1 individual donation testing sites.
2 [Slide.]
3 The clinical utility of this assay was
4 further established by testing 10 seroconversion
5 panels in comparison with antibody and antigen
6 assays, HIV-1 RNA was detected 10 and 3 days
7 earlier at 1 to 16 dilution, and 12 and 7 days
8 earlier, when tested undiluted.
9 The test met the current FDA sensitivity
10 standard of 100 copies per ml.
11 [Slide.]
12 Subsequent to licensure, two reports of
13 HIV transmission involving three recipients were
14 identified. The first case was at the South Texas
15 Blood and Tissue Center in San Antonio and the
16 second at Florida Blood Services in St. Petersburg.
17 [Slide.]
18 Dr. Busch and Dr. Leparc will review these
19 cases in detail, but the next two slides present
20 the key points of this report.
21 In the San Antonio case, transmission to a
22 single recipient occurred from a unit of red cells
23 that tested negative by an investigational minipool
24 NAT assay, p24 antigen and antibody assays.
25 The implicated unit was tested at

1 different dilutions by unlicensed and FDA licensed
2 assay. Importantly, inconsistent detection was
3 observed in diluted samples, but the undiluted
4 samples were detected suggesting that ID-NAT may
5 have detected this donation. The viral load was
6 approximately 150 copies per ml in the sample, so
7 we are looking at a very low viral load sample
8 here.
9 [Slide.]
10 In the Florida case, FFP and red cells
11 manufactured from a unit that tested negative by a
12 licensed minipool NAT assay, p24 antigen and
13 antibody assays, transmitted HIV to two recipients.
14 The cases were identified by lookback.
15 Genetic studies are underway to establish linkage
16 between donor and recipient, but in this case, the
17 implicated sample is not available for further
18 testing.
19 [Slide.]
20 These cases indicate that rare event/HIV
21 transmissions continue to occur even after
22 implementation of pooled sample NAT, which reduces
23 risk to 1 in approximately 2 million and the window
24 period to 11 days. ID-NAT is expected to further
25 reduce this to 1 in approximately 3 million and the

1 window period to 7 days. This is for HIV.

2 [Slide.]

3 Although ID-NAT is technically feasible,
4 further refinements are needed for efficient
5 nationwide implementation. Current platforms for
6 ID-NAT are semi-automated and require manual
7 specimen preparation, reagent addition, et cetera.

8 [Slide.]

9 Upgrades are needed to maximize efficiency
10 for high volume use and these upgrades and the
11 regulatory submissions for approval will require
12 time.

13 Automation capabilities and associated
14 training of lab technical staff will be necessary
15 to minimize error and assure component safety and
16 availability.

17 [Slide.]

18 So, in conclusion, FDA strongly encourages
19 manufacturers to expedite development of fully
20 automated platform for high volume use of ID-NAT to
21 further reduce the low risk of HIV transmission
22 from window period donations.

23 FDA will work with manufacturers to
24 expedite the review process to ensure timely
25 implementation of ID-NAT nationwide at some point

1 in the future.

2 Thank you.

3 DR. NELSON: Thank you very much for that

4 succinct and complete summary.

5 Are there any questions? No.

6 Dr. Leparc wanted to report on the Florida

7 case.

8 **Case Report - Florida Blood Services**

9 **German Leparc, M.D.**

10 DR. LEPARC: Thank you.

11 [Slide.]

12 Following is a summary of the donation

13 data associated to the investigation of the

14 recipients of a newly seroconverted volunteer donor

15 on whom serologic markers for HIV were found to be

16 positive on the last of five blood donations that

17 were collected in the course of eight months.

18 [Slide.]

19 This is a depiction of the total donor

20 history. In yellow you will see the seropositive

21 donation that took place in May, and all products

22 from that donation were discarded. In red, you

23 will see the donation immediately prior to the

24 seropositive one during the window period that

25 resulted in two of the components being made

1 available and eventually transfused into two
2 recipients, red blood cells and fresh frozen
3 plasma.
4 The platelets were discarded after their
5 expiration date, five days after collection.
6 [Slide.]
7 The prior three donations were part of our
8 lookback, also an effort and failed to reveal any
9 patient, recipient of this blood, who seroconverted
10 as a result of the transfusions of those
11 components.
12 The first donation by the donor was
13 collected exactly a year ago today, during the
14 massive public outpouring that followed the tragic
15 events of September 11th, 2001. Subsequent to
16 that, a whole blood donation from the same
17 individual was collected every 56 to 61 days, so
18 this person became a first-time donor and a very
19 regular donor after September 11.
20 Each and every one of those donations
21 prior to seroconversion was tested individually for
22 HIV-1/2 antibodies, for p24 HIV antigen using FDA
23 licensed enzyme immunoassays, as well as for the
24 presence of HIV viral genome using nucleic acid
25 testing based on transcription-mediated

1 amplification using reagent in a 16-member
2 meaningful configuration as specified by the test
3 manufacturer and within the testing protocol
4 established in the IND approved by FDA to evaluate
5 the feasibility of nucleic acid testing for the
6 screening of blood donations.
7 Seroconversion of the donor was detected
8 in the last blood donation in May of this year.
9 All blood components, as I mentioned before, were
10 appropriately quarantined and discarded.
11 [Slide.]
12 The seropositive condition of the donor,
13 once confirmed, prompted the initiation of lookback
14 procedures that led to the discovery of
15 seroconversion in the recipients of blood
16 components from the immediately preceding blood
17 donation.
18 Both the recipient of red blood cells and
19 the recipient of fresh frozen plasma from the blood
20 donation in March were found to be seropositive for
21 HIV, as well as have positive HIV RNA by nucleic
22 acid testing.
23 The inner platelets from this donation
24 again was discarded after reaching the five-day
25 expiration date.

1 [Slide.]

2 As far as the prior donations, we have at
3 least one living accessible recipient for each one
4 of those, and in every case we have no evidence of
5 seroconversion indicating that there was no
6 exposure to the HIV virus in those prior donations.

7 [Slide.]

8 An exhaustive analysis of the testing
9 performed on samples of the index donation to runs,
10 as well as testing on all of those who participate
11 in the same donor drive did not uncover any testing
12 anomalies and we had the conclusion from those
13 results that the donation linked to the
14 transmission of HIV occurred during that brief
15 period estimated to be somewhere between 7 to 11
16 days after exposure when the donation cannot be
17 interdicted by the use of current testing methods.

18 [Slide.]

19 Review of the testing data for the
20 seropositive donation shows that the seropositive
21 was clearly positive with the ELISA test on the
22 initial testing being 7 times the cutoff, as well
23 as on the repeat testing.

24 The NAT-HIV Multiplex Minipool had values
25 of almost 22 times the cutoff. In the Multiplex

1 Singlet for HIV, it was about 18 times the cutoff,
2 and in the Discriminatory HIV and Singlet, about 15
3 times.
4 The immunofluorescence assay gave a
5 positive result of 2-plus negative control and
6 positive, so it was not the strongest
7 immunofluorescent assay, but showing that there was
8 some degree of early seroconversion.
9 [Slide.]
10 The donor at the time was notified of the
11 abnormal results and actually follow-up samples
12 were obtained and with similar results. By
13 contrast, when we reviewed the results of the
14 testing performed in the donation collected during
15 the serological window period, we found no evidence
16 of either HIV antibodies with a very low optical
17 density and a signal-to-cutoff ratio of 0.2, the
18 signal-to-cutoff ratio for the antigen, again these
19 are tested on in singlet, was low, at 0.1.
20 The nucleic acid testing in the multiplex
21 configuration in a minipool of 16 members, purple,
22 showed a good internal control with over 173,000
23 relative light units. The anilide was well below
24 the internal control and with a signal-cutoff ratio
25 of 0.2, close to 0.3, so this was a clearly

1 negative result.

2 [Slide.]

3 In conclusion, we could not determine the
4 viral load on the donor at the time of the
5 collection, during the window period, and this was
6 because no archival samples were available. The
7 red blood cells were transfused, the plasma was
8 transfused, and the platelets were discarded after
9 expiration date. As a result of that, we are
10 looking at the feasibility of maintaining archival
11 samples for future investigations.

12 Our laboratory, however, tests
13 approximately 9 percent of the nation's blood
14 supply for nucleic acid testing, and at that volume
15 to have a feasible archival and retrieval system
16 that can allow efficient aliquotting and store for
17 long term, at this point we haven't figured how to
18 accomplish that.

19 We had components. As opposed to the case
20 in Texas where there was a remnant of fresh frozen
21 plasma that provided plenty of material for study,
22 we didn't have anything like that.

23 As Dr. Hewlett mentioned, there are
24 studies ongoing on the HIV genotyping for donor and
25 recipients to establish a link. These studies are

1 being done both at the CDC and FDA laboratories
2 from samples obtained at different times from each
3 one of the three parties.
4 Lastly, we plan to perform an HIV
5 infection dynamic staging on the seropositive
6 samples that are archived from the donor. There
7 are ways where you can approximately determine the
8 time when the donor could have become infected
9 prior to donation by doing some staging tests that
10 Dr. Busch will describe later.
11 So, that is a brief summary of the case
12 that we had.
13 DR. NELSON: Thank you very much.
14 Neither the donor nor any of the
15 recipients had a seroconversion illness of any
16 type?
17 DR. LEPARC: No. Actually, this was, of
18 course, a surprise for all three parties. There
19 was no indication whatsoever that infection had
20 occurred.
21 DR. SIMON: Did you find any risk factors
22 in the donor?
23 DR. LEPARC: Yes, and I cannot go into
24 much details about this because, of course, there
25 is litigation now in progress, and our counsel has

1 advised us not to discuss this, but there was a
2 risk factor which was unknown by the donor at the
3 time.
4 DR. NELSON: Thank you.
5 Dr. Busch.
6 DR. NELSON: I think this case and these
7 cases are important because they certainly say
8 something about the sensitivity of our surveillance
9 and the usefulness of lookback and the whole issue.
10 I am impressed that we were able to find some cases
11 where there was still an issue that all of us
12 hypothesize might not have disappeared completely.
13 DR. SIMON: I guess in the interim, even
14 with individual NAT based on what Dr. Hewlett
15 showed, you still have a few days there, so we are
16 not going to get to zero until we get to pathogen
17 inactivation theoretically is my feeling.
18 DR. NELSON: I was a little surprised
19 given the doubling time of HIV, at the very low
20 copy number, which should be a fairly small window
21 on average, but maybe this patient wasn't average.
22 Maybe there was something going on leading to this
23 very low copy number.
24 **Viral Dynamics in Early Seroconversion**
25 **Michael Busch, M.D.**

1 DR. BUSCH: I can start just talking
2 through the slides. The first few slides are the
3 summary of the case reports both from the San
4 Antonio transmission case and an earlier published
5 study that we did in collaboration with CDC related
6 to a transfusion in Singapore that transmitted HIV
7 from a window phase unit.
8 The San Antonio case, the first slide is a
9 timeline. It is very similar to Dr. Leparc's study
10 in that a donor seroconverted to HIV antibody, and
11 the prior donation from that donor had been
12 transfused, and through lookback, the recipient of
13 that donor was recalled and found to be infected.
14 Fortunately, in that case, the recovered
15 plasma had actually been shipped to Europe but not
16 yet pooled, so it was able to be brought back to
17 the States and studied, and it is through studies
18 of that plasma, as well as follow-up samples from
19 the donor and from the infect recipient that we
20 were able to, first, confirm that this was the
21 source of transmission, so extensive sequencing
22 studies were done to unequivocally demonstrate
23 that.
24 The other thing we were able to do was to
25 do viral load analysis and most importantly,

1 dilutional studies to assess what the detectability
2 of that unit would have been had it been tested
3 singly or at intervening dilutions relative to the
4 current pooled test systems.
5 So, there is a table that demonstrates the
6 detection. The sample was detected undiluted and
7 there was detection, and as the sample was diluted
8 out on both the Roche and the Gen-Probe systems
9 both at 1 to 8, 1 to 16, 1 to 24, we began to lose
10 detection a fraction of the replicate tests.
11 Importantly, this original NAT was
12 actually what is considered a home brew NAT, San
13 Antonio brought up their own assay system under IND
14 from FDA, but this particular donation was just
15 given at a viral load of about 150 that was just
16 detectable essentially at the pool sizes being used
17 with some relative rates of detection.
18 The other case that is described in there
19 was published a year and a half ago. It was again
20 a transfusion in Singapore, same story in that a
21 donor seroconverted. They were not screening by
22 pooled NAT at the time, but the prior donation
23 plasma that was determined to have infected a
24 recipient was again available and was subjected to
25 the same kind of sequence proof of transmission and

1 then characterization of the viral load.

2 The same sort of story played and that the

3 unit was detected consistently by both the Roche

4 and Gen-Probe systems undiluted and was detected at

5 serial pooled dilutions with relative frequencies

6 that eventually, essentially became negative out at

7 the 1 to 24 pool size.

8 So, these are two additional examples

9 although in these cases, the plasma from the

10 implicated unit was available.

11 That was the time course, the sequencing.

12 [Slide.]

13 This is the dilutional data on the San

14 Antonio case, and again at 1 to 8, both

15 manufacturers essentially picked it up. At 1 to

16 16, it was still picked up 3 out of 3 by one, but a

17 portion on the other, and at 1 to 24, both

18 companies missed it, about a third or a quarter of

19 the time.

20 [Slide.]

21 The Singapore case, I talked through it.

22 [Slide.]

23 So, this is the dilutional work on the

24 Singapore case. Again, the upper part is controls,

25 importantly undiluted both Gen-Probe and Roche

1 systems detected consistently, but as you began to
2 dilute it out 1 to 8 and then 1 to 16 and 1 to 24,
3 you see the sample is negative, so, just as
4 predicted from the earlier studies, as you will
5 see.
6 [Slide.]
7 I just want to quickly, though, run
8 through our understanding, which we have had for
9 quite a long time, of the evolution of viremia. We
10 really predicted these cases would happen, and it
11 shouldn't have been a surprise, talk a little about
12 the sequential stages of early infection for both
13 HIV, HCV, and a little bit about HBV, and then get
14 into really what we would predict would be the
15 frequency that we would be missing units that could
16 be detected by individual and are being missed by
17 minipool.
18 [Slide.]
19 Just HIV, the early dynamics. Many of you
20 have seen this many times in this arena.
21 Importantly, I think this so-called eclipse period
22 following exposure before we can detect virus even
23 by single unit NAT, there are observations when we
24 test back samples from infected people of transient
25 periods of very low level viremia during this

1 period, which we don't know for sure, but may be
2 infectious, as well.
3 Then, we have this brisk ramp-up viremia
4 followed by antibody conversion and stabilization,
5 steady-state RNA.
6 [Slide.]
7 This is just one of the examples of a blip
8 viremia for HIV, so this is a plasma donor who was
9 detected by pooled NAT at day zero. That is the
10 definition here. Then, as we test back, day minus
11 4 on back, we can detect by full-input,
12 high-sensitivity studies single unit type testing.
13 Immediately prior to the early consistent
14 minipool positive, we can detect low level
15 frequency viremia, which essentially is analogous
16 to these transmission events that we are observing,
17 but interestingly, if we look back in a number of
18 these panels a week or so before that early
19 viremia, we detect another transient phase of
20 viremia, sort of primary viremia phenomenon similar
21 to what you heard this morning about West Nile.
22 Again, whether this is infectious, we
23 don't know. Again, it is erratically detected even
24 by the individual NAT, and we think this eclipse
25 phase between here is probably not infectious, but

1 studies are in process to study that further.

2 [Slide.]

3 By looking at a large number of panels, we

4 can quantify the ramp-up viremia, and it is really

5 this data that allows us to estimate the doubling

6 time and project the relative window closure

7 achieved by individual versus minipool NAT or

8 intervening pool size.

9 [Slide.]

10 HCV, a similar summary graph. Again, I

11 will show you some examples of really a very common

12 phenomenon, that before ramp-up viremia, there is

13 frequently a transient very low level viremia that

14 is observed for weeks before this explosive ramp-up

15 phase, and then you go through a very long, almost

16 two-month plateau viremia, very high titer, readily

17 detected by minipool NAT, which explains why we are

18 seeing such a relatively high yield of HCV minipool

19 NAT.

20 [Slide.]

21 This is just one example of an HCV blip

22 viremia, so this donor, plasma donor was picked up

23 at day zero by minipool NAT. They had one sample

24 here that had about 100,000 copies that was

25 initially missed by the large plasma pooled NAT,

1 but what I want to emphasize is this period of
2 actually several months prior to ramp-up viremia,
3 during which we could detect viremia.
4 This is four replicate, full-input TMA
5 assays, and the portion of the bars that are filled
6 here are the percentage of the four reps that were
7 positive by the single sample input full
8 sensitivity TMA, so you see this donor went through
9 sort of cycles of a week of very low level viremia
10 erratically detected even by individual NAT, then
11 negative for a week, and then positive for a week,
12 then negative, then positive.
13 [Slide.]
14 Just shows a series of these. This is a
15 group of fix panels that are actually, as I will
16 show you later, being transfused into chimps now,
17 serial samples from these human plasma donors, but
18 you can see here this blip viremia extending back
19 from day zero in six of these cases with a sort of
20 similar cyclic kind of viremia.
21 Again, this is the proportion of four
22 replicate individual donation NATs that are
23 positive. An important point here is this strongly
24 suggests that even individual donation NAT is
25 unlikely to interdict all infectivity because it is

1 only able to erratically detect the viremia that
2 exists in this early eclipse phase.
3 [Slide.]
4 Just one slide. This is from some work
5 that Fred Prince is just publishing where they
6 infected chimps with very low level, exposed chimps
7 to one viral particle, then 10, then 100.
8 What you can see here is that a single
9 viral particle actually can lead to--this doesn't
10 show it on this slide--but to transient viremia and
11 a low level T-cell immune response, and then as you
12 get to 10, there is actually even a low-level
13 antibody response, and then at 100 copies you get
14 full infection.
15 So, the message here is that we think
16 these blip viremias, they are either an early phase
17 of virus just smoldering in the liver and just
18 beginning to get a foothold in the body, or they
19 may represent repeat exposures in these high-risk
20 people at very low doses that are unable to
21 establish a full infection.
22 [Slide.]
23 These, as I indicated, in collaboration
24 with Harvey Alter and Chris Murphy, these units
25 from these pre-blips in the valleys between the

1 blips and ramp-up, and then the blips are being
2 transfused into chimps to try to really define when
3 is infectivity established relative to the
4 detectability of viremia either during the blips,
5 which is very erratic, or if necessary, into the
6 early ramp-up phase.
7 So, we are really trying to do the studies
8 that will better characterize infectivity versus
9 viral load in the early phase of infection.
10 [Slide.]
11 Just for HCV, similar, we have got a
12 number of these cases, 37, where we have good
13 ramp-up phase viremia load data and can, from that,
14 derive a doubling time estimate, and then the next
15 slide shows just one example of how we can use that
16 ramp-up phase viremia and the differential
17 sensitivity of minipool versus individual NAT,
18 which is about a 20-fold difference.
19 [Slide.]
20 Given the rapid ramp-up phase, a 20-fold
21 difference in sensitivity, testing a sample
22 essentially in pools of 20 versus singly with the
23 same assay, only translate into about a four-day
24 difference in the window period closure.
25 This is the important sort of conversion.

1 It allows us to project the yield of the new assay,
2 single versus pool.
3 [Slide.]
4 The same thing we have for HBV, a doubling
5 time of about two and a half days.
6 [Slide.]
7 This is actually a summary of the work we
8 did with FDA, Biswas and colleagues looking at the
9 performance of different antigen tests versus
10 pooled sample versus single sample NAT on HBV. The
11 important point here is with HBV, we actually
12 achieve much more window closure with the
13 conversion from pooled to single unit because the
14 doubling time is much slower, so the ramp-up is
15 slower, so you actually get about a 20 to 30-day
16 further closure of the window by going for minipool
17 to single unit.
18 So, as we begin to get HBV, then, clearly,
19 single unit NAT will be an important advance.
20 [Slide.]
21 So, how do we take this window closure
22 data and tell you how many people will get infected
23 because we are not doing individual NAT? To do
24 that, we need to know the rate of new infections in
25 the donor pool, and that is the incidence rate, and

1 this is data from the REDS group looking at
2 incidence rates for the main viruses.
3 You can see actually that the incidence
4 rates have dropped and that we are now looking at
5 incidence rates of about 2 per 100,000 person years
6 for HIV and about 3 for HCV, higher incidence for
7 HBV.
8 [Slide.]
9 The incidence rate parameter is adjusted
10 to account for higher incidence in first-time
11 donors and to exclude non-transfusable units and
12 then we multiply that adjusted incidence rate times
13 the window period to estimate either the residual
14 risk or the yield of going to individual NAT.
15 [Slide.]
16 In terms of the duration of the
17 pre-detectable window, what we have done is to take
18 the current sensitivities of the assay system, so
19 the pooled NAT systems currently are detecting at
20 about 80 copies per ml for HIV and 190 for HCV, the
21 50 percent hit rates for HBV. We are still using
22 surface antigen tests, so we are picking up at
23 around 2,200 copies, and then we estimate based on
24 the doubling time how far back in time would these
25 donors, these people have had a viral load of 1

1 copy per 20 ml, which is the infused volume of
2 plasma.
3 So, we are now using a new, more empiric
4 dataset to estimate the duration, the theoretical
5 duration of infectious viremia that would be
6 present at the level, sort of worst case estimate
7 that one copy in an infused volume of blood could
8 transmit.
9 [Slide.]
10 When we do that, we take the detection
11 limits of the current screening systems, the
12 minipool NAT or HBsAg. We take the doubling time
13 of the virus and from that doubling time and viral
14 load, we can project back that there is about 8 to
15 9 days of probably infectivity for HIV and HCV
16 preceding detection by the minipool NAT.
17 [Slide.]
18 Then, we can take those periods of time
19 and multiple them times the incidence rate to get
20 current risk estimates. So, this is how we kind of
21 talk in terms of the risk now for HIV is in the
22 range of 1 and 2 million, and for HCV is in the
23 range of 1 and 1.5 million, and we now have
24 estimates with confidence bounds integrating the
25 incidence rate and the window period estimate.

1 [Slide.]

2 The critical question today, though, is
3 how much extra closure of the window would be
4 achieved if we moved from minipool to individual
5 NAT. As I showed you on that one graphic, and do
6 statistical modeling of the data, we can estimate
7 the window period difference by increasing the
8 sensitivities of these assays 20-fold by going from
9 an average pool size of 20 to single, and we
10 estimate that really there is only about a
11 three-day for HCV and about a four-day for HIV
12 window period difference between the minipool and
13 single unit.

14 When you them multiply those window
15 closures times the incidence rate, you get around 2
16 per 10 million, 2 to 3 per 10 million, which would
17 be about 3 to 4 per year predicted donations that
18 are missed by minipool NAT, that could be
19 interdicted were we doing single unit NAT on an
20 annual basis.

21 [Slide.]

22 Now, there has been discussion, and you
23 will hear some suggestions that perhaps we should
24 move the pool size from 16 to 8, or 24 to 6, and
25 this is actually the same data as I showed before,

1 but instead of on a logarithmic scale, it shows it
2 on a linear scale to give you a better sense of why
3 that doesn't get you much.
4 This shows, for HIV, the rate of ramp-up
5 viremia, and for HCV, and what you can see here is
6 that going from an assay that has 80 to 40 copies,
7 so twice the sensitivity, really only gets you a
8 very modest closure of the window, because you are
9 in an exponential growth phase of the viral load.
10 So, this just graphically illustrates what
11 I will show you in the next slide, which is the
12 statistical analysis of what would you get if,
13 instead of testing with Gen-Probe at pools of 16,
14 we went to Gen-Probe at pools of 8, or a similar
15 analysis on the right side for Roche if you went
16 from the 24-member pools to test the intermediate 6
17 pools, so let's just focus on the Gen-Probe because
18 I think that is the assay where there is serious
19 discussion about reducing pool size.
20 [Slide.]
21 What you can see for HIV is that by
22 reducing pool size in half, you will only detect 5
23 per 100 million donations so it is 1 in 20 million
24 units would be predicted to be detected by going
25 from a pool size of 16 to 8.

1 In contrast, if you went all the way, and
2 you took it that additional 8 individuals, you
3 would pick up an additional 15 per 20 million--0.14
4 per 10 here. The bottom line is you will only pick
5 up 4 by going all the way from 16 to neat.
6 If you go from 16 to 8, you will pick up 1
7 of those 4, from 8 to 4, you will pick up a second
8 one, from 4 to 2, a second one, so you will only
9 pick up one-quarter of the yield that you would get
10 if you went all the way to single unit NAT by going
11 from 16 to 8. That is the big message of this
12 analysis with confidence bound, so essentially
13 there is not even a statistically significant
14 window closure given all the data we have by going
15 from 16 to 8.
16 [Slide.]
17 This slide is just to emphasize, this is
18 the summary of the risks, that pre-NAT, you know,
19 we had risks in around 1 in a million for HIV.
20 Post-minipool-NAT, we are down at close to 1 in 2
21 million, but even after we go to indication NAT,
22 because of that low level viremia that exists, we
23 think the risk will remain and we will still be
24 talking about risks with individual NAT of about 1
25 in 3 million, so don't think that by going all the

1 way to individual NAT we will eliminate risk,
2 because we won't. We will still have breakthrough
3 transmissions and still have risk.
4 [Slide.]
5 This is just one other way that we can
6 estimate the residual risk and the impact of going
7 to individual NAT and what we realized is that we
8 actually have an unbelievably accurate measure of
9 the rate at which donations are being given in this
10 early window period. That is the NAT yield that we
11 are picking up.
12 So, what we realized is if we take the NAT
13 yield rate as observed and then we simply factor
14 the NAT yield rate times the relative durations of
15 the minipool-positive window and these earlier
16 window periods, either the pre-minipool NAT,
17 potentially infectious window, or the ID-NAT
18 window, we can calculate out the projected risk
19 with minipool NAT or the project yield of
20 individual donation NAT, so a very simple
21 calculation of taking the yield of minipool NAT and
22 adjusting it by the relative lengths of these
23 window periods allows us to derive an independent,
24 but on the next slide you will see a virtually
25 identical way of estimating the risk, and they come

1 out almost identical to the rates that I presented
2 earlier.
3 So, we have picked up so far in the first
4 three years, about 145, 145 HCV yield cases and 10
5 HIV yield cases. When we take these through those
6 calculations, we estimate the same risk factors of
7 about 1 in 1.5 million for HCV and 1 in 1.7 million
8 for HIV, and we also can predict the yield of
9 ID-NAT going all the way to single unit would pick
10 up about 1 in 5 million donations that are
11 currently being missed. So, I think strong
12 corroborating data to support the predictions that
13 were based on the window period model.
14 [Slide.]
15 I just want to take a moment, I don't have
16 time to go into any detail, but just to mention
17 that there are a number of studies that demonstrate
18 the relationship between viral load and
19 infectivity. I don't have time to talk about it,
20 but there is animal studies analogous to kind of
21 the studies I showed you, the infection of chimps
22 with serial doses of virus or the transfusion of
23 plasma units from these window period donors to
24 understand when does infectivity exist.
25 All of these studies for certainly HBV and

1 HCV indicate that as few as 10 viruses transmit 50
2 percent of the time to chimps, so in my opinion,
3 infectivity probably exists. Certainly single unit
4 NAT positives are infectious and probably exist
5 even in the low level that may exist in a component
6 undetectable by single unit NAT.
7 [Slide.]
8 Then, the human data, these kinds of cases
9 we are talking about, the transmissions from these
10 lookback studies are actually very important cases
11 to study to understand that window period
12 infectivity, so we are really trying to compile as
13 many of these cases into a national effort to get
14 the data and the samples that may exist from these
15 cases to build a model and understand infectivity
16 in real humans from transfusion of these
17 pe-seroconversion units.
18 [Slide.]
19 This is what I did want to talk very
20 quickly about, though, if that, you know, when we
21 talk about picking up on or two additional
22 infections per year, how much does that translate
23 into really health care and human savings.
24 Obviously, for each of these patients that
25 gets infected, it is a tragedy, and if we could do

1 it, we should clearly move to individual NAT, but
2 just to emphasize that the number of quality life
3 years that are lost by virtue of transfusion of an
4 HIV infected unit, because of the age of patients,
5 the underlying, you know, morbidity of patients
6 that are transfused translates into about seven
7 quality life years for HIV and 0.6, so HCV is much
8 less clinically important than HIV from a health
9 care outcome perspective.
10 When you then ask, okay, how many cases
11 will be prevented per year by minipool NAT and how
12 many quality life years gained by going to doing
13 what we are doing now in minipool NAT. We are
14 really, with current minipool NAT, only gaining
15 about 60 quality life years by doing the
16 combination HIV-HCV minipool NAT.
17 By going the next step of introducing
18 single unit NAT, We are only going to buy an
19 additional total of about 20 quality life years.
20 The final slide I will show is this one,
21 which just puts into context that as we have moved
22 from introducing the first generation assays in
23 this example HIV, we interdicted a very large
24 number, about 1 in 10,000 units was infected, and
25 those units were causing 92,000 lost quality life

1 years by transfusion of those unscreened units.
2 Introducing the first generation assay
3 essentially saved 90,000 quality life years of
4 morbidity and life. In contrast, as we
5 progressively move to first generation, second
6 generation, third generation antibody assays,
7 closing the window, we really have only picked up a
8 few hundred quality life years with each of those
9 progressive improvements in the antibody test.
10 Then, as we bring in antigen or NAT,
11 because there is so little residual risk, the
12 incremental gain both in terms of infections
13 prevented and in quality life years gained is
14 really extremely modest, only about 20.
15 I think the point here is we have made
16 enormous progress and clearly I think there is
17 agreement that we need to get to individual
18 donation NAT, but I think the additional gain that
19 we will be gaining by doing so is very modest
20 relative to where we have come.
21 Thank you.
22 DR. NELSON: There were a number of people
23 wanted to comment.
24 Dr. Andrew Heaton from Chiron.
25 **Open Public Hearing**

1 DR. HEATON: Thank you for the opportunity
2 to review the recent introduction of the Chiron
3 Procleix NAT test and the implications for a
4 potential reduction in pool size.
5 During my presentation, I will review
6 Chiron's experience in the introduction of NAT on a
7 worldwide basis to highlight the implications as
8 the committee considers the appropriate pool size
9 for nucleic acid testing.
10 When the Procleix assay was approved in
11 February of 2002, this was the conclusion of an
12 extraordinary rapid development cycle from the
13 challenge of FDA Commissioner Kessler in 1994
14 through the NHLBI contract in 1997, to the launch
15 of an IND in 1999 of a completely new technology.
16 That was an extraordinarily rapid development
17 cycle.
18 As a result, although the assay was
19 developed very quickly, Chiron and Gen-Probe
20 elected to upgrade the original semi-automatic
21 system to an enhanced semi-automatic system, and it
22 was this system that was used to pursue regulatory
23 approval and is now used routinely by U.S. blood
24 centers.
25 The more fully automated walkaway system

1 for routine testing has taken longer to develop
2 with the result that industry is continuing to use
3 the original system.
4 [Slide.]
5 During the period of evaluation under IND,
6 routine blood testing was performed in pools of 16
7 with the remaining samples added at the end of each
8 run, but in parallel with the trial, the U.S.
9 military initiated individual donor testing, and
10 this data, combined with the individual samples,
11 were used to support the claim, which is listed up
12 here, which allows both pools of 16 and individual
13 donor testing.
14 The specificity of the assay was excellent
15 with minimal pooling-induced cross-contamination
16 and the sensitivity of both pooled and individual
17 donor testing was excellent, and as expected, there
18 was a small but measurable improvement in the
19 specificity of those samples tested individually.
20 [Slide.]
21 Assay analytical sensitivity of 30 copies
22 per ml easily exceeded the 100 copy per ml design
23 goals on the standards of the FDA, and in pools of
24 16, the assay also meets European and FDA
25 regulatory standards.

1 The yield reported in the package insert
2 is summarized in this table and it has been
3 consistent with the experience of that of most
4 other developed countries where similar pool sizes
5 have been used.
6 [Slide.]
7 In France and Australia, which were two
8 countries that rapidly adopted NAT testing, the
9 assay was, and still is, used both in pools and in
10 individual testings in the same system using common
11 training systems, common procedures, and common
12 applications.
13 In Australia, the larger centers use pools
14 of 1 and 24, and France's pool are 1 and 8, and in
15 each system, smaller centers use individual donor
16 testing. In practice, the test performance was
17 similar within a blood system and the level of
18 false positivity and invalid run rates were not
19 significantly different between IDT and minipool
20 for a given blood system.
21 In Australia, there was no evidence that
22 pooling increased initial reactive rates and the
23 frequency of true test positivity was similar.
24 Consequently, there appears to be no operational
25 difference in test performance where individual

1 donor testing is performed in blood centers with
2 small collection volumes compared to larger centers
3 in the same system.
4 [Slide.]
5 Summarized in this slide is the Chiron
6 worldwide experience with pool sizes. This ranges
7 from individual donor testing in Singapore and
8 Portugal to 8 pools in much of Europe, 16 pools in
9 the U.S.A., and 24 sample pools in Australia and
10 Hong Kong.
11 [Slide.]
12 Summarized in this slide is the
13 relationship between pool size and donation
14 collection volume in blood centers. Although
15 two-thirds of the blood centers perform individual
16 donor testing, 75 percent or approximately 75
17 percent of blood is actually tested in pools of 1
18 and 16 or 1 in 24 because the larger centers
19 process such a greater proportion of the world's
20 blood supply.
21 Chronologically, there has recently been a
22 trend towards reduced pool sizes as new systems
23 have come up.
24 [Slide.]
25 In order to respond to the requests of

1 industry, Chiron has modeled the impact of
2 decreasing pool size. Our model includes workload
3 equipment requirements and test requirements and
4 represents a very conservative approach, and we
5 believe that blood centers in practice would likely
6 improve on this.
7 As shown in the bottom left of this slide,
8 1 run of 100 tubes allows the generation of 88
9 results and most centers require a technician to
10 pull and complete testing of 1 run since this fits
11 well with the average 8-hour work day.
12 In the case of pooling, while the assay
13 may take approximately 6 hours to complete, the
14 pooling adds an addition 2 hours. Subsequently, a
15 2-run processing protocol has been developed and
16 technicians are now being trained using this
17 workflow system. This would have the effect of
18 decreasing the workload by approximately a factor
19 of 2, and is now used routinely in Australia in
20 those centers where IDT is performed.
21 At the request of the blood bank industry,
22 we assess both IDT and pools of 1 and 8 and if you
23 look on the top line, in blood centers of 100,000
24 per year, assuming a work week and consistent
25 sample receipt, the model predicts that testing the

1 daily requirements could be handled in 1 run per
2 day and pools of 1 and 16 or 1 and 8, and the
3 workload would only increase to 2 runs per day or
4 double the workload for individual donor testing,
5 which of course explains why the smaller blood
6 centers perform individual donor testing.
7 In the case of large centralized
8 laboratories, testing 1 million or more per year,
9 pools of 16 would require 3 runs per day or 2 assay
10 technologists, while individual donor testing would
11 require 37 runs per day, dramatically increasing
12 personnel requirements.
13 This does not directly translate into
14 technologist head count requirements, since
15 technologists are already being trained to perform
16 2 runs in a shift and centers have begun to adjust
17 the workflow to do even better than that through
18 improved staging of the different assay processing
19 steps.
20 [Slide.]
21 Using current eSAS automation for
22 individual donor testing, a technician can complete
23 2 runs in a shift, which depending on the time
24 available and the scheduling of the workflow, could
25 as much as double equipment requirements.

1 The additional workflow increases the
2 demand, so the software control pipetting devices
3 and the frequent contamination may reduce the
4 equipment service life, so there are significant
5 equipment effects.
6 Since blood centers are under great
7 pressure to minimize turnaround time, most samples
8 are tested overnight on the third shift, which
9 maximizes simultaneous throughput requirements.
10 Consequently, although staggered or sequential
11 shifts would maximize efficiency, concurrent assays
12 of common practice to maintain high throughput and
13 minimize turnaround times.
14 In addition, the separate components of
15 the test kits must be stored at three different
16 temperatures, placing great demands on
17 refrigeration to frozen storage, and since all NAT
18 tests are subject to significant contamination
19 risk, special cloth, unidirectional workflow, and
20 custom designed facilities are essential to
21 maintain the consistency of results.
22 [Slide.]
23 Consequently, based on modeling, our
24 analysis for the conversion of blood centers
25 currently converting testing in pools of 16 to

1 pools of 8 would take six to nine months to
2 complete once the decision had been made. This
3 would require that all technicians convert to
4 2-rack processing and labor requirements would
5 likely increase by as much as 10 to 20 percent.
6 This could be achieved in less than six
7 months. The key limiting factor is the time to
8 rewrite the computer software that controls the
9 pipetting devices, the length of the validation,
10 and the length of the regulatory cycle.
11 Although individual donor testing would
12 require much greater increases in test reagent
13 manufacture and operating equipment, the longer
14 implementation cycle is principally the result of
15 the need for additional space buildout of test
16 facilities and the hiring and retention of
17 additional staff.
18 Both Chiron and Gen-Probe would need to
19 expand customer support and manufacturing personnel
20 where the customers will need to identify
21 additional assay personnel who must often meet
22 extremely demanding State requirements for the
23 performance of complex laboratory testing.
24 A limiting factor in this conversion is
25 that of personnel since equipment and reagent needs

1 could be met in a six- to nine-month, but the
2 personnel and space requirements would take longer.
3 [Slide.]
4 In order to facilitate the assay
5 performance, upgrades are planned for the Procleix
6 System. These include automation of the reagent
7 and addition steps which are currently handled
8 manually.
9 The automation, which is anticipated to be
10 available for trial in approximately 12 months,
11 would also assist in recordkeeping and process
12 control. The second upgrade would automate the
13 addition of target capture reagents and the
14 subsequent wash steps, and further upgrades of the
15 luminometer and software are also planned to follow
16 the first two steps.
17 For the long term, the fully automated
18 Procleix automated system being developed as the
19 TIGRIS by Gen-Probe is expected to enter clinical
20 trials by the end of 2003. Consequently, there are
21 both mid-term and long-term automation plans which
22 would support the introduction of reduced pool
23 sizes.
24 [Slide.]
25 In summary, I hope that I have been able

1 to provide a review of worldwide testing practices
2 using the assay. The systems achieve turnaround
3 times comparable to the immuno tests. Clearly,
4 blood center test volumes have influenced the pool
5 sizes.
6 A transition to smaller pool sizes or
7 individual donor testing is clearly possible and
8 Chiron and Gen-Prove anticipate being able to meet
9 reagent and equipment demands rapidly. A limiting
10 factor is for testing pools of 8 is the existing
11 eSAS System and the time to rewrite, validate, and
12 secure approval of the pooling software.
13 In the case of individual donor testing,
14 the limiting factor is identifying appropriate
15 facilities to support the specialized equipment and
16 staffing needs together with the time required to
17 train the personnel.
18 Midlife improvements to the current system
19 are in process and walkaway automated system will
20 be available by the end of the next year. This
21 combination should allow the transition to reduce
22 pool size or individual donor testing based on the
23 needs of industry.
24 The development cycle has already greatly
25 benefited from a collaborative relationship between

1 the FDA, NHLBI, Chiron, and Gen-Probe, and Chiron
2 stands ready to assist the policy makers in their
3 decision of the pool size of choice.
4 Thank you.
5 DR. NELSON: Thank you, Dr. Heaton.
6 Next is Karen Long from Roche. Is Karen
7 Long here?
8 DR. GALLARDA: I am not Karen Long.
9 DR. NELSON: You don't look like Karen
10 Long. I am Jim Gallarda. I am Director for Blood
11 Screening at Roche Molecular Systems, and I will be
12 giving a synopsis of our assessment of the
13 situation.
14 [Slide.]
15 I want to thank FDA for allowing us to
16 participate in today's discussion. We have been
17 asked to address two general areas. The first is
18 what are the current constraints in doing single
19 unit testing using the COBAS AmpliScreen System
20 that Roche has developed, and secondly, what are
21 our future plans for our single unit testing
22 program.
23 [Slide.]
24 In answer to the single unit nucleic acid
25 testing question with the current system, can it be

1 done? The simple answer is yes, but it has a
2 string of caveats associated with it.
3 Our system has been designed to a
4 three-tiered algorithm to do either pools of 24,
5 which resolve through secondary pools of 6, which
6 are then resolved at the tertiary level to single
7 unit. We provided data in our submissions
8 demonstrating this fact.
9 The implementation issues associated with
10 the current system to be used as single unit NAT
11 testing are rather complex, and I have just listed
12 a few of them.
13 Mike Busch has given a very lucid
14 explanation about the incremental yield that one
15 can expect with single unit NAT, and this has to be
16 viewed in the context of what are the labor
17 resources, both availability of trained labor and
18 the cost to implement single unit testing with the
19 current semi-automated systems, and also it should
20 be viewed in the context of the additional risk of
21 documentation errors or other type of errors that
22 are due to the increased testing demands.
23 [Slide.]
24 Dr. Hewlett mentioned earlier in her talk
25 that in 1994, we kicked off to a discussion of how

1 to capitalize on the power of NAT to interdict
2 infectious units that were in the
3 pre-seroconversion window period.
4 Retrospectively, looking at what happened,
5 this has been a success story for both programs.
6 For the COBAS AmpliScreen system, in our
7 submission, we cited that we had over 40 HCV window
8 period cases that were successfully interdicted
9 using minipools of 24, and for HIV, there were
10 three window period cases that were interdicted,
11 again using pools of 24, and we just learned this
12 morning that in our currently IND for the HBV
13 clinical trials, we screened for three weeks now,
14 40,000 samples, and we have identified our first
15 window case for HBV.
16 So, the good news is the current system,
17 semi-automated, has done a good job.
18 [Slide.]
19 Going to a single unit discussion, the
20 incremental yield, the fact is that yes, we are all
21 I believe in agreement, let's head towards single
22 unit testing. Having said that, Mike has shown
23 that it will be an incremental yield, but there
24 will be, in the blip area of the eclipse phase of
25 the pre-seroconversion infectious time period,

1 samples that are infectious, that cannot be
2 detected even with single unit, so we will not have
3 a zero risk blood supply even with single unit
4 testing.
5 [Slide.]
6 The workload issues with the current
7 system. Both systems are semi-automated. They
8 require substantial manual labor, and it is our
9 view that higher workload may lead to increased
10 operator error, and I might say that this is not
11 simply Roche's opinion. This has been validated
12 with the practitioners of NAT in the country.
13 [Slide.]
14 Potential risks. A 16 to 24-fold increase
15 in a single unit scenario with the current systems
16 could create inventory shortages. We don't know,
17 but it is a plausible scenario.
18 [Slide.]
19 There is a shortage of skilled medical
20 technologists in general required for the rather
21 complex NAT testing in the semi-automated systems.
22 [Slide.]
23 So, our view is that for sure with our
24 system, we feel that it is not the best approach to
25 go to single unit testing with the semi-automated

1 systems. So, I would like to switch gears to the
2 next topic, and that is what are we doing about
3 this.
4 It is our view, Roche's view, that we
5 should invest heavily into a fully automated single
6 unit system for the three viruses now that are
7 being screened.
8 [Slide.]
9 I just want to say that we are putting out
10 eggs into a basket, and that basket is to develop a
11 sample in, results out, high throughput system for
12 a multiplex detection of the three viruses that are
13 mainly being screened for currently.
14 [Slide.]
15 Our strategy for a single unit system is
16 to really rely on what we have already historically
17 proven an aptitude for, and that is what I would
18 call as our core competencies.
19 [Slide.]
20 We have developed a robust back-end PCR
21 walkaway machine, the COBAS Amplicor Analyzer. The
22 users in our clinical trial all agree that this is
23 probably the most robust element of our system.
24 So, we have a very excellent Swiss
25 engineering firm that has designed complex

1 instrumentation for such type of testing.
2 [Slide.]
3 We have a very promising program in Japan
4 where the Japanese Red Cross has been using a
5 system that we call the AMPLINAT system. The front
6 end of that is our GT-X automated sampler
7 extraction device, and this is being used to
8 extract simultaneously all three viruses in a
9 multiplex format.
10 [Slide.]
11 On the back end, we have a lot of
12 experience developing complex TaqMan master-mix
13 reagents for the simultaneous detection of the
14 three viruses. So, our core competencies cover the
15 hardware and associated software for complex
16 instrumentation, and our reagent groups have
17 experience in developing field-proven multiplex
18 reactions for multiplex detection of the three
19 viruses.
20 [Slide.]
21 I will just go over a couple of slides,
22 what are the critical customer requirements.
23 [Slide.]
24 The first one is it has to be able to fit
25 into their routine workflow. It must be the

1 ability to have sufficient automation to reduce
2 operator involvement and associated human errors,
3 and, of course, have positive ID throughout the
4 entire process.
5 [Slide.]
6 So, we have a large program with very
7 large teams in multiple countries working on an
8 automated solution for extraction and simultaneous
9 amplification detection.
10 [Slide.]
11 It should be able to handle single unit
12 testing with minimal increase in labor
13 requirements, and importantly, the ability to
14 process at small and large centers, the same number
15 of donations that would be covered in the time
16 period in our current 24-pool system.
17 [Slide.]
18 It will be a multiplex assay covering
19 HIV-1, HCV, and HBV. The system will provide for
20 general menu expansion. We are actually looking at
21 Parvo B19, HAV, CMV, and most recently, looking at
22 West Nile virus.
23 Full process control both for the target
24 analyze, as well as the hardware critical control
25 processes, and, as I mentioned, positive ID.

1 [Slide.]

2 There have been some discussions about
3 alternatives, and we view these as second choice
4 alternatives to a fully automated system, but they
5 are things that we are looking at. We can go to
6 pools of 6 with the manual sample prep. You don't
7 have a 24-fold increase in problems, you have a
8 4-fold increase in problems.

9 Back up one slide, please.

10 [Slide.]

11 We have several systems, in Japan, as I
12 mentioned already, and other diagnostic
13 applications that are automated sample preparation
14 devices. These are not currently being pursued for
15 licensure in the U.S., however, that is something
16 that Roche conceivably could move to.

17 [Slide.]

18 So, in conclusion, we believe strongly
19 that moving to single unit NAT with the current
20 semi-automated systems may pose a greater risk than
21 the benefit provided, and that single unit NAT is
22 best accomplished by aggressively pursuing and
23 devoting sufficient resources to create these high
24 throughput, fully automated systems.

25 Finally, we believe that we have got

1 experience, tested experience in developing complex
2 systems and reagents to meet the interim and
3 long-term needs.
4 Thank you very much.
5 DR. NELSON: Thank you.
6 The next group that wanted to speak is
7 from Gen-Probe. Dr. Sherrol McDonough.
8 DR. McDONOUGH: Hopefully, we will get the
9 slides going in a moment.
10 I will be continuing the discussion on the
11 Procleix System and I am really going to cover two
12 topics. The first is the manufacturing facility
13 that Gen-probe has built to address the ability to
14 manufacture reagents.
15 The second will be our fully automated
16 system, Procleix Automated System or TIGRIS.
17 [Slide.]
18 This is a picture of our facility in the
19 San Diego area. It was commissioned for use in
20 1999. It was designed and built specifically for
21 the production of nucleic acid testing reagents and
22 was used to build conformance labs for the HIV-HCV
23 product. It was licensed in February of this year,
24 and when we look at the capacity, we believe that
25 we could adjust to the market requirements whether

1 that is a move to pools of 8 or movement to
2 individual donation testing in a period of 6 to 7
3 months from the time the decision was made.
4 [Slide.]
5 Now, I would like to talk about the fully
6 automated instrument.
7 [Slide.]
8 Some of the design features of the
9 automated system are listed on this slide. First
10 of all, primary tubes can be loaded directly.
11 There is no requirement for an ultra-centrifugation
12 step or any serious manual steps.
13 180 tubes can be loaded on the instrument
14 at a time. The instrument creates a worklist by
15 scanning those bar codes, so that is all done
16 automatically.
17 Once the sample processing begins and the
18 first 180 tubes have been sampled, they can be
19 removed from the instrument and another 180 tubes
20 can be added.
21 When you start the day, you can put out
22 enough reagents and fluids to do 1,000 tests. At
23 that point, you need to stop, remove the wastes,
24 and replenish the fluids.
25 [Slide.]

1 The Procleix System is a single tube
2 assay. That means all the steps from sampling
3 processing, amplification, and detection are
4 performed in the same reaction tube, so there is no
5 need for the instrument to transfer from one
6 reaction vessel to another during the entire
7 process.
8 That helps maintain specimen I.D. and also
9 reduces a source of contamination within the
10 instrument.
11 The productivity targets for this
12 instrument are to have time to first result about
13 3.5 hours and then 125 test results released per
14 hour thereafter. We are developing multiplex
15 tests, for example, for our HIV/HCV tests, that
16 would be 250 results per hour, 125 results for HIV
17 and 1 25 results for HCV.
18 The instruments maintains full
19 traceability through positive identification of the
20 specimens, and the assay performance will be
21 comparable to that seen in the already licensed
22 system.
23 [Slide.]
24 This is a picture of the instrument. It
25 looks big here, but it actually takes up much less

1 room than the semi-automated system, so if a
2 laboratory has space for the semi-automated, they
3 will have space for this instrument.
4 Specimens are loaded in the bay that is
5 shown open on the right side of the instrument.
6 Reagents are loaded on the top left. All the
7 sample processing occurs in that middle part of the
8 instrument. All of the assay performance steps are
9 performed there, and the intervention is through
10 the computer on the right.
11 [Slide.]
12 The development timeline for this
13 instrument is as follows: We are to the point in
14 development where we are doing evaluations with
15 customers. I am happy to report that we have
16 already performed an evaluation with customers for
17 the diagnostic side. The instrument is being
18 developed for both diagnostic and blood screening
19 applications.
20 So, the initial evaluation with customers
21 was completed earlier this year, and we are in the
22 process of setting up the evaluation with blood
23 center customers, and that will take place in
24 fourth quarter.
25 As you already heard, the goal is to start

1 the clinical trials on this instrument at the end
2 of 2003.
3 [Slide.]
4 So, in conclusion, we have a manufacturing
5 facility specific for nucleic acid testing reagents
6 with capacity up to 100 million tests per year.
7 The automated system will give results
8 similar to the semi-automated system that is
9 available now. The instrument will reduce
10 personnel time and increase adherence to GMP by
11 performing many of the steps that have to be done
12 by humans now, such as worklist creation, correct
13 placement of Cals and Controls, ensuring use of
14 master-lotted materials, in-date materials, et
15 cetera.
16 Thanks for the opportunity to present.
17 DR. NELSON: Thank you, Dr. McDonough.
18 Dr. Gilcher from Oklahoma.
19 DR. GILCHER: What I want to talk about
20 briefly, very briefly, is an overview of nucleic
21 acid testing at the Oklahoma Blood Institute. We
22 began in April of 1999 using HCV-RNA-PCR with a
23 minipool of 24.
24 In November of 1999, we added then
25 HIV-RNA-PCR at a minipool of 24. In March of 2000,

1 we set up a separate HIV-HCV-RNA-TMA, that is a
2 Chiron/Gen-Probe laboratory as a minipool of 16 to
3 compare workflow of the minipool PCR versus the
4 minipooled TMA, and assuming at 100,000 donations,
5 the PCR would be 8,333 tests. The TMA would be
6 6,250 tests.
7 [Slide.]
8 In running that particular study, and it
9 was a study for workflow, our conclusions were that
10 for a large laboratory, and our collections at that
11 time were about 170, 175,000. We will do over
12 200,000 donations this year that will be tested by
13 NAT.
14 For a large lab, over 100,000 TMA-enhanced
15 laboratory workflow as far as NAT testing
16 operations.
17 On July 1st of 2002, we then switched to
18 single donation nucleic acid testing as our test of
19 record at OBI. So we have, in a sense, done both
20 the minipool PCR, the minipool TMA, and now the
21 single donor or the ID TMA.
22 [Slide.]
23 There is a particular case that I want to
24 talk about. We have not had any forward misses or
25 front-end misses as we have heard about, and I will

1 mention that in a moment, but we have had an
2 interesting, what I call "back end" miss.
3 This occurred on February the 9th of 2000.
4 We had an EIA and Western blot-positive HIV
5 donation, which was minipool PCR-negative at a 1 to
6 24. The same donation sample, that is, a frozen
7 sample that was tested 21 days later, and that is
8 important that it was the same sample, and it was
9 frozen and thawed, and that is important.
10 I thought Dr. Busch might talk about the
11 concerns of aggregation, but that doesn't seem to
12 be the case here, because testing that thawed
13 sample by minipool PCR at 1 to 24, it was still
14 negative. We did a 1 to 16, it was negative, but
15 the "Neat" was, in fact, PCR-positive.
16 [Slide.]
17 There are a number of objections to single
18 donor NAT that you have heard about - too costly,
19 too much space, too many technologists, possibility
20 of increase human errors, lack of total automation,
21 increased opportunity for contamination, increased
22 run failure rate, increased delay, and inventory
23 release. All of those were concerns that we had
24 when we addressed the issue of single donor NAT.
25 [Slide.]

1 These are our reasons that we made the
2 switch. First, was the "Back end" miss that I
3 showed you with HIV, and by the way, there have
4 been a number of those with HCV.
5 Then, the reported HIV "front end" misses
6 that you have heard about, the San Antonio, later
7 the Tampa case. There is one in France. There is
8 the Singapore case.
9 Then, the third point was that we had
10 operational challenges, and we felt that we could
11 overcome those. We overcame the issue on cost,
12 space, technologists, compliance, test performance,
13 and obviously operational impact.
14 When presented to our Board, they felt
15 that for us in Oklahoma, that it was the right
16 thing to do.
17 [Slide.]
18 The cost was justified by the elimination
19 of HIV antigen, the absence of pool discrimination,
20 and that is extremely important because that
21 resulted in the capture of lost products, and the
22 objection that is made that it will delay the
23 release is simply not true. In fact, we are able
24 to capture platelets that would have clearly been
25 lost during the discrimination period, because our

1 discrimination is a pool size of one, then, other
2 cost reduction measures that were introduced at the
3 blood center.
4 To accommodate this, we built two mirror
5 image laboratories, each with the potential
6 capacity for up to 500,000 single donor tests.
7 Now, the numbers of techs that we had to
8 hire is important. We went from 4 with our
9 minipool to 10 for the single donor NAT, and those
10 10, it is estimated can perform up to the 250,000
11 tests. To do 500,000, obviously, we would have to
12 increase significantly.
13 180,000 donations then tested by the
14 minipool would be 15,000 tests by PCR, whereas, the
15 single donor TMA was 180,000 tests or 12 times as
16 many tests for us as what we had been doing.
17 [Slide.]
18 No pooling steps - reduces the time to do
19 the NAT. There is clearly a faster turnaround time.
20 There is, in our opinion, less chance for error
21 without the pooling. There is the same degree of
22 manual testing as with the minipool. Clearly, we
23 would like more automation.
24 Testing time is faster by getting rid of
25 the pooling, and this is very important, laboratory

1 operations return to a single test platform, and
2 Kendra Ford has accompanied me here today, the Vice
3 President of Operations, who can talk more about
4 that if you have questions afterward. That is an
5 important point.
6 [Slide.]
7 This is really our learning curve that I
8 am demonstrating here. This is the Chiron validity
9 statistics. When we started out, you can see we
10 have a very high invalid run rate, the purple line.
11 That was a number of factors. One of the
12 most important factors for us was an environmental
13 factor that we had not expected. We built the two
14 new laboratories that I told you about, and
15 inadvertently, the plumber hooked up the drain
16 lines to the wrong system, and we had a sump pump
17 pumping backward.
18 We had the second lab which we have not
19 used contaminated before we entered the lab, and
20 finally figured it out. So, that is included in
21 that. But our invalid run rate has come down and
22 continues to come down. That is a learning curve.
23 [Slide.]
24 So, lessons learned. The total space for
25 the two labs interestingly, without pooling taking

1 up that space, is only slightly larger than the
2 prior space. 180,000 donations is 15,000, as I
3 mentioned before, with PCR minipool versus 180,000
4 tests with single donor TMA or 12 times more tests,
5 but with only 2.5 times as many technologists to
6 perform the tests.
7 Detraining of existing technologists to
8 convert from PCR to TMA was absolutely critical in
9 our system. It was easier to train technologists
10 who had not performed NAT testing ever than to take
11 techs who had done the test and detrained them, and
12 then trained them on a different test.
13 Clearly, as I said before, it is easier to
14 operate in a single test environment versus a
15 pooled test environment.
16 So, for us at the Oklahoma Blood
17 Institute, we are doing individual donor nucleic
18 acid testing, and we are making it work.
19 Thank you.
20 DR. NELSON: Thank you. Comments? Did
21 you have viral load on the one case that was the
22 back end failure?
23 DR. GILCHER: Excellent question. We
24 don't, but we have sample. One thing that we do at
25 the Blood Institute is we maintain two years plus

1 the current year as repository samples, so we have
2 repository samples on everything, and that is
3 something that will be done.
4 DR. NELSON: Susan Stramer, American Red
5 Cross.
6 DR. STRAMER: Thank you for those who are
7 left. I don't even know if we have a quorum, if
8 it's legal to have a meeting.
9 Even so, I will read my statement. Thank
10 you very much.
11 I am Susan Stramer, the Executive
12 Scientific Officer for the American Red Cross.
13 The American Red Cross through its 36
14 regions and nine testing laboratories supplies
15 approximately one-half of the nation's blood for
16 transfusion needs. We thank the FDA and the Blood
17 Products Advisory Committee for this opportunity to
18 speak on the implementation of single unit NAT to
19 reduce the remaining risk of HIV transmission
20 through transfusion.
21 I see I am clearing the room.
22 Recognizing the potential significance of
23 NAT for HIV and HCV, the Red Cross initially began
24 exploring the implementation of NAT in 1997 using
25 pools of 512, in an approach similar to that used

1 by much of the plasma industry.

2 However, to achieve the needed turnaround

3 times for the release of cellular components, we

4 instead implemented the Gen-Probe test in March

5 1999, first in pools of 128, followed in 6 months

6 by the transition to pools of 16.

7 We recognize that NAT implementation

8 represents a step-wise progression towards an

9 automated technology using individual units. We

10 greatly supported the industry-wide effort to

11 implement NAT under IND and were pleased to

12 participate in the studies in support of NAT

13 licensure.

14 Over the past three-plus years of NAT

15 screening for HIV-1 and HCV, the Red Cross has

16 detected 90 HCV NAT confirmed-positive,

17 antibody-negative units in approximately 23 million

18 donations screened for a yield of 1 in 240,000 and

19 5 HIV NAT confirmed-positive, antibody-negative

20 units, of which only one was HIV p24 antigen

21 positive for a yield of 1 in 4.6 million.

22 Viral loads at index for the HCV yield

23 cases ranged from 100 copies/ml to 190 million

24 copies/ml; viral loads for the HIV yield cases

25 ranged from 390 to 750,000 copies/ml.

1 At an approximate sensitivity of 30
2 copies/ml, at 95 percent confidence for the
3 Gen-Probe test, as indicated in the package insert,
4 and using a pool of 16, the expected viral load
5 reliably detected is estimated at 480 copies/ml.
6 Three HCV yield cases and one HIV yield
7 case were each detected below this level. We
8 recognize that we were lucky in these four cases,
9 and as experience has now demonstrated, there will
10 be breakthrough cases of HIV and HCV with viral
11 loads around or below the assay cutoff that we are
12 using today, which is set by our pool size.
13 We also recognize that when the same
14 assays are used to test individual units, there
15 will be cases where the viral levels will be below
16 30 copies/ml and perhaps below 1 copy/ml, so that
17 the expectation that NAT will detect all infectious
18 units even with single unit testing is likely to be
19 in error.
20 Recent data also indicate that the
21 residual risk for both HIV and HCV following the
22 implementation of pooled NAT is approximately 1 in
23 2 million donations and that with the additional
24 sensitivity of single unit NAT, the residual risk
25 is estimated at 1 in 3 million.

1 So, the question that is before us is:
2 what approaches, if any, can be implemented during
3 the time between our current use of pooled NAT for
4 HIV and HCV using the available technology and an
5 automated assay that has sufficient throughput and
6 process control such that single unit NAT is
7 feasible in high-volume laboratories.
8 The current testing technology, although
9 labeled as semi-automated, is for the most part
10 manual with numerous manual pipetting steps for
11 both sample and reagent addition and removal, along
12 with many manual vortexing and incubation steps.
13 Processes are segregated in separate
14 laboratories for pooling, amplification and
15 detection, all of which required significant
16 laboratory renovation prior to the implementation
17 of NAT.
18 Even with all that has gone into
19 implementing and performing NAT, this assay has
20 performed equal to, or better than, any other test
21 used in our system as evidenced by donor losses due
22 to contamination of less than 1 in 30,000.
23 Therefore, given the systems that are
24 available today, pooled NAT has been optimized and
25 is a success. I would also like to mention this

1 was true even after the outpouring of donations
2 after last year's 9/11 tragedy when our volume
3 doubled by 2- and 3-fold, our error rate and
4 contamination rate virtually was unchanged.
5 What can we learn from the four donors
6 with early HIV infection that have been reported to
7 have transmitted HIV to recipients of their
8 donation? The first case from Singapore that was
9 p24 antigen-negative has been discussed already; in
10 dilutional studies using the frozen plasma unit it
11 was shown that detection decreased as pool size
12 increased.
13 HIV detection using the Gen-Probe assay in
14 a pool of 24 occurred in 2 of 3 replicates tested;
15 using pools of 16, 1 of 3 replicates were reactive
16 and using pools of 8, all 3 replicates were
17 reactive.
18 The second case from South Texas from
19 which a pool of 24 failed to detect HIV RNA by an
20 in-house assay was also discussed. In this case,
21 dilutional studies showed that using the Gen-Probe
22 assay on the frozen plasma unit, 1 of the 3
23 replicates was reactive at a 1 and 24 dilution,
24 whereas all 3 replicates were reactive at a 1 to 8
25 and 1 to 16 dilution.

1 Therefore, the Gen-Probe assay using
2 undiluted samples, or a dilution of 1 to 8, was
3 able to detect HIV RNA in all replicates tested
4 from these two cases. The last two cases of
5 failure of pooled NAT to detect HIV RNA did not
6 have residual sample from which to perform these
7 types of studies, that is, the case reported from
8 South Florida that was negative by the Gen-Probe
9 assay in a pool of 16 and a case reported by the
10 French in which the Roche assay in a pool of 24 was
11 negative.
12 So, although the estimated window period
13 reduction with each pool size reduction of one-half
14 is one doubling time, or just under 1 day of an
15 estimated total 4-day window period to individual
16 unit NAT, one could argue that a decrease in pool
17 size will increase the reliability of detection of
18 samples having viral loads close to the current
19 assay cutoff, and will likely detect additional
20 cases where the viral loads are below the level
21 that we are currently capable of detecting.
22 However, it should be recognized that
23 neither a decrease in pool size, nor addition of
24 single unit testing will completely close the
25 infectious HIV window.

1 The paradigm of step-wise improvements in
2 assay sensitivity leading to an automated platform
3 is not new to NAT. It has occurred for every virus
4 for which we perform blood donor screening. Some
5 changes were as simple as a reduction in assay
6 cutoff to achieve increased sensitivity.
7 If we look to our antibody screening
8 systems as a model, we have still not implemented
9 an automated testing system with improved assay
10 sensitivity and specificity and all the desired
11 process control features to minimize documentation
12 and other potential errors.
13 For example, the PRISM system has been in
14 development for over 15 years and although used
15 outside of the United States, we are still waiting
16 for licensure and implementation in the U.S.
17 Therefore, a comparable automated NAT
18 platform may be years away; consequently, we must
19 examine all that can be done within our current
20 systems to achieve whatever improvements in
21 sensitivity are possible.
22 There are many variables that would have
23 to be considered prior to a transition to a smaller
24 pool size. Does the small increase in sensitivity
25 justify the changes that would be required for this

1 single modification? This would include the hiring
2 and training of additional staff and additional
3 costs for disposables not related to reagents.
4 Additional costs for upgrades to, and
5 validation of, the automated pipetting system and
6 upgrades to our NAT laboratory management software
7 including 510(k) submissions and approvals would
8 also be required. Regarding reagent costs, blood
9 centers have invested an unparalleled amount for
10 this technology.
11 There likely will be an increase in
12 reagent price of an unknown amount at this time
13 that could be mitigated by volume. Decreasing pool
14 size could occur without the need for additional
15 testing equipment or laboratory renovation, but the
16 total costs are unknown at this time.
17 In summary, data show that single donor
18 testing could enhance our ability to detect window
19 period donations. In the interim, a reduction in
20 pool size may have some impact on safety by
21 increasing the reliability of detection of some
22 samples.
23 At the present time, the Red Cross is
24 looking into the option of decreasing pool size,
25 but no decision will be made until all variables

1 related to this effort have been reviewed.
2 But if a reduction in pool size occurs, we
3 believe that it could occur without compromising
4 the quality or efficiency of testing. We will then
5 have considered all that may be done within the
6 current systems and available technology until
7 automated single unit NAT is available.
8 Thank you.
9 DR. NELSON: Thank you.
10 Next is Dr. Paul Holland.
11 DR. HOLLAND: Thank you. I am Paul
12 Holland from Blood Source, a large regional blood
13 center in Sacramento, and is a regional NAT testing
14 lab for our own collections in two other centers.
15 I had sent in a few slides to make the
16 three points I wanted to make, but I believe you
17 have the handouts, and I will describe pretty
18 briefly because of the time.
19 I wanted to discuss the elements of the
20 testing, and as Dr. Stramer pointed out, they are
21 often described as semi-automated, they are very
22 manual.
23 The second point I wanted to talk about is
24 the reliability. While these nucleic acid
25 technology tests are fantastic in terms of

sensitivity and specificity, they are no more reliable in terms of failure rates than our standard serologic EIA tests.

I want to end up briefly with my concerns regarding reducing the pool size or even going to individual NATs, because of the concerns, and I will point out that they are real, of the staffing, of the burnout of that staff, and of the errors which result.

As I said, a lot of the testing is already quite manual. This means a lot of meticulous, repetitive motion, and the single biggest problem we have is burnout of the staff. I recently visited Singapore where I was there for 10 days evaluating their system, and they are testing 60,000 units a year by single unit NAT, and that is their single biggest problem is constantly having to rotate technologists through to do this repetitive, highly meticulous type of work.

In California, we require licensed medical technologists, not techs, licensed medical technologists to do laboratory tests. We are already in a critical shortage. We would not be able to do the kind of testing that would be required with single unit testing.

1 We already have to constantly supplement
2 the NAT lab staff where we run two runs a day, five
3 days a week, and a run on each day on Sunday to
4 have enough staff to complete the testing now with
5 mini-pools.
6 I mentioned the failure rates. The
7 impression I think some of you have gotten is that
8 a false negative is purely due to low copy number,
9 and that individual NAT may pick up at least some
10 of these, but clearly not all.
11 In our evaluation from the Roche survey,
12 in looking at failed runs, our false negative
13 samples that should have been picked up in the
14 pool, half of the time the level of virus was far
15 above what should have been detected in the pool,
16 but we believe due to technical error it was
17 missed.
18 I have given you some data. Anywhere from
19 3 to 4 percent of runs fail because of the positive
20 or negative external controls fail or the internal
21 control fails. Included in this failure rate is
22 also equipment failure and technical failure.
23 People are human and they are doing a lot of us
24 manually.
25 So, about 4 to 5 percent of the time, each

1 one of our tests fails, and when you are doing a
2 dozen different tests, almost every run is held up
3 because either a serologic test or a NAT has failed
4 and has to be repeated.
5 This causes additional stress in a
6 production environment and really would be I think
7 magnified by single unit or even smaller pool
8 testing. In essence, without further automation
9 and without validation and licensure of that
10 automation, I think it would be foolhardy, I think
11 we would add to our problems, and potentially
12 create more risk than the very minimal decrease in
13 risk that might be bought without going to zero
14 risk, with single unit or even smaller pool
15 testing.
16 Thank you.
17 DR. NELSON: Thank you. Comments? Toby.
18 DR. SIMON: I just wanted to make just a
19 couple of comments, mostly I guess at this point to
20 get it on the record, but I think to put things in
21 context, we need to remember that the pooled NAT
22 method was originally developed for plasma
23 fractionation and it was spurred on by a
24 requirement in Europe for HCV testing because of
25 that longer window, and the pooled NAT made a lot

1 of sense for plasma because of the inactivation
2 procedure, the occasional unit that is missed
3 doesn't cause a serious problem.
4 The blood banks I think originally got in
5 because of selling of plasma into Europe, and then
6 I think everybody recognized the possible benefits
7 to the patients who received transfusion, and that
8 increased the momentum.
9 I think from the beginning we realized
10 here we were talking about a unit here or a unit
11 there, and single unit NAT made a lot of sense, and
12 was the ultimate goal, but couldn't be achieved
13 immediately, so the pooled NAT was better than
14 nothing.
15 I think from what we have seen here, my
16 thought would be we will certainly save a case here
17 or case there, but we are making another one of
18 these small incremental steps, and as I said
19 before, until we really get pathogen inactivation,
20 we are still going to occasionally have these cases
21 that get through the system and tragically cause
22 disease.
23 I think people, Dr. Gilcher and others who
24 want to lead the way in single unit NAT obviously
25 can do so providing they file the appropriate INDs,

1 but I don't think it is a time necessarily for the
2 committee or FDA to try to mandate this path until
3 we see how technology moves and how things
4 progress. That would be kind of the sense that I
5 would take away from what I have heard.
6 DR. NELSON: I think that plus the review
7 of the fact that we have had some still rare
8 documented cases that pass through even with the
9 pooled NAT.
10 DR. SIMON: We knew that, though, as Dr.
11 Gilcher pointed out, we knew that was going to
12 happen.
13 DR. NELSON: Yes, we did, but our
14 suspicions were validated, but again we were able
15 to pick up these few cases.
16 DR. SIMON: We picked up some.
17 DR. NELSON: Some of them, yes.
18 DR. SIMON: We picked up some of them and
19 not others, and that will continue even with the
20 three- or four-day further closing of the window,
21 there will be that occasional case, but obviously,
22 if I were the recipient of that 1 in a million
23 cases, I would be appreciative of the single donor
24 NAT, but over the aggregate, it is a very small
25 effect.

1 DR. SCHMIDT: Ron Gilcher, who is
2 certainly dedicated to stamping out every vestige
3 of disease, has pointed out to us in his statement
4 something mentioned earlier. He had to sell it to
5 his board of directors because again we are all
6 committed to stamping out every element of disease,
7 but when you get into the local community, it is a
8 question of can we still exist.
9 Now, I know it is not the function of the
10 FDA to talk about cost, however, cost relates to
11 supply, and as I understand it, they were reminded
12 recently by the Senate Appropriations Committee
13 that maybe some of the idea of keeping prions out
14 of New York might result in no blood for New York,
15 so for whatever that is worth, I mean there is a
16 sort of a kickback here, and although the
17 individual patient, you know, it happens to a
18 patient, it's 100 percent.
19 The community that provides blood has
20 something to say about it, as well.
21 DR. NELSON: Celso Bianco from America's
22 Blood Centers.
23 DR. BIANCO: I am Celso Bianco from
24 America's Blood Centers.
25 As you know, this is an organization of 75

1 member centers that collect about half of the U.S.
2 blood supply. You have copies of my statement, so
3 I am going to skip about half of it because it
4 would just reiterate the effect, all the
5 difficulties with moving from mini-pool testing to
6 individual donor testing using the current
7 technology, semi-automated or semi-manual.
8 However, I would like to read the part
9 from the middle where we start discussing
10 intermediate changes in pool size. I also would
11 like to note that Dr. Gilcher, that just spoke and
12 presented his change, is a member of America's
13 Blood Centers and decided to implement single donor
14 NAT.
15 Besides the concerns about the movement to
16 single donor NAT contamination, staff burnout, and
17 all the issues that were raised here today, we are
18 also very disturbed by the proposals to implement
19 partial reductions of pool size as interim
20 measures, simply to reassure the public. Those
21 were comments that were made by the members.
22 We introduced minipool testing as an
23 intermediate step in order to further reduce the
24 window. We knew from the beginning that the window
25 would not be totally closed and accepted, and this

1 was the best we could do considering the
2 limitations of semi-automated technology.
3 We also know that individual donor testing
4 will reduce , but not close the window. What
5 changed today that forces us to reconsider the
6 approach we took when we introduced NAT in 1999?
7 We used the same tests, we have
8 essentially the same knowledge that we had at that
9 time, but however, because of these few cases of
10 transmissions and concerns in the press, we are
11 reconsidering our thinking.
12 A reduction of pool size by half, as some
13 have proposed, to 8 samples instead of 16, or 12
14 samples instead of 24, according to what Dr. Busch
15 just showed us, would reduce the window by less
16 than a day.
17 The reduction of pool size might be
18 feasible for certain testing laboratories, it would
19 not achieve the goals of individual testing.
20 Furthermore, intermediate reductions of pool size
21 are not clearly justifiable.
22 Why reduce by half? Why not go to a pool
23 size of 2 or 1? Why not double the sample volume
24 whether in pools or in single donation testing, and
25 thereby double the amount of potentially detectable

1 nucleic acid.

2 There is no rational limit to this kind of

3 thinking.

4 It is the opinion of the majority of the

5 ABC members that any decrease in the window period

6 that may result from the reduction in pool size or

7 a move towards individual donor testing using

8 current technologies could be neutralized by the

9 potential increase in human error during the

10 performance of manual steps. There is also an

11 increased potential for delays in the release of

12 blood that may threaten the patients' lives.

13 Furthermore, we are concerned that such

14 intermediate and small safety improvements will

15 divert assay manufacturers, and I think that this

16 is the different message that I would like to

17 emphasize from the pressure to develop automation

18 and test enhancements in a timely fashion.

19 Without that pressure, the current

20 semi-automated technologies may remain as

21 state-of-the-art for many years to come. For

22 instance, one of the test manufacturers has been

23 advocating for migration to individual donor

24 testing using current technology.

25 It will actually not support minipool

1 testing for centers that screen less than 100,000
2 samples a year. This manufacturer,
3 Gen-Probe/Chiron, received an NHLBI contract in
4 1995 to develop NAT for HIV and HCV, and an
5 automated instrument for the TIGRIS that we just
6 heard about.
7 Seven years later, we heard today, and
8 this is a change here, that the instrument will be
9 in clinical trials by the end of next year. Why
10 should they continue to work on this equipment if
11 they could sell individual donor testing using the
12 current semi-automated or semi-manual technology?
13 Roche is one of the biggest manufacturers
14 of assay systems in the world. There are European
15 centers performing NAT for donor screening with
16 automated instruments provided by Roche. Why
17 aren't these systems available in the U.S.?
18 The ABC members urge Gen-Probe/Chiron and
19 Roche to continue their productive collaboration
20 with the transfusion medicine community and apply
21 the maximum possible efforts and resources to the
22 final development and validation of automated
23 systems for donor screening by NAT in the United
24 States.
25 You are almost there. Please, get there.

1 We also urge FDA to accelerate the review, and we
2 heard Dr. Indira Hewlett commit herself to that, to
3 accelerate the review of these instruments in order
4 to allow fully automated NAT screening to start as
5 soon as possible.
6 Thank you.
7 DR. NELSON: Thank you.
8 Finally, Kay Gregory from the American
9 Association of Blood Banks.
10 MS. GREGORY: Again, in the interests of
11 time, I will abbreviate my statement, but I would
12 like to request that both of my statements be
13 reflected in the transcript in their entirety.
14 The American Association of Blood Banks
15 believes that the blood community, the Food and
16 Drug Administration, and manufacturers should move
17 with deliberate speed to bring single donor nucleic
18 acid amplification testing to donor screening
19 laboratories throughout the United States.
20 The community has made significant
21 progress in improving blood safety through nucleic
22 acid testing of minipools. Now, we should continue
23 our efforts by moving toward our goal of single
24 donor testing.
25 Although some laboratories may be in a

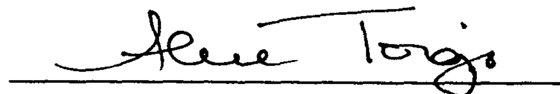
1 position to implement additional NAT improvements
2 now, it is important that these initiatives not
3 divert resources from the ultimate goal of
4 nationwide NAT performed on automated systems.
5 Prior to the implementation of single
6 donor NAT, it is critical that the following issues
7 be addressed:
8 Both the licensed and IND NAT assays are
9 substantially manual procedures not suited to
10 single donor testing in the majority of blood
11 center labs performing NAT now.
12 At present, these is insufficient capacity
13 in existing laboratories to perform single donor
14 NAT nationwide. The increased number of
15 laboratories will require a significant commitment
16 of support from manufacturers for materials,
17 equipment, training, and maintenance.
18 There is a known shortage of medical
19 technologists within the health care industry, and
20 hiring additional qualified staff to implement
21 single donor testing will require time.
22 We appreciate the public discussion this
23 meeting will provoke which should begin to solidify
24 a timeline for the orderly implementation of single
25 donor NAT. We also urge the committee and the FDA

1 to expand this discussion to enumerate the
2 noninfectious serious hazards of transfusion that
3 are responsible for significantly more transfusion
4 associated morbidity and begin prioritizing the
5 safety initiatives to which the entire blood
6 banking community should be committed.
7 Thank you.
8 DR. NELSON: Thank you. Questions or
9 comments?
10 DR. SIMON: I think it was about three or
11 four meetings ago when we discussed the same thing
12 that is in the last paragraph of the AABB
13 statement, which was the need for prioritization of
14 infectious disease, hazards, and noninfectious
15 disease, hazards of transfusion, and the need to
16 prioritize that list and provide a recommendation
17 to the FDA for what would provide the greatest
18 impact to the blood supply in the country and
19 patient safety.
20 I think in the fact of West Nile and what
21 we heard about Chagas, and now the move to single
22 donor NAT, that maybe we should reassert that
23 recommendation and ask for that at a future
24 meeting.
25 DR. NELSON: You are recommending we

1 review the global issue at a meeting. Okay. Any
2 other comments?
3 I think this was a good and important
4 afternoon. I think we have had substantial
5 successes and yet things still aren't perfect, but
6 I think this was useful.
7 Any other final comments?
8 [No response.]
9 Thank you.
10 [Whereupon, at 6:15 p.m., the meeting was
11 adjourned.]
12 - - -

C E R T I F I C A T E

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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