate for HIV, you are
15 enrolled in a three-month follow-up study or until
16 seroconversion occurs. If you're HCV NAT reactive,
17 you're enrolled in a 12-month follow-up study or
18 terminated if seroconversion occurs.
19 For the undiscriminated, non-discriminated
20 donors, they're enrolled in follow-u[and we test
21 them for both markers of HIV and HCV, because we
22 don't know which marker to test for. For donors
23 who test HIV NAT reactive, we test them by NAT,
24 PCR, so we do two NAT--TMA and PCR--we do two NAT
25 methods, and we do relevant serology. For HCV, the

1 same is true. We do TMA, PCR, and we repeat the
2 relevant serology and do ALT testing.
3 This is the outcome of follow-up testing.
4 Clearly, any donor who seroconverts to HIV or HCV
5 or has a repeatedly reactive outcome would be
6 permanently deferred. Those donors who don't
7 discriminate based on one follow-up sample, that
8 is, they're negative for all markers of HIV and
9 HCV, we terminate donor follow-up, and we have
10 proposed to FDA that these donors be eligible for
11 donation at their next donation, that is, in 56
12 days, based on the negative follow-up sample.
13 One additional test that we do on all NAT
14 reactive is, we obtain the plasma unit, the index
15 plasma unit, and test that by all tests: TMA, PCR,
16 and serology. This confirms the result, or refutes
17 the result in the case of sample contamination, of
18 the index test result of the sample. So in fact on
19 most donors, not only will we have follow-up
20 samples to identify true versus false reactivity,
21 but we also have the plasma sample to give us an
22 additional measure of what the status of these
23 donors are.
24 Now, for donors who have discriminated
25 test reactivity, what we have proposed, whether

1 they're HIV or HCV, to be reinstated after six
2 months, because as Mike said, it just gives enough
3 time for the donor to resolve and clear any
4 ambiguities that may exist, and it's consistent and
5 easier for the blood center. We also, if we were
6 to reenter, the plasma unit that has been tested
7 would have to test negative.
8 So, in summary, this is what we have
9 proposed for donor reinstatement. It would require
10 that two independent samples test negative for all
11 markers by NAT, and what we have been doing,
12 although not necessary perhaps for the future,
13 because we have collected quite a bit of data, but
14 we are now running two NAT methods, the primary and
15 the alternate NAT, and we also do serology as
16 appropriate.
17 The first sample, as discussed, is the
18 follow-up sample, and the second is the subsequent
19 donation sample, and this would be true for both
20 HIV and HCV. The donor reinstatement subsequent
21 donation can occur 56 after the index donation for
22 a non-discriminated NAT reactive result, or six
23 months following the index donation, so we're
24 giving the entire interval period of 56 days if
25 you're non-discriminated or six months if you do

1 discriminate, and I've already mentioned the
2 testing that goes on for both categories.
3 This is specifically Red Cross data, to
4 help focus on some of the slides I'm going to show
5 you. For the period of time that we were testing
6 pools of 16, the yield here, as shown on the first
7 slide, we've had 53 total HCV NAT reactives that
8 have been true positives, for a yield of, our total
9 yield now running at about 1 to 250,000 to 260,000,
10 our four HIVs. But this slide also shows you types
11 of false positives, and these are the categories
12 that we're concerned about either for product use
13 or for donor reinstatement.
14 As Paul Mied said at the last BPAC
15 meeting, we resolved basically the case of
16 unresolved pools, and said that the individual
17 donation test out of NAT reactive pool becomes the
18 boss test, so to speak. But what we will focus on
19 primarily here is a category, albeit small, of
20 donors who are not yield samples, so those donors
21 are the false positive donors.
22 Just again to show you what some of our
23 seroconverting donors look like for HIV and then
24 HCV, this shows you our first HIV case; our second
25 HIV case, who was also p24 antigen at the time of

1 donation, antigen confirmed positive at the time of
2 donation. Here are the viral loads. So again you
3 can see very high viral loads, p24 antigen, only a
4 transient marker, and you can note seroconversion.
5 Now the point here, as Mike said, is
6 seroconversion in HIV-infected donors is a very
7 rapid and a very reproducible event. Over any
8 donor we have studied over time, we see
9 seroconversion occur within days or weeks.
10 This is the third HIV positive we had,
11 again showing the same phenomenon of high RNA viral
12 loads, transient p24 antigen, and rapid time to
13 seroconversion.
14 I'm not sure why my data didn't transmit
15 well on this slide, but what this slide should say
16 is, of the 53--and the point I want to make on this
17 slide, which certainly got mangled in the export--
18 of 53 HCV NAT reactive donors, we've had 27 now who
19 have enrolled in follow-up, and of those 27, 19
20 have seroconverted.
21 This shows the one long-term immunosilent
22 donor that we've had, but for the purposes of this
23 discussion, the point of the matter is, this person
24 has remained high titer HCV positive during the
25 entire time, so he would never be eligible for

1 reentry.

2 Here it just shows you, and I've showed
3 you the second half of our follow-up, up to 587
4 days, the donor has remained flat negative, or flat
5 normal, I should say, for ALT; has remained
6 consistent in the TMA assay, whether the multiplex
7 or the discriminatory test; and has remained high
8 viral load during this entire time.

9 This is the slide that Mike showed,
10 showing you this donor, the donor that I just
11 showed you at about 600 days, who refuses to
12 seroconvert, so in a sense is immune tolerant,
13 meaning the donor and virus seem to have developed
14 a good relationship where neither appears to be
15 harmed.

16 Here we have another immunosilent donor
17 who continues, just like this first individual, to
18 not seroconvert. Here, this donor we had who did
19 seroconvert but became RNA negative at
20 seroconversion, so this would be a resolved case of
21 HCV.

22 This particular donor did seroconvert at
23 this time and was RNA negative at seroconversion.
24 However, disturbing, and like the Florida case that
25 Mike showed and I will show again, there was a

1 period of time of about 100 days where the donor
2 failed to be RNA positive even by individual
3 testing, because all of these tics show you the
4 follow-up sample. So this donor remained RNA
5 negative or became RNA negative and remained
6 antibody negative, but after this 100-day period
7 the donor did seroconvert, so this was relatively
8 transient within that 100 days.
9 The only disturbing donor is this donor
10 here, who on index was absolutely confirmed as RNA
11 positive for HCV. the plasma unit that we obtained
12 confirmed to genotype the RNA status of that
13 individual, but then upon subsequent follow-up
14 samples of one, two, three, four samples, the donor
15 was RNA negative in individual testing by TMA and
16 high input sensitivity PCR, and failed to
17 seroconvert.
18 So what I call this donor is likely an
19 abortive infection, where the donor probably was
20 exposed but for whatever reason cleared the virus
21 before they were ever infected. I don't know that
22 that's true, but that is certainly one hypothesis.
23 Okay, this shows the Florida case that
24 Mike showed, but the only reason I show this,
25 again, is to emphasize the time. This particular

1 column represents the reactivity on the TMA NAT
2 test, and the numbers over 1 here are all the
3 positive results. However, what you see here are
4 the two bleeds that Mike showed that went negative
5 at the time of seroconversion.
6 However, what Mike didn't focus on was the
7 fact that these were individual tests but, when
8 diluted 1 to 16, these samples were also negative.
9 So we did have relative intermittent viremia over a
10 longer period of time, and if you look at a broad
11 worst case time frame, this is about 79 days, or
12 not similar to the 100 days I showed you in the
13 previous slide.
14 To focus on the various groups that we're
15 talking about reinstatement for, this first shows
16 you the total number of NAT reactive donations that
17 the Red Cross has had while we've been testing
18 pools of 16 over approximately 12 million
19 donations, so we're dealing with a universe of a
20 really small number for a year and a half, of 529
21 donors.
22 And this of course excludes those that
23 were yield samples for HCV or those that were yield
24 samples for HIV, but you can see of those that
25 discriminated for HCV, the difference between 163

1 and 46 does represent a category of false
2 positives. There were no yield samples here in
3 which we couldn't complete testing because of QNS
4 sample. These were all false positives. The
5 difference here represented false positivity, and
6 these 318 certainly are all false positive.
7 We're not going to go through these slides
8 other than to say these are the algorithms that we
9 use to confirm a donor is true positive or false
10 positive. It's based on the supplemental NAT test.
11 It's then based on the plasma unit we get in for
12 additional testing, followed by follow-up of those
13 particular donors.
14 This represents the subset of HCV NAT
15 reactive donors. Those donors that were PCR
16 negative, that is, supplemental NAT negative, those
17 that are the Group 2 donors that FDA is discussing,
18 when you rule out any other causes of positivity or
19 who didn't clear in follow-up or plasma, we had a
20 total of 63 here who would be eligible for donor
21 reinstatement.
22 One category FDA isn't considering, but we
23 should consider, is during the process of pooling
24 or testing you can have source tube contamination.
25 So in the case of source tube contamination, when

1 we do supplemental NAT on that same sample, you
2 would expect the supplemental NAT to be positive
3 because the tube itself was positive.
4 Well, that in fact happens. Some PCR
5 positives of course represent our yield cases, but
6 some could also represent contamination, and we've
7 had 22 here by plasma and follow-up who have
8 cleared, who should be eligible for reinstatement.
9 This shows the same type of data for HIV,
10 and when all is said and done, a very small number
11 of HIV NAT reactive donors would be eligible for
12 reinstatement.
13 This slide combines those that were QNS
14 for discriminatory with those that were
15 discriminatory nonreactive. Of this very large
16 category, combining plasma and follow-up data for
17 those that we do have complete data, we know that
18 260 should be eligible for donor reinstatement.
19 Following along the same pathway here of those that
20 are PCR negative, and then plasma and follow-up
21 data available, we have 19 here who would be
22 eligible for donor reinstatement.
23 So if you combine the data for those
24 donors who would be eligible for donor
25 reinstatement from the flow diagrams I just showed

1 you, we have these broad categories. We have
2 discriminated TMA reactive, either that were
3 supplemental NAT negative or positive. We have
4 discriminated HIV reactive donors who were PCR
5 negative. Then we have those donors who were QNS
6 supplemental test negative, and those donors who
7 were non-discriminated supplemental test negative.
8 So taking this as our total universe,
9 which turns out to be a whopping 366 donors, this
10 shows you now the results we have, the absolute
11 numbers that we did confirm as negative in plasma
12 by a series of tests; those that we confirmed on
13 follow-up in a series of tests. And this gives the
14 time interval.
15 We didn't wait necessarily 56 days or 6
16 months to get a follow-up. We had a follow-up
17 immediately because the donors are very anxious and
18 want to know the status of their health. And even
19 in these short times, if something is a false
20 positive, it certainly is not going to reproduce as
21 we see here.
22 So this gives you the mean time, 39 days,
23 47, 11, etcetera, and the ranges here. For
24 example, for those that didn't discriminate, we
25 have a range of follow-up from three days, showing

1 the results were not reproducible, to 278 days.

2 If we annualize this, since this is based
3 on greater than a year data, we would say that the
4 annual projection from this 366 turns out to 204
5 donors or an annual yield of 1 in 31,900.

6 The next two slides show data from non-Red
7 Cross sites that are also using the Gen-Probe test
8 and have had very similar experience. This
9 represents the period of time from April '99
10 through August of 2000, all the data for Blood
11 Systems Laboratories on testing of over 2 million
12 NAT reactive donors.

13 Here they have had two HIV yield cases,
14 one that was also confirmed by p24 antigen. Of
15 those that discriminated for HCV, they have had 15
16 yield samples and 44 that are false positive, based
17 again on a compilation of supplemental test NAT
18 negativity and follow-up negativity, listed here in
19 the different categories.

20 For those non-discriminated donors, who
21 were 327, they were also able to confirm by
22 serology follow-up and NAT follow-up that these
23 donors were false positive, so they had 169 to add
24 to the numbers that I just showed for Red Cross.

25 This shows an updated slide, including

1 Blood Systems, Florida Blood Services, and Blood
2 Center of Southeast Wisconsin, from September of
3 last year through April of this year, adding about
4 another 2 million donations to this number. No HIV
5 yield cases, 25 discriminated HCVs, again with the
6 majority believed--well, at least four false
7 positives based on additional data, 14 pending
8 additional data, and here we have an additional
9 seven yield samples.
10 Looking at the non-discriminated results,
11 the Gen-Probe users who are non-Red Cross had a
12 change to their algorithm in their IND, and what
13 they do is, when they have any NAT reactive result,
14 they repeat it on the test, multiplex test, on the
15 same sample or an alternate sample. And based on a
16 non-reproducible result, one could say analogous to
17 an initial reactive result, they will reverse the
18 temporary deferral on those donors and reinstate
19 them. So there are 94 donors here who have not
20 been deferred, who are active donors, but their
21 products of the index donation were discarded.
22 Now, going through the other categories,
23 not just those that were NAT reactive false
24 positive and seronegative, now we've taken the
25 category and made the situation more complicated by

elw

1 adding in serology.

2 For HCV, and this does represent one year

3 of data

4 --it's a nice summary to tell you what the one-year

5 numbers are so I haven't updated it yet--but we

6 have about 8,000 repeat reactives, 4,566 have

7 confirmed by RIBA. As has been discussed here, we

8 have 80 percent that are RIBA positive and NAT

9 positive. Clearly, this category is one that we're

10 not going to entertain reinstatement on.

11 RIBA positive and NAT negative, we have

12 913, and although we will not talk about

13 reinstatement of these, I will show you subsequent

14 data for these showing the frequency of these NAT

15 negatives actually being NAT positives, which as

16 Mike said are relatively low but they do occur.

17 This category here, which is the Group 2

18 donors, RIBA indeterminates that are NAT negative,

19 if they are truly positive, will continue to be

20 RIBA indeterminate. If they are seroconverters,

21 they will progress to be RIBA positive, and they

22 should be RNA positive. Any seroconverters

23 shouldn't be in this category because their RNA

24 levels should be very high.

25 The only type of true positives that could

1 be in this category would be any long term resolved
2 HCV positives who still have antibody reactivity
3 due to their previous HCV infection, and over
4 periods of time these donors will remain antibody
5 positive or antibody reactive, and either RIBA
6 negative or RIBA indeterminate. So one shouldn't
7 be concerned with these donors because we know if
8 they're real, the RIBA pattern will persist and
9 they will not go, probably for years, into
10 negativity.
11 Looking at this category, which is the
12 Group 1 category, the incredibly small number of
13 donors who were false positives based on double
14 hits by serology and NAT, we do have small numbers
15 that are positive in the multiplex test by NAT,
16 that are indeterminate by RIBA and negative.
17 Now, based on the multiplex test, the
18 algorithm then goes on to discriminatory testing,
19 and then we do PCR testing on these donors. So of
20 those that were multiplex reactive, we do have 47
21 that discriminated, and of those, 43 that were
22 truly positive by PCR with this viral load. But
23 the difference between the 62 and the 43 would
24 represent the small number of false positive donors
25 that we could entertain reinstatement for.

1 In the RIBA negative category, we have had
2 34 multiplex reactives but only seven were
3 discriminatory reactive, and of those only five
4 were PCR reactive with lower viral loads. So there
5 are small numbers of false positives buried in
6 these data.
7 This shows retesting of those samples that
8 were RIBA positive but NAT negative. So of those
9 that were NAT negative, they either were NAT
10 negative because they were tested in pools or
11 because they were tested neat.
12 If we take those that were tested in
13 pools, we take an independent sample and test that
14 by PCR in individual donation to see if it's a real
15 result or not, the negativity, that is, we see only
16 a very small number, only 2 percent that will
17 repeat as NAT reactive in an individual donation.
18 Curiously enough, even if we take the neat sample
19 and retest it, there will be a small number, here
20 less than 1 percent, that will repeat as PCR
21 positive.
22 And this just shows you the viral loads,
23 the low viral loads and the RIBA patterns for those
24 samples that did repeat as NAT positive.
25 Okay, here are the same data for HIV.

1 We've had 4,000 annual repeat reactive donations
2 for combi testing. Only 6 percent are Western Blot
3 positive, and higher numbers are NAT positive. So
4 now we have the two categories again to deal with,
5 these 13 that are Western Blot positive, NAT
6 negative, and the category here that we could talk
7 about reentry for, Group 1, of those that are
8 indeterminate or negative but NAT positive.
9 Looking at these, most of these are false
10 positive. In fact, 36 of these 38 that were
11 multiplex reactive were false positive, so there
12 are actually higher numbers of HIV double hits,
13 theoretically, that could be reentered.
14 For those that were multiplex reactive,
15 none were discriminatory reactive and none were PCR
16 positive. So if you're asking the question, why do
17 these happen, it's just intra-assay contamination
18 that occurs while we're testing. The testing is
19 very manual, and it's very easy to have
20 contamination.
21 Just looking at those samples that were
22 NAT negative but Western Blot positive, are these
23 samples real or are they not real? These next two
24 slides just focus on the large number of Western
25 Blot positives that are NAT negative, that are in

1 fact false positives and really could be almost
2 indistinguishable from the indeterminates. They
3 have low reactivity on the EIA, relatively weak
4 patterns on Western Blot, in fact many with only
5 one gene product envelope reactivity. Samples that
6 have envelope bands only that are positive, have
7 never been shown to be from an infected donor, so
8 these are all false positives.
9 The only ones that are real are those that
10 have high EIA signals, all bands present on Western
11 Blot, and in fact these probably all have very low
12 viral loads, even though when we've repeated PCR
13 with sensitive methods, they have been negative,
14 and this case here has been positive with only 200
15 copies.
16 Same story, and in this positive sample
17 the viral load was too low. We couldn't even
18 quantify this because of low viral copy number.
19 So now to summarize all the data that I
20 have shown you, for the Group 1 donors that FDA is
21 discussing, these are NAT reactive, supplemental
22 nonreactive, although I will include supplemental
23 reactives in here. Actually, Group 1 is NAT
24 reactive, supplemental nonreactive; screen antibody
25 repeat reactive that are supplemental indeterminate

1 or negative.

2 So if you combine HIV with HCV and look at
3 the categories of indeterminate and negative, and
4 deduct those samples that were real positive, we're
5 dealing with indeterminates on an annual basis from
6 Red Cross, 36; 21 that are negative; for a total of
7 57, or a yield of 1 in 114,000. For HCV, 19 that
8 were indeterminates, false positive by both tests;
9 29 that were RIBA negative, false positive by NAT;
10 for a total of 48. So putting these two numbers
11 together for the Red Cross, which is about half of
12 the collections in the United States, we're talking
13 about a total of 100, approximately 100 donors.

14 Okay, for those Group 2 donors, those that
15 were NAT reactive, supplemental NAT nonreactive,
16 and here I've also included those that were
17 supplemental NAT reactive due to source tube
18 contamination but they were screen antibody
19 negative or antigen negative, I showed you a total
20 of 366 over approximately 12 million donations, but
21 if we annualized that, that was 204, for a yield of
22 1 in 31,900 or double the number I just showed you
23 for the Group 1. The number is a little bit higher
24 for non-Red Cross sites, but still relatively low
25 yield.

1 For the Group 3 donors, these are the NAT
2 negatives, screen repeat reactive, supplemental
3 indeterminate or negative, this is where we get the
4 most bang for our buck. And 7,000 here multiplied
5 by 2 for the entire industry is the 14,000 number
6 that Paul Mied spoke of earlier, for a yield of
7 about 1 in 1,000 donors.
8 Just to get on my soap box a little bit
9 about serological tests, since we're talking about
10 Group 3, it's important to entertain the idea of
11 reinstatement of indeterminate and negative donors
12 because even though we've been doing serological
13 testing for over 15 years, the tests are still not
14 stable, and there are frequently changes in
15 manufacturing lots that cause huge increases in
16 repeat reactives, and we happen to be undergoing
17 two right now.
18 This is the performance of the p24 antigen
19 Coulter test, and the number of samples we get per
20 month for confirmatory testing is in green.
21 Actually it should be blue, but it doesn't matter.
22 It's in green. Those that are neutralized
23 negative, which we call indeterminate, superimpose
24 this line because virtually everyone who is p24
25 antigen reactive is a false positive. We do have

1 antibody positives that are p24 antigens, small
2 numbers, and that line has remained fairly
3 consistent even though since November we've seen a
4 huge deterioration in the performance of the
5 Coulter p24 antigen kit.
6 I don't want to single out one vendor, and
7 in being fair we'll go to the next slide. This is
8 the data for the HIV antibody test which
9 serendipitously over the same period of time
10 happens to also be running rather poorly.
11 This is the total number of samples per
12 month submitted for confirmatory testing. These
13 are the numbers of indeterminates and negatives,
14 increasing in proportion to the total number, and
15 the number of positives you can see here actually
16 looks fairly constant, but by linear regression the
17 number is actually decreasing. Be that as it may,
18 reentry of these donors is important because we
19 still haven't reached nirvana with the performance
20 of these serological tests.
21 So now to group all of the groups together
22 and give you a total comparison, at least for about
23 50 percent of the blood industry, we have higher
24 yields for the Group 3 donors, about 1 in 1,000.
25 These numbers are very--these are the important

1 numbers here, since they're 35 times higher than
2 the Group 2 donors and 66 times higher than the
3 Group 1 donors, the Group 1 donors being the double
4 hits, NAT reactive and seroreactive, these being
5 the NAT reactive seronegatives.
6 So, in conclusion, I've shown you that our
7 NAT yields has been consistent for two years, about
8 1 in 250,000 to 300,000 for HCV; for HIV, about 1
9 in 3.5 million. Seroconversion in NAT reactives
10 occurs within days to weeks for HIV, and for 90
11 percent of cases within six months for HCV.
12 The exceptions are the next two bullets.
13 Immunosilent donors remain consistently HCV NAT
14 reactive, so those should not be a concern. And
15 donors with fluctuating viremia and delayed
16 seroconversion, in the cases that I showed you,
17 which is a huge number of two, did resolve within
18 100 days.
19 TMA false positive, seronegative donors
20 occurred a frequency of 1 in 6,000 to 1 in 31,900.
21 For all the TMA users, we have a total of 854 that
22 I could count, 541 that have additional negative
23 test results demonstrating false positivity.
24 Most of these donors don't even
25 discriminate, so we know we're in just the presence

1 of one assay contamination event, which I just say
2 here: Are the results of contamination either of
3 the sample, which would cause repeated NAT
4 reactivity, or a single event, which is from intra-
5 assay contamination? Pending NAT negative,
6 seronegative results on follow-up and or a
7 subsequent donation, these donors should be
8 considered safe.
9 NAT reactive, seroreactive, supplemental
10 indeterminate or negative donors are infrequent.
11 It is my opinion, due to low yield and dual
12 positivity, these donors should not be reentered.
13 We should be spending our time on where our maximum
14 yield is.
15 The vast majority of false positive
16 donors, these are the seroreactive, NAT negative,
17 pending NAT negative, seronegative results of
18 follow-up and/or subsequent donation, also these
19 donors should be considered safe.
20 Thank you very much.
21 DR. NELSON: Thank you, Susan.
22 John?
23 DR. BOYLE: Could you just clarify one of
24 the last numbers? Your yield of 7,000 from Group
25 3, how many of those, based upon your experience,

1 if they were not deferred would actually donate
2 again?
3 DR. STRAMER: Small numbers. Even though
4 donor reentry is not going to improve the
5 availability of blood, absolutely not, unless we're
6 talking about anti-core. Anti-core is a different
7 story, because that likely will increase the
8 availability of blood.
9 This is an issue that has to do with the
10 donor and the donor's status of their health, how
11 many phone calls I get a day from physicians, from
12 donors. You know, they don't believe that they're
13 really healthy unless we reinstate them. You know,
14 it's a really mixed message. "We believe you're
15 healthy, all the tests are negative, however, don't
16 donate blood." So, I mean, that's the purpose of
17 all of this.
18 DR. NELSON: Toby?
19 DR. SIMON: I want to just check a couple
20 of questions, see if I'm interpreting correctly. I
21 had not been at least aware of this problem of the
22 false positive Western Blot as frequently, and I've
23 heard several of you who do these studies talk
24 about the fact that NAT might be coming of an age
25 to be confirmatory testing now.

1 Am I correct that with the HCV and
2 immunosilence, we would certainly want to retain
3 the RIBA there, but that with HIV we conceivably
4 could use NAT, supplemental NAT, instead of using
5 Western Blot?
6 DR. STRAMER: Unfortunately, for HIV the
7 Western Blot is a test we probably would all race
8 to eliminate because there are more problems with
9 that test than there are solutions. However, in
10 the slide that I showed you with the 13 Western
11 Blot positives, there were three donors that were
12 actually Western Blot positive, that even in single
13 donation, high input PCR, were not NAT positive,
14 and we believe those donors are probably really
15 infected.
16 DR. SIMON: Even with supplemental NAT?
17 DR. STRAMER: Yes. They had full bands.
18 I mean, they had a 20 s to col EIA, 9 bands on
19 Western Blot, and--
20 DR. SIMON: Yes, but they were positive on
21 EIA.
22 DR. STRAMER: Yes, they were positive on
23 EIA.
24 DR. SIMON: So if we defer donors based on
25 either an EIA positivity or NAT or supplemental

1 NAT, would we be home safe without Western Blot?

2 DR. STRAMER: Well, I guess I'm confused,

3 because the only reason we do a Western Blot is on

4 a repeat reactive serological sample.

5 DR. SIMON: Okay.

6 DR. FITZPATRICK: Toby, are you saying

7 that if you had a NAT positive, EIA repeat

8 reactive, you wouldn't want to do Western Blot on

9 those samples?

10 DR. SIMON: Yes, that's what I'm

11 suggesting.

12 DR. STRAMER: Yes. I mean, that is

13 certainly possible, but the numbers for HIV are

14 dramatically low. For HCV, I think there has been

15 a lot of--well, I don't think, I know there has

16 been a lot of discussion whether we could replace

17 RIBA with NAT for those who are NAT positive. Why

18 even do a RIBA? I mean, there will be a small

19 number who will be RIBA indeterminate, and even a

20 smaller number who will be RIBA negative, who will

21 be NAT reactive and not know their RIBA result, but

22 that may be a meaningless piece of information.

23 DR. SIMON: Then my second question I

24 think is more practical and related to the

25 discussion of the questions. I believe that the

1 American Red Cross today is not using the FDA-
2 approved algorithms for reentry. That's correct?
3 If the committee would vote as you have suggested
4 we logically should, and allow these Group 3's to
5 be reinstated, is it your feeling that the American
6 Red Cross would be convinced to utilize that
7 algorithm?
8 DR. STRAMER: The Red Cross does not
9 reenter not based on the FDA algorithms. The
10 American Red Cross's intention is to reenter. We
11 have some other internal issues that we need to
12 clean up before we do reentry, that are related to
13 consent decree, but once those consent decree
14 issues are resolved and we have a process defined
15 for reentry and FDA allows us to, it is our
16 intention to reenter.
17 DR. NELSON: Yes?
18 DR. SCHMIDT: If the intent is not to get
19 more donors but to reassure the donors you're
20 worried about, why not contract with some
21 outstanding hepatologist to run the people who
22 really want to know through this system, and not
23 involve the whole Red Cross system in setting up
24 this great scheme?
25 DR. STRAMER: Well, in fact, I mean, there

1 will be some. We will increase donations somewhat
2 by those donors who are healthy. And even if we
3 sent all of our HCV reactives to Blaine and he
4 agreed to take them, you know, the message is still
5 the same to the donor. You're paying all this
6 money and sending me for all this testing and
7 telling me, "You're negative," but if you believed
8 I was negative, you would use my blood.
9 So it's still a very mixed message, and
10 frequently those physicians who we refer the donor
11 to, call me or call the blood center and then ask,
12 you know, the whole same litany of questions. And
13 we repeat testing on yet another follow-up sample,
14 they still test negative, we still can't enter
15 them. Donors want themselves, other family
16 members, removed from our DDR's, and then all the
17 stigma associated, they believe, with being a
18 positive in a blood donor screening test.
19 DR. SCHMIDT: But you're presuming that
20 these donors have more faith in the Red Cross than
21 they have in this outstanding clinical
22 hepatologist, as far as reassurance.
23 DR. STRAMER: It's not a question of
24 faith. It's just a question of black and white.
25 If these are the data, you should be able to

1 reenter me.

2 DR. NELSON: Yes, and the Red Cross was
3 the lab that got the initial test, and if you send
4 them to somebody else who may do a different test,
5 I mean--

6 DR. STRAMER: Right. It's a whole other
7 problem.

8 DR. NELSON: I think it's the
9 responsibility of the blood bank who got the
10 original results to somehow resolve this.

11 DR. STRAMER: Yes, and we do, and that's
12 why we do all the additional testing.

13 DR. NELSON: You know, otherwise--

14 DR. STRAMER: It's part of good public
15 health, right.

16 DR. NELSON: What's the sensitivity of the
17 genetic, the single, the very sensitive? How many
18 copies will it pick up?

19 DR. STRAMER: According to NGI, it's like
20 four copies per mL as a percent hit.

21 DR. NELSON: Down from 2,000 with the
22 pool?

23 DR. STRAMER: No, no, no. Well, the pool,
24 if we're doing it in a pool and the pool
25 sensitivity is somewhere around, you know, 300 or

1 500 copies per mL in the pool, the TMA test on an
2 individual basis is almost as sensitive as the NGI
3 test.
4 Yes? Oh, sorry, I don't call on you.
5 Sorry, Ken. I was taking over.
6 DR. NELSON: Go ahead.
7 DR. KOERPER: Thank you. It strikes me
8 that there is a tremendous amount of bookkeeping
9 involved in keeping track of all of these donors.
10 DR. STRAMER: Thank you. You need to tell
11 that to my manager. We do have a lot of paperwork
12 involved in this. It's a nightmare.
13 DR. KOERPER: Do you have a computer
14 algorithm that helps you track these donors? I
15 mean, because that's my biggest concern, is not
16 that you didn't do the right thing but somewhere
17 along the line, somebody manually transcribed
18 something wrong or what have you.
19 DR. STRAMER: I mean, your concern is
20 absolutely valid. For NAT, it has been a
21 relatively manual process. I mean, all the data
22 are stored in a huge database that is backed up and
23 validated, etcetera, but I mean the process of
24 collecting the data, the data input, is all manual,
25 and that likely isn't going to change. So that is