frequency of false positive as was expected. With the current data set, Roche feels that the current AmpliScreen protocol can be modified to allow test results investigation to resolve true NAT positives from false positives.

In addition, using the information and data from the current clinical studies, Roche recommends and supports the convening of a joint workshop with the FDA and industry to align language for testing, donor and produce management.

Thank you.

DR. NELSON: Thank you very much. Questions, comments? Thank you.

Dr. Chuck Watson from Aventis Bioservice.

DR. WATSON: I am Chuck Watson and I am here to present on behalf of Aventis Bio-Services. We have been testing NAT in plasma since 1998.

[Slide.]

For those of us who sit in the back and can't see, I am showing some of these, the overheads. All of our samples are serology-negative, like all the others. We test in 2-dimensional grids, and I think this is one of the problems why it is so hard to come up with an algorithm is that there a couple of different ways to skin this cat and do the test, and actually do the test right and get valid results.

Part of the algorithms for unexpected results

really need to take a look at what are the sensitivities of the pools, the subpools that are being tested. There is a big difference between the whole blood industry and the plasma industry, and there probably does need to be two separate algorithms. If the plasma industry is to test and go to either 500 or 1,200 individual tests, you are going to stop the testing. The labs will not be able to put that kind of work out.

We have a lot of data and hopefully, I can show some data to try and simplify at least from our point of view what we do and we think it is right, but it is just one way to be right, there are many others.

[Slide.]

The way we pool, we start with 12 donations, and that is because we ship 12 units in a box and it is easier for us to handle. We pool them together into what we call minipool, if you want. You can call this a small, medium, and large pool. Our minipool, we then take 10 of them and pool them into one test tube to provide us with a midipool or medium pool of 120.

We then take 100 of the midipools, the 120, and put them together. The computer does this, we don't do it literally, the computer does this and gives us a grid of 12,000, which is our starting point. 12,000, 100 times 120 is a 12,000 unit working group.

Each of the maxipools consists of 1,200 samples, because each midipool is pipetted both a horizontal direction and a vertical direction, so you have 10 times 120 to give you the 1,200, but you have 100 midipools to make up the initial working unit. Each of the maxipools is tested in duplicate. So, that is our test system and how we form our pools.

[Slide.]

This is just a simple diagram to show that theoretically at least, and we really like it when we have horizontal and vertical positives, it makes it a lot easier. We can draw a line from the positives to determine what we need to look at, what are the indicated pools that we might need to do further testing on.

This is a simple case. In this particular case, we can either test the midipool, then to go the minipool, and then go to individual donors, or we could go directly to the minipool, there is no reason to test the midipool.

[Slide.]

More complicated cases. In this particular case, we have 4 indicated pools, but in reality this may be caused by as few as 2 positives. Because you draw the intersections, you are not always going to find a positive in each of the pools, but you should explain each of the maxipools. So, in other words, we should find one of the

two positive and one of these two positive in a normal case. Hopefully, it is, let's say, one here and one here that explains all the four lines, all the four intersections.

[Slide.]

This is an unexpected case for us although it does happen. You will get a maxipool that is positive in both replicates with no intersecting positive maxipool. In this case, we actually test all 10 of the midipools.

This is the end, I guess, of the different types of positives that we can have. The next slide, I believe shows our algorithm.

[Slide.]

We do our maxipool test. If everything is negative, we love it, we release results, everybody is happy. If there is a positive, we can test the midipool. When we test the midipool, we can get two types of results. We can get results, a positive that explains our maxipool, in which case we can release the negative midipools and we go down with the positive midipool, and we continue to work trying to identify a positive reason for it.

However, we can have another result. All the midipools are negative. What we do is if all the midipools are negative, we take and do all the minipools for the negative midipools. We go back down the second level.

Part of the reason for this is sensitivity. Our

midipool and our maxipool, there is not a statistical separation that we can live with and say that this is, statistically speaking, a more sensitive test when you look at the unit level. So, therefore, we don't want to trust that this negative result might just be that we have a low level, we caught it at the maxipool, we ran it at the midipool with an equivalent sensitivity, but we weren't able to pick it up, so therefore, we go down to the next level.

This is a group of 12 remember. If the minipool is negative, we release negative results for the minipools. If it is positive, we will do an individual sample test on the individual test tube. If that is negative, we will release negative results. If it is positive, we then look at the donor history and we do a unit test.

In the plasma industry, you have closed collection systems and you have open collection systems. The open collection systems at the collection centers are subject to contamination, and you need to avoid that. So, you look at the donor history. If the donor history shows that this is a multiple positive, you have had another PCR-positive, run it before, or NAT-positive, run it before, or let's say in the meantime there has been serology-positive, you can release without obtaining the unit, without testing it.

However, if it is the first positive on an individual at the individual sample tube, we actually obtain

the unit, bring the unit into the laboratory and test it. If the unit is positive, we will report positive results, we will destroy all units, destroy those units, and we will gather all the look-backs and notify everyone. If the individual unit is negative, we will release negative results.

Now, originally, what we did was if the maxipool was positive and the midipool was positive, if we believe going from a maxipool to a minipool is 100-fold more concentrated, and we release from there, then, if the midipool is positive, we would have to go to the individual samples to release from there, again 100-fold more concentrated sample.

However, we did a lot of work and got nothing, lots of work.

[Slide.]

So, what we did, in 2000, actually, it is the first six months of 2000, we actually did that. If we had a positive midipool, and every minipool in that midipool was negative, we tested all individual donor samples.

Now, this is with all five viruses, this is not just HCV and HIV. The majority of these are HBV actually. There is at least 1,300 samples in here that come from HCV. We found zero positive individual sample results when we tested over the 7,000 samples. So, we feel very comfortable

in releasing from the minipool level when the minipool itself is negative.

One of the other things that we believe in, and which I really spoke about earlier, is that the test sensitivity of your smaller pools, if you have a better sensitivity on those smaller pools, that is one of the reasons why I say you need to look at the test sensitivity, what are you actually testing.

You are not retesting something that you have already tested before. You are testing a lower pool, smaller concentration. You should be able to detect that.

In our industry we have found, you know, parvovirus B-19 concentrations are up to 10^{14}. We have got HCV concentrations of around 10^{8}, 10^{9}. No one in our industry has really seen a prozone effect.

The other thing that we feel comfortable with is the fact, for Europe, we have fractionation pools that have to be tested, and I can guarantee you if an HCV got through, and we tested it in the fractionation pool level, we would not be using fractionation pools, and that is thousands of liters of plasma, and we have not seen that.

So, we do not believe that you need to go to the individual donor test itself when you have unexpected results. We believe if you have an appropriate algorithm, you can safely release product into production.

I want to thank you very much for your time.

DR. NELSON: Thank you. Are there any comments or questions?

Is Dr. Craig Halverson back?

DR. HALVERSON: Thank you, Mr. Chairman.

[Slide.]

My name is Craig Halverson, Director of Regulatory Affairs for Gen-Probe, Incorporated, and I will briefly review with you the clinical results from our license application that is presently under review. After that, Dr. Chyang Fang is going to detail the Gen-Probe algorithm.

[Slide.]

The Gen-Probe assay is comprised of three distinct assays - the multiplex and two discriminatories. Each tube in each assay contains an internal control, as you have already heard. The discriminatory assays allow the user to determine which type of viral RNA is present in a multiplex-reactive sample.

The three assays are used in the follow sequence. First, the multiplex is used to screen pools of 16. Then, individual samples from a reactive pool are tested again, and the multiplex assay is used to identify the positive individual. Finally, the two discriminatory assays are used to identify which viral RNA is present in the reactive individual sample.

[Slide.]

Specificity for the three assays was 99.69 percent or better.

[Slide.]

In high risk subjects, such as I.V. drug users, the Gen-Probe assays were found to be 100 percent sensitive versus serology or alternative NAT for the detection of HIV-1. Sensitivity for HCV was 98.8 percent or better.

[Slide.]

We saw sensitivities of 99.3 percent or greater for NAT-positive samples. Individual samples were tested in the multiplex assay, either neat or diluted 1 to 16, and individual samples were tested neat in the discriminatory assays.

[Slide.]

For pooled specimens containing either one or two positive samples, we saw 100 percent sensitivity.

[Slide.]

Reproducibility was studied using both positive and negative samples, and there was 99.6 percent or better agreement with the expected results for all three assays. The Gen-Probe assays met or exceeded all of our expectations for sensitivity, specificity, and reproducibility.

Right now I would like to introduce Dr. Chyang Fang to review with you the Gen-Probe algorithm.

DR. FANG: For the next few minutes I will show you the testing algorithm used in our clinical study and the data to support the product and donor management described in algorithm and also to demonstrate that the Chiron Procleix assay performs well in the setting.

[Slide.]

First, I will take you through the testing algorithm in the clinical study by ABC and the AIBC sides for seronegative samples. The numbers in the slide reflect pools that contain only seronegative samples.

Pools are first tested with the HIV-1/HCV multiplex assay. If the pools are reactive, all samples in the pool are tested individually. There are two possible outcomes. All 16 samples are non-reactive or at least one sample is reactive. Either way, non-reactive samples are considered negative and units are released since they are also seronegative.

For the reactive samples, units are quarantined and donor temporarily deferred. Reactive samples are further tested with the two discriminatory assays. If both discriminatory assays are non-reactive, the samples are retested with the multiplex assay. If non-reactive, the donor deferred is reversed. If again reactive, the donor is notified to follow-up testing.

If the multiplex reactive samples are also

reactive in either discriminatory assay, and alternate samples from the indexed donation, if available, is tested with the multiplex assay to check if the NAT tube was contaminated. The serology is also repeated to confirm seronegativity.

If both NAT and the serology are non-reactive, the donor is notified for follow-up testing. This situation indicates that the original NAT tube was likely contaminated. If again NAT-reactive and seronegative, this represents a potential true yield case, and the donor is followed for seroconversion. If both NAT and serology are reactive, the donor is indefinitely deferred based on serology, this situation, such as error in initial serology testing.

[Slide.]

In the clinical study, overall, there were 31 false positive pools for initial false positive rate of 0.26 percent for pool testing. All 496 samples comprising the 31 pools were non-reactive and were also seronegative. There were 22 donations considered false positive for a rate of 0.01 percent. Fifteen of those false positive results were likely due to technical errors since they were non-reactive in discriminatory testing. All 15 samples were seronegative and most had low assay signals. Seven false positives were likely due to contamination since alternate and follow-up

samples were NAT-negatives.

[Slide.]

In the clinical study, we also look into the internal control failures. Forty-six or 0.3 percent of results were invalid due to low internal control signals, however, when this 46 samples were retested, all were non-reactive with normal internal control signals. Therefore, these internal control failures were due to technical errors rather than inhibition reaction or prozone effects in initial testing.

[Slide.]

In summary, based on clinical data, the assays met or exceeded all specificity, sensitivity, and reproducibility expectations. Data from the clinical study and additional data presented by us at last year's AABB indicated that there was no inhibition reaction or prozone effect for this assay.

The BLA is completed and has been accepted by the FDA for filing.

[Slide.]

Low false positive rates were observed in clinical study. We believe that the false positive results were caused by technical errors and/or contamination during pooling and testing process.

[Slide.]

As described in the testing algorithm, we believe that seronegative donations are considered NAT-negative with no donor impact if the samples are found non-reactive when tested individually in the multiple assay, whether in the pool first or not, the unit is released, or if the sample were found initially reactive when tested individually in the multiplex assay, but non-reactive in both discriminatory assays, and non-reactive in repeat multiplex assay, however, the units are quarantined once a sample is found individually reactive in the multiplex assay.

In conclusion, the Chiron Procleix assays perform well with low false positive rates, show no inhibition reaction or prozone effects, and are suitable for routine plus screening use. In addition, the product and the donor management described in the algorithm is appropriate.

Thank you.

DR. NELSON: Thank you, Dr. Fang.

Questions for Drs. Halverson or Fang? Okay.

Next, Dr. Louis Katz from American Association of Blood Banks.

DR. KATZ: Thank you, Dr. Nelson. The AABB is still a professional society of 8,000, so I will leave that alone.

The AABB compliments the FDA and the blood community for the timely and efficient implementation of

routine whole blood donor screening by nucleic acid amplification under IND. The encouragement and flexibility shown by the agency in this effort helped to overcome the critical hurdles that such a project faces, and the result is a quantifiable decrease in potential window period transmissions of HCV and HIV.

The IND holders, manufacturers, and FDA need to cooperate now for timely submission of the voluminous data from these unprecedented clinical trials and equals 25 million, leading to expedited licensure hopefully of both platforms in use in this country. Licensure will be our members best assurance of continued research and development to improve the current assays and develop more robust tests.

A pressing need is application of the levels of automation required for the tight process control we are now demanding in blood collection facilities.

Data presented in public forums and to this committee from the ongoing INDs, as well as the historically low yield of the HIV-1 p24 antigen tests, strongly support the feasibility of discontinuing the requirement for testing volunteer whole blood donors for p24 antigen. We encourage the IND holders to submit their data as quickly as possible and the FDA to consider discontinuation of p24 as soon as they have adequately evaluated the information.

Today, you have seen draft owner management

algorithms to be applied to NAT-screened populations. We encourage the agency to adopt common sense approaches, and not unnecessarily complicate donor requalification algorithms in the event of false positive testing with NAT.

In this context, we support the use of Option A in the algorithms presented by Dr. Dayton in all cases, and oppose, based on the data you have heard, a requirement for replicate tests in negative samples.

Finally, there is, based on the data we have seen, no reason for FDA after licensure to continue requirements for supplemental more specific serologic assays, such as RIBA, western blot, and immunofluorescence, in EIA-reactive, NAT-reactive volunteer whole blood donors.

FDA rules requiring these tests should be reassessed as soon as possible to reflect the additional information we are now routinely and rapidly receiving on our donors, so that it can be used in counseling, deferral, and medical referral messages.

Thank you.

DR. NELSON: Thank you, Dr. Katz.

Questions or comments?

Dr. Bianco.

DR. BIANCO: I will, because of the time, try to shorten a little bit. You have a written statement. We essentially want to congratulate a lot of the people that

helped in the implementation of NAT under the IND, the FDA, the leaders of our effort in ABC. I want to recognize Sally Caglioti and Mike Strong.

In terms of the issues that we would like to raise, we would like very much to see those tests licensed. We urge FDA to issue guidelines that address supplemental confirmation and a rational process for donor reinstatement after documented false positives.

We also urge FDA to modify guidelines that require performance of supplemental serological tests that have been superseded by NAT technology.

Finally, we urge FDA to consider dropping the requirement for HIV-1 p24 antigen for screening of whole blood and source plasma donors.

Regarding the questions to the committee, this is a revised statement that we provided you, we think that to the question, "Should a single negative test be sufficient for release," yes, this is the basis for release on individual screening tests. In addition, all NAT tests under IND have internal controls.

"Should negative subpools lead to release of the units?" Yes, the subpools are more concentrated than the minipools - increasing chances of detection. Again, we still have the internal controls.

"If master pool and subpool are reactive, but

individual donations are non-reactive," our answer is Option A, yes, because we believe that the ultimate results--and actually, Dr. Dayton said a gold standard--should be the individual samples when they are tested.

"Should replicate testing be recommended as a general way of confirming the status of initially reactive pools?" Our answer was no, because this really, particularly in the whole blood screening, leads to a delay in the resolution of the pool. The pools are relatively small, 24 or 16 samples, and they can be proceed to a more definite result, that is, the individual testing of minipools or subpools and the individual samples.

Finally, ABC wants to congratulate all participants, FDA, the test manufacturers, and the blood centers for their contributions to the success of this enterprise. We want to thank effusively our colleague scientists Susan Stramer and Roger Dodd from the American Red Cross for the spirit of collaboration and sharing of experiences.

Finally, we want to thank our courageous and tireless volunteer blood donors. They put up with a painful screening process, informed consents, deferral files and call-backs for follow up, in order to help patients in need of blood in our communities and support the research protocols for NAT. Without them, we would not be here now.

Thank you.

DR. NELSON: Thank you, Dr. Bianco.

Dr. Stramer.

DR. STRAMER: I am Sue Stramer. I am from the American Red Cross. The American Red Cross also has a written statement which you all have. I don't think I need to read it. It has the same information that I presented, and just for the record, I want to say that we concur with ABC on the answers to the questions posed to the committee.

DR. NELSON: Thank you.

We are closing the open public hearing at this point. Now, we are quite a ways beyond where we were supposed to have been at this time, and indicates that I am a soft, weak, inefficient chairman, but that's what you got.

[Laughter.]

DR. NELSON: I would suggest that maybe we could take like a five-minute stretch, and then we go to the committee discussion and some discussion on the questions posed by Dr. Dayton.

[Recess.]

Open Committee Discussion and Recommendations

DR. NELSON: The next item on the agenda is open committee discussion. It might actually facilitate the discussion if Dr. Dayton could put the questions up or something like that. Would that be helpful?

DR. DAYTON: Why don't I put the algorithm up specific to the first question.

DR. NELSON: I would like to focus the discussion on the issues that the FDA has raised and see how we can deal with them.

DR. DAYTON: The first question--and I will put that back up in place of this algorithm in a second--the first question pertains to the testing algorithm for whole blood, which is the first figure in the three figures in your packet from my talk.

It is going to involve what happens if the master pool is NAT-reactive, seronegative. This is HCV/HIV ELISA. Then, you go directly to testing individual donations using the same NAT, and the question is going to involve what do you do when all of the individual donations are non-reactive.

In this case, you have a positive master pool, but you haven't done any subpools, you just go directly to the individual donations.

So, in this case, with reference to figure 1, if the master pool is NAT-reactive and all individual donations are non-reactive, you haven't done any intermediate pools - Option A, should a single negative test on the individual donations be sufficient for release? In other words, you have done the individual donations, they are all non-

reactive, should you now be able to release? That is Option A.

If you are not comfortable with Option A, then Option B suggests the possibility of is it sufficient to retest the master pool in replicate, so that if you get a negative result on replicate retest, you can then release everything. Again, these are not mutually exclusive possibilities. Is it sufficient to retest the individual donations (neat) with the same NAT, in other words, should you do a second test on the individual donations?

Then, Options (iii) and (iv) involve diluting the individual donations and retesting, or retesting the individual donations with alternate NAT.

DR. NELSON: Are there comments opinions on these various alternatives? It seems like the alternatives, first of all, is to if the individual donations are all negative, but the pool is positive, is that enough, or do we need something else.

Are there comments on this?

DR. SIMON: Again, I will try to deal a little bit of divergence in terms of industry point of view as to what has been reflected here, and I think we have heard that the whole blood group, based on quite a bit of data, feels basically that they can answer "yes" to Option A, and that that can be the way of going, and the plasma industry has

expressed a somewhat more complicated opinion that one size doesn't fit all, it should be specific to SOP.

I think, however, from a philosophic or I guess from a general regulatory point of view, I would speak to Option A, that is, in favor of Option A with the idea of being permissive to allow that protocol to be approved providing the FDA is satisfied that the license application and the methodology that will be followed indicates all appropriate investigation is taking place to determine where contamination is occurring, why there is a false positive, and so forth.

I think Option B gets very complicated and would be very difficult, so I would I guess speak for being permissive and in support of Option A with the proviso that it is probably more complicated than that, there should be investigation of different SOPs as they are submitted.

DR. NELSON: I interpret this algorithm to primarily apply, or maybe not only, but to primarily apply to the whole blood industry where there are individual donations available that can be individually tested.

DR. SIMON: Right, this one gets more complicated as we go through, but I am probably going to say the same thing about all the options, the first three, I guess, Option A's. This one, since I believe it would only apply to the whole blood at least as represented here today, I

think we could proceed based on the data that they presented.

DR. NELSON: Although these algorithms are fairly complicated, I was impressed that we do have a lot of data, and, you know, on experience with this, and it is different than some questions we vote on with no data.

DR. BOYLE: There is one additional piece of data that would be helpful, and if Sue Stramer could answer it, a lot of the reassurance is based upon, at least in whole blood, of these repeat donors who are negative in subsequent donations, and the question is, is the proportion of false positives who donate again the same as the general pattern of subsequent donations?

DR. STRAMER: Yes. What we are seeing is just random events occurring independent of the population you test.

DR. NELSON: I guess it depends on which technician they get to dilute the sample.

Are there other comments? Do you think we could vote on this at this point? Okay.

How many would agree with Option A?

[Show of hands.]

DR. NELSON: Opposed?

[No response.]

DR. NELSON: Abstaining?

[No response.]

DR. NELSON: The industry rep?

DR. SIMON: Agree with the "yes" votes.

DR. NELSON: And the consumer representative?

MS. KNOWLES: Yes.

DR. NELSON: That was pretty easy.

DR. SMALLWOOD: Results of voting for Option A, there were 14 "yes" votes, no "no" votes, no abstentions. The industry rep and the consumer rep agreed with the "yes" vote, 14 with the voting strength.

DR. NELSON: Dr. Dayton, do you want to put up the second set of questions?

DR. DAYTON: Yes. I believe now we clearly don't need to consider Option B.

DR. NELSON: But you have another algorithm, right?

DR. DAYTON: Oh, yes. Let me just make sure I get the right diagram for you here. Okay. This is the subalgorithm A. As you remember, you get to this at the beginning of the figure 2 algorithm.

In this case, the master pool is NAT-reactive, seronegative, and then subpools have been tested with the same NAT and all subpools are non-reactive. Now, we get down to here, what do you do? It is going to be the similar structure, do you release or do you do additional testing.

Let me put up the questions that we have for that.

With reference to figure 2, if the master pool is NAT-reactive, but all subpools, either archived or freshly pooled, are non-reactive, then, as shown in figure 3, Option A, should all the units be released?

If not, then Option B, additional testing. If you go the Option B route, four questions: Is it sufficient to retest the master pool in replicate or after repooling? Or is it sufficient to test individual donations using the same NAT method, releasing those that test negative? Or, and then we have the dilution option or the alternate NAT option.

DR. NELSON: Are there comments on this? I will say that we were presented a whole array of different algorithms by the plasma and the pools, and some of them did, in fact, have another master pool which was retested.

My sense is that if a manufacturer has developed an algorithm that seems to be working well, that the FDA is also happy with it, I don't think that we necessarily want to recommend that they do something different. Probably the committee feels that way, but are there any comments on this? Mary.

DR. CHAMBERLAND: It is a question. This algorithm can apply to both whole blood and source plasma, correct?

DR. DAYTON: Actually, all of these algorithms can be used in either type of blood collection. It is just that whole blood is more likely to go the first route with small pools, and plasma, of course, with the large pools are going to tend to go towards this, but we are certainly not saying that someone with a 1,200 size pool can't do to individual testing if they don't want to.

DR. CHAMBERLAND: I believe the vast majority of the data that we saw actually came from the whole blood industry, Sue Stramer's data. Is there any reason to think that we should have comparable kinds of data at the level of detail from source plasma in order to make a decision about this algorithm?

DR. NELSON: Well, there was data presented by source plasma, although--

DR. CHAMBERLAND: Not as detailed.

DR. NELSON: --not as detailed, but I didn't see issues there. Now, the other issue, of course, is that it may undergo viral inactivation and what have you, but nonetheless, even putting that aside, I didn't see evidence from what was presented that the algorithms that were in use were problematic, at least I didn't detect that, but maybe others did.

DR. DAYTON: Perhaps I can make a comment. Again, I think it was hard for a lot of us to digest the situation

when you have intersecting layers of deconstruction, but in a situation where you have, let's say, three dimensions of intersecting pools--how shall I say this--the problems we got into, when one or two out of three dimensions were reactive, but the final dimensions to close it were non-reactive, now, in either of those cases, you can't say that all subpools are non-reactive.

So, in this case, you couldn't certainly release the master pool, but then there is another level of questions which we haven't specifically addressed. Consider the possibility again where you are doing the deconstruction by dimensions. One layer is positive, the other two dimensions--and, of course, all the other layers in that dimension are negative--but then the other two layers or even one of the other layers is positive, how do you handle that, or negative, how do you handle that?

Could you, for instance, cordon off everything in the positive layer, and then release all the others? That is how the intersecting dimensions play into the questions we are asking.

DR. NELSON: I think it is problematic. I don't know if these dimensions correlate with the subunits and pool. If so, then, it could be contamination in constructing the pool, but in some of these, I thought that these may have been independent and that you might be able

to take out, you know, if you couldn't isolate the unit, you could take out a portion or a number of units or a subcomponent that was positive, but I would be concerned about a pool that a subunit, a part of it was positive, but you couldn't actually isolate the individual. I mean somehow this would have to be resolved in some way.

DR. DAYTON: The algorithms are clear explicable with respect to a pyramidal pooling where you get non-intersecting dimensions. Actually, if you wanted to split it up so that this question here only covered the situation where all subpools are non-reactive, we could get an answer there. The intersection problem actually could be handled in another part of the algorithm, but it might be a little bit difficult to do.

DR. NELSON: I think I would prefer to do that, but just because there are multiple scenarios and multiple ways of creating subpools that are sort of complex and individual, but if we dealt with the overall general situation where the pool was positive, but all the components that we could figure out were negative, it would more easily resemble what we just voted on, I think. Do you agree?

DR. SIMON: I think it says all subpools.

DR. FITZPATRICK: Even in the NGI and 3-dimensional and 2-dimensional algorithms that were

presented, when all the subpools were negative, they considered it resolved and released the lot.

DR. NELSON: Okay. Those who would vote in favor of Option A?

[Show of hands.]

DR. NELSON: Those opposed?

[One.]

DR. NELSON: Abstaining?

[One.]

DR. NELSON: The industry representative?

DR. SIMON: In favor.

DR. NELSON: The consumer representative?

MS. KNOWLES: Yes.

DR. SMALLWOOD: Results of voting for Question 2, Option A, there were 12 "yes" votes, 1 "no" vote, 1 abstention. The consumer and industry representatives agreed with the "yes" vote.

DR. NELSON: Thank you. Was that helpful?

DR. DAYTON: Yes, very helpful. We haven't really developed a question specifically for what you get into with these intersecting layers. With that in mind, do you want to proceed to the next Question 3, and let's do what we can while we can?

DR. NELSON: Okay.

DR. DAYTON: This is the figure 2 of the three

figures. This is the second algorithm. Again, master pool is reactive, seronegative. Now, in this case, we are asking what happens when you come down here, and the way you get there is that at least some subpools have been reactive.

This, by the way, could be several layer, you could run into this on the different layers of the deconstruction. This doesn't mean just one layer of deconstruction.

Then, you go to testing individual donations using the same NAT method, and here is where you run into the problem. All individual donations are non-reactive. Again, it is basically the same set of questions, are you going to go to release or additional testing.

Let me put up the questions that we are going to pose for the committee.

Again, in this situation, master pool reactive, one or more subpools are reactive, but all individual donations in the reactive subpools at least are non-reactive.

Option A: Should all units be released?

Option B: Should you do additional testing?

Considering our recent successes with Option A, should we discuss that before I go into the details of additional testing in the interests of time?

DR. NELSON: Comments?

DR. BOYLE: Just a point of clarification. When we talk about reactive here, we are talking about it on any of the three or two layers, is that correct?

DR. NELSON: We are talking about a subpool or individuals, a subpool that went into making the minipool, maxipool, whatever, but we can't figure out which sample in there is positive, or subsequently all the samples are tested and they are all found negative. Now, which of those, it is all of the individual samples are tested and they are found negative?

DR. DAYTON: All of the individual samples are tested and found negative, but the samples could be just from the subpool that was positive, so master pool positive, 6 pools, one of them is a positive, the rest are negative.

Now, you go to this guy over here that is positive, and all of his individuals are negative.

DR. NELSON: But that subpool could have been contaminated in the process of making the subpool, and then also in the process of making--

DR. DAYTON: The assay. That would be again what Sue Stramer's data was saying.

DR. NELSON: Right. Okay.

DR. MITCHELL: I think that the feeling is that the individual donations, the test on the individual donations is, in fact, the gold standard and that that is

what we are agreeing with the industry that that should be the case.

DR. NELSON: Do you want to vote on this?

Option A, all in favor of Option A, which is all units should be released.

[Show of hands.]

DR. NELSON: Opposed?

[No response.]

DR. NELSON: Abstaining?

[One.]

DR. NELSON: Industry?

DR. SIMON: I vote yes.

DR. NELSON: Consumer?

MS. KNOWLES: Yes.

DR. SMALLWOOD: The results of voting for Question 3, Option A, 13 "yes" votes, no "no" votes, 1 abstention, both the consumer and industry representatives agreed with the "yes" vote.

DR. DAYTON: We did have one more question. It may not be so important at this point. Also, I think I might like to introduce another question which can at least partially help the dimension deconstruction problem.

Let's see if we even are worried about Question No. 4, which is not specific to a particular algorithm, but we had considered that this might be a question.

This is should replicate testing be recommended as a general way of confirming the status of initially reactive pools. Basically, we had asked this question with the idea that, well, you got a positive pool, can you go back and do replicate tests on it to then call it negative.

This again is the idea of if it is due to contamination, can you test it under conditions which you are convinced that you don't have contaminations and then say we really measured it carefully and can we now say that that pool, which we had formerly called reactive, is now considered non-reactive.

If you got to this point in any of these algorithms--and this is a general question--if you got to this point in any of these algorithms where you retest a pool that was positive and now you say, oh, look, we have done the correct testing, we now test it as negative, if that is the case, that you accept this, then, what you do is you just go back to the algorithm and find out where you would be if that pool were non-reactive instead of reactive.

So, the question is, as a general question, does the committee feel ready to--well, if you vote on this, it would be recommending that yes, this is a reasonable route to go, and against it, you would say you wouldn't recommend it at this time.

DR. KOERPER: So, in other words, what you are

saying is rather than going through all the various algorithms we have just voted on, the first step is retest the master pool.

DR. DAYTON: It would be an option. This would be particularly valuable for people with large pools, could you as an option go and do that, or can you just, you know, accept a negative result further down.

DR. KOERPER: But if you retested it, then, you get it negative, how do you know which was the correct answer, so it seems to me you would have to do it a third time and take the majority.

DR. DAYTON: That is sort of what the next questions address. It is definitely confounded with the other questions.

DR. NELSON: But that wouldn't substitute for testing the pools necessarily.

DR. KOERPER: That is what he is suggesting, is that that would substitute, that if you got a positive and then, let's say, two subsequent negatives on the master pool, then, you would not have to do the testing of the subpools or the individual.

DR. DAYTON: Right. In other words, that is what the question would ask for, it would say you have got your master pool positive, now, do you really have to go to the subpools or can you just test it more carefully and accept

the negative results. FDA is not strongly backing one answer over the other.

DR. NELSON: You get the Poisson problem in a diluted sample there. As I understand it, it is not what the plasma industry is doing at the moment. Maybe I am wrong on this, but it seems like there are potential problems, I don't know.

DR. SIMON: As far as I know, that is correct. The industry is not doing that. Just a quickie, I think this hits that one size fits all comment and that probably this is one method that one could follow in order to try to figure out the contamination, but I don't see a rationale for pushing this as the method.

DR. NELSON: For instance, you could read this question that they tested all the subpools and they can't find anything positive, or they found a row or something. They go back, and the main pool is not positive, I don't know.

DR. SCHMIDT: I believe your Question 4 does not apply to Question 1, am I right? Your Question 4 is not applicable here.

DR. DAYTON: Actually, Question 4 would be applicable to Question 1 because you would be intercepting the events of Question 1 before you got to the--Question 1, you go directly from a positive master pool to testing

individual donations. Question 4, if answered yes, would say you don't necessarily have to go test individual donations, it is sufficient to double-check the master pool and determine whether it is really positive or really negative.

That is how it fits in with Question 1.

DR. NELSON: This would apply to pools of 16 or pools or 1,200, correct?

DR. DAYTON: Yes, any pool size.

DR. STRONCEK: We have been here all day, and unless I missed something, we haven't heard any data on this, so I would contend that, you know, we have had a beautiful day with wonderful data that relates to the questions, and then you are coming in with a question that is totally out of the blue, that relates to nothing in here. I think that if this is of value to the FDA, you should come back and present some data and we should discuss it at another time.

DR. DAYTON: Well, we felt obligated to ask the question and I think you have made a very reasonable point.

Jay?

DR. EPSTEIN: Well, the rationale behind the question is that this is exactly the strategy that is pursued with the EIA, and we are really asking do we think it is relevant in this context.

Now, it has been pointed out that there is a fundamental difference, which is that here you have the Poisson problem with low copy numbers, and that would change things significantly because if the answer were yes, then, you have to think about much larger numbers of replicates than 2.

I agree that we haven't seen the data, but there is a good reason for that. FDA discouraged this at the IND level because we didn't think that it was the way to really find out the answer. We thought that if we were to let it go at that, that, you know, if we never required testing on the deconstruction pools or individual units, we would never find out the truth.

So, a little bit we created the conundrum. That is why there are no data. So, we are really just asking conceptually. We are not saying should we implement this. We are saying should we even be thinking about it at this point. If we should be thinking about it, yes, we are going to need some more data, and we are going to need statistical analyses, but if we think that it is sort of moot, because it is just not the way to go, given the nature of the NAT system and pool testing, then, we can dismiss it up front.

Now, there has been use made of repeat replicate testing of a minipool as a secondary strategy as was heard when you had negative discriminate assays. Some companies

are recommending going back and retesting the master pool, but that is sort of like a secondary reassurance. They think they already know the right answer.

So, we are really just asking in concept here, and that is why it is tacked on the end. In other words, have we overlooked something potentially useful, because if the answer is that this is useful, it is really cost effective, right? I mean you don't have large numbers of retests. You just retest your master pool.

Let me just point that if the sources of false positivity had mainly been assay contamination rather than contamination in pooling, this would make a lot of sense. I think the reason that everybody is feeling that this doesn't make sense is that the data suggests that most of the cause of a false positive master pool is, in fact, contamination during pooling. This attempt to clarify by retesting won't fix that.

DR. DAYTON: Jay, are you finished?

DR. EPSTEIN: Yes.

DR. DAYTON: Okay. I mean if I could elaborate on what Jay has been saying. Actually, I don't think it is accurate to say there hasn't been any data presented that is relevant to this, and particularly Sue Stramer's data showing that the source of false positives is contamination during the assay.

So, that means that if you can run an assay under conditions in which you can rule out contamination, for instance, there are no other positives in that run or something, if you can run it and get positives, and let's say you can take care of the Poisson problem by doing it 10 times or 20 times, then, actually, according to Sue's data, it is actually a reasonable way to go.

DR. BUSCH: This is attractive to me just in a rare scenario, which is where you have a blatant contamination in the lab, and this has happened where you have had 30 or 40 pools in a single run that are all reactive, and to have this scenario as an option to resolve those pools as non-positive, I think is attractive.

Once you start getting into doing 10 or 20 reps, then, it is no better than doing the individual samples to resolve it out.

DR. DAYTON: It depends on your pool size. If you are dealing with a pool size of 500 or 1,000, it is definitely attractive.

DR. KATZ: I would also very briefly point out that in the whole blood where we are using small pools, even if this was available for other than that gross contamination, we would be unlikely to use it because the specificity of these tests has turned out to be so good that it would just be another round of testing delaying our

release of platelets.

I think this would not, even if available, be well received in the whole blood industry because of the high specificity.

DR. DAYTON: And we would intend it as an option to be chosen by the establishment that is running it. Obviously, the people who would have 500 and 1,000 pool sizes are going to find this attractive. People who have very small pool sizes will probably find it more efficient just to go right to either small pools or individual donations, but they key thing here is whether the committee feels that this is a reasonable option to offer establishments.

DR. MITCHELL: I think it is clear from the discussions that this is not a reasonable option for the primary. If the major pool comes up reactive, I don't think that this is a substitute for going back to at least minipools.

I think that I differ from a number of the members, and I think that if the minipool is non-reactive, that you may consider repeating as a way of clarifying, but I think that everybody is in agreement that it shouldn't be used for the primary pool.

MR. RICE: I agree with Mark. One of the largest problems in having a contaminate event occur in the master

pool is technical error when combining the aliquots to make that master pool, and I think having any sort of second chance at it might cause the ability to make it right the first time and to keep the attention to making all of your pools the first time you bring them together as best a job as possible as opposed to saying, you know, I could get a second shot at this, because we all agree that there will be errors, and that is what all these false positives are coming from, but I think it would be less incentivewise or just as likely to occur if you had to go on to the next, more expensive step if you really didn't do it right the first time.

DR. NELSON: Are we ready to consider this question? A brief comment? Yes, go ahead.

DR. WATSON: My name is Chuck Watson from Aventis, and as a user of large pools, this is not an option that we would readily embrace.

DR. NELSON: So, the question is should replicate testing of the pool be recommended as a way to confirm that it is initially reactive.

How many would vote yes on this?

[No response.]

DR. NELSON: "No" votes?

[Eleven.]

DR. NELSON: Abstentions?

[Three.]

DR. NELSON: Industry?

DR. SIMON: No.

DR. NELSON: Consumer?

MS. KNOWLES: No.

DR. SMALLWOOD: The results of voting for Question 4. There were no "yes" votes, 11 "no" votes, 3 abstentions. Both the consumer and industry rep agreed with the "no" vote.

DR. NELSON: Do you have another algorithm?

DR. DAYTON: No, but since we are on a roll here, again, this is up to committee to decide whether they want to go a question that we haven't actually given them, but if we wanted to help out or give an answer to the plasma industry that runs into problems on intersecting layers, should we consider the possibility of the question, should individual donations be the final way of calling those incongruities.

In other words, they get into a problem with the deconstruction, do they have the option of going to the individual donations and releasing on the basis of those results. I don't know if you want to consider that question or what, but if you do want to consider it, I could frame it into something votable.

DR. BOYLE: I think we have already agreed upon

that because we basically said any reaction in any of the layers is treated as reactive, and you have an algorithm of where to go when you are reactive, so I think we are done.

III. Blood Bags for Diversion of the Initial Collection

Background and Introduction

DR. VOSTAL: Thank you very much. We are now going to switch from viruses to bacteria.

[Slide.]

I would like to thank you for the opportunity to let me present the background and some of the concepts to this initial collection of blood-volume diversion.

[Slide.]

We had a workshop on the Bacterial Contamination of Platelets in 1999. At that workshop, Dr. Mo Blajchman summarized the bacterial contamination for different blood products. He summarizes from a number of studies he reviewed in the literature.

The contamination rate that he reported was that, for random donor platelets, one in 3,000 units are contaminated with bacteria. For pooled random donor units, which are usually--pools are four to six units of random donor platelets--the contamination rate would be about one in 500 units. For apheresis platelets, the contamination rate would be one in 5000 units. For red cells, the rate would be one in 30,000 units.

If you compare this to what the viral contamination rate is for HCV, HBV, HIV, those would be in the rate of one per 100,000-plus. You can see that the bacterial contamination rate is one to two orders of magnitude bigger than what we see with viral contamination.

[Slide.]

What kind of bacteria are found in blood products. This is a list that was put together by Dr. Keya Sen and Chang Syin at the FDA. It is a list of bacteria that have been reported in the literature to contaminate blood products. It is a pretty broad list covering Gram-negatives and Gram-positives.

If you look at this list, you could say, well, there are a few bugs in blood products but are they clinically significant..

[Slide.]

This is a list that we reported of bacteria associated with transfusion fatalities reported to the FDA between 1976 and 1998. This list was compiled by Dr. Lee at the FDA and it was also presented at the Bacterial Contamination of Platelet Workshop. You can see that there are bacteria that are specific for red cells, platelets and also found both in red cells and platelets.

The difference between bacteria that grows in red cells and platelets is that red cells are stored at

4 degrees whereas platelets are stored at room temperature, so these bacteria proliferate at cold temperatures.

[Slide.]

We may be on a different set of slides than I put in there. I had a set of slides that had a blue background. I had a second set of slides that had a couple of different slides. But we can continue here.

This is a slide taken out of--reviewed by Dr. Kirshan and Brecher. They summarized the factors that affect patient outcome with the transfusion of bacterial-contaminated blood products. He arranged the factors nicely to spell out the word VICTIM. You can see that, if we just briefly run through this list, it depends on the virulence of the organism.

Certainly, a bacteria that is Gram-negative, that has got lots of endotoxin production, would cause more problems to a recipient of that blood product than a bacteria that doesn't produce endotoxin. Certainly, the underlying immune status and general condition of the recipient play a big role in the outcome.

Then you have to consider the concentration and the bolus dose of the bacteria transfused. A big role is played by the recognition of the reaction and the therapeutic intervention. Also, this goes hand-in-hand with the intensity of the patient monitoring, whether it is an

in-patient or an out-patient, and what kind of underlying medicines the patient is receiving, for example, antibiotics.

[Slide.]

Once the bacteria get into the blood product, they have a tendency to proliferate, especially in platelets. This is a study done by Dr. Curry in Transfusion in 1997. What they did was they intentionally inoculated platelet concentrates with bacteria. Here, they put in about 100 colony-forming units.

You can see that in a span of three days, they are up to a million colony-forming units. So, at least in platelets, there is a relatively rapid growth of bacteria. A similar things happens in red cells, but it is at a slower pace since it is grown at 4 degrees.

[Slide.]

So how does the bacteria get into the blood product? One way is that it thought that it is introduced during the venepuncture and that the needle, as it goes through the skin, cuts a core of the skin and that the skin plug ends up in the blood product.

Another way to get bacteria into the blood product is if the needle cuts through a pocket of bacteria, that could be created by some scar tissue. This would be a case when there are frequent blood donors and have a number of

venepunctures so scar tissue can form.

So the bacteria can be introduced into the product this way. It has been thought, for a number of years, that, if this is the case, then diversion of some of the initial blood to a separate blood bag, separate from the final product bag, could decrease the contamination rate.

[Slide.]

This is a study done by Dr. Wagner. He put this concept to the test. He developed an in vitro model of the blood-diversion concept. This was published in Transfusion last year. What they did was they took a bag of blood and they intentionally contaminated one of the quarts. They painted Staph aureus on the septum.

Then they punctured that with a needle and collected the blood that was coming out, collected that into a diversion, a side arm, and they collected sequential 7-cc fractions. Then they measured the number of bacteria found in the sequential fractions.

[Slide.]

This is the data that they published. These are the colony-forming units found in the sequential tubes. You can see that there is a large number in the beginning tube and it decreases as you go down to the last two. They were able to show that, in the first three fractions, they collected 88 percent of the bacteria and, if they extended

up to six fractions, they collected 95 percent of the bacteria.

So, overall, they were able to show that there is about a one-log reduction in the amount of bacteria that would get to the final blood product.

[Slide.]

I did have a second set of slides in there. There was a clinical study done in Europe that I wanted to talk about. The study done by Dr. Wagner was an in vitro model. This is a study done by Dr. Bruneau in Europe. This is an actual clinical study where they collected whole-blood donations from 3385 donors.

They had a unique setup in their collection system. They had two side pouches and they initially collected the first 15 ml and then the second 15 ml, and then they collected their final product. They did cultures on these first two bags.

They were able to show that bacteria was present in either sample in 76 out of 3385 donations, or a contamination of 2.2 percent. So they argued that this 2.2 percent would be the contamination rate in the blood bag if there was no diversion pouch present.

In their study, they also showed that the first sample was positive and the second one was negative in 55 out of 3300 donations. That was a 1.6 contamination

rate. They argued that, in this case, this would be protected, that all of the bacteria would have ended up here and none would have got into the bag.

So you subtract the rates, 2.2 minus 1.6, and you get a final rate of 0.6 percent. So they concluded that this arrangement could have decreased the bacterial contamination rate down to 0.6 percent.

However, the problem with this study was that they never cultured the final product, so there really is no true demonstration that having these side pouches present protects the final blood product.

[Slide.]

If I could summarize. Bacterial contamination of blood products is a significant problem. Some preliminary trials suggest that a diversion of a small volume of blood away from the main storage bag may be beneficial in decreasing the contamination rate. A clear demonstration of this is lacking but, in order to demonstrate this, a clinical trial to show a benefit would need to be quite large.

[Slide.]

There do not appear to be any negative effects of using a diversion system to collect blood. There could be additional benefits such as using the diverted blood for testing may also save units lost to inadequate sample

collection. This last part here is what we think could be used, if you do divert the blood up front, you could use that blood for regulatory type testing.

Sometimes, when you are collecting blood and you collect the product first and then you go back and collect the samples, you may use the venous access and you may not be able to collect those samples in the end. Under those circumstances, you would lose the whole blood product. So that may be an additional benefit of having the diversion up front so you could get your samples at that time.

[Slide.]

So this is the design that we were considering that may be beneficial either from the decreasing bacterial contamination and saving some of the samples, some of the products, due to inadequate sample production.

We think it should be a closed system. The diverted blood is separated from the final blood product by a unidirectional flow, so we think that there should be a closure to the main product bag at the time of initial collection so that the blood can go to the sample bag.

At that point, once the sample bag is filled up, we envision that this would be closed by a permanent seal and at that point, the seal could be broken and the full product could be collected. Finally, the volume of the bag should be sufficient to achieve the potential benefits; that

would be the reduction of the bacterial contamination and sufficient volume to run all the sample testing.

So thank you very much. I think today we are going to ask you the questions whether you would think that these changes would be of benefit to the blood-banking community.

DR. NELSON: Thank you.

Are there questions from the committee?

DR. BOYLE: How much of the product is lost by using the blood bags, the diversion?

DR. VOSTAL: Do you mean in terms of volume?

DR. BOYLE: Yes.

DR. VOSTAL: You really wouldn't be losing any volume because you are going to collect that extra blood anyway for sample testing.

DR. NELSON: You mentioned 33 ccs would be the sample, at least that was studied in the European study, which would be replaced, would be added.

DR. VOSTAL: Right; but you would actually collect those 33 ccs anyway.

DR. NELSON: Yes; right.

DR. VOSTAL: It is the order of collection that we are talking about.

DR. LINDEN: This sample-collection bag, would this be anticoagulated so that this would all be plasma?

DR. VOSTAL: This is actually an interesting point. We think it probably shouldn't be anticoagulated because, if you have anticoagulant present, you could dilute out the blood and that may cause some problems in the testing, itself.

But that is open to discussion, whether that would be a problem or not.

DR. LINDEN: If you are collecting serum then how, logistically, would you do that?

DR. VOSTAL: To collect serum from those samples, if it wasn't anticoagulated, or if it was anticoagulated?

DR. LINDEN: What you showed in your diagram was a single bag, not going into tubes. So I am just questioning what--

DR. VOSTAL: I think you can go back and enter that sample bag to collect your individual samples. We think you would be able to divert those 33 ccs and then you could go into those 30 ccs with your individual collection test tubes and get the specific samples that you wanted.

DR. KOERPER: But it depends on how quickly you do it. I mean, once it clots, you can't go back and get a sample to do a blood count, for instance. So another option I saw on some of the handout was that it had a vacutainer adapter on the end. And so you could actually put the individual vacutainers and collect directly into the

separate tubes.

DR. VOSTAL: That is also an interesting point for discussion because a vacutainer, by itself, we don't really consider that a closed system. So you have to be able to fill up the bag first, close it off and then put the vacutainers on it. But I agree with you that you have to do that rather quickly so you wouldn't get a clot in the bag.

DR. FITZPATRICK: Since all the tests we are doing now are on plasma samples or cells drawn into an anticoagulant, for the most part, we are not doing tests on serum, why would you suddenly decide that we should not be using an anticoagulant in those samples?

DR. VOSTAL: I think we were just concerned that some tests would be--if you are at the level of detection and if you have a diluted blood, that you could run into a problem of missing a positive signal. But I am aware of all the tests being done on non-serum samples.

DR. KOERPER: But are serologies being done on plasma as opposed to serum? Okay. Then, it seems like you need anticoagulant in that little bag, t

DR. STRONCEK: I am not involved in the day-to-day basis with the collection, but my understanding is that the problem is not getting anticoagulated blood. It is getting blood with exactly the right anticoagulant you want. So I think the preferred way to do it is get it unanticoagulated,

then transfer it quickly to something else.

I don't know all the details, but I think on some of the platelet-apheresis kits, they have this type of thing already and it meets the needs of blood center. So I don't think it is an issue whether or not this is anticoagulated or not.

I think the point of bringing this to the committee is to endorse the concept of pre-storage, collecting these samples to reduce bacterial contamination, to hopefully move the collection centers and the bag manufacturers in this direction.

DR. NELSON: Other comments?

Thank you.

We next have Dr. Vander Poel from The Netherlands.

Presentation

DR. VANDER POEL: Thank you, Mr. Chairman. I am Cees Vander Poel from Amsterdam, The Netherlands. I represent the recently unified Dutch Blood System.

[Slide.]

I will present these data on behalf of Dr. Marcelis who is our bacteriologist who cannot come today and Dr. DeKorte who is from the technology laboratory for blood transfusion techniques.

[Slide.]

While there was, of course, bacterial

contamination of blood products due to the studies on recipients, like the FDA data, but also the SHOT data of the United Kingdom where they look more intensely that the side effects of blood transfusion and the French data on their hemovigilance studies.

Early data in Holland suggested that 1.6 percent of whole blood units were contaminated. But the problem was the scope of the study was too small and results in a very large confidence interval because of the statistics.

The possible effects of overnight storage should be taken into consideration in our study because we feel that most of our blood banks store the blood overnight before doing the primary spin which is a hard spin. As you know, we prepare platelets from the buffy coat.

We feel we get a better spin if we at least store the blood for six hours or more so, in practice, it becomes overnight storage. So it has to be sorted out whether the overnight storage influences the growth of bacteria or not because this storage is at 20 degrees centigrade.

Of course, we also wanted to study the possible reduction by removal of the initial volume.

[Slide.]

So the study is in two phases. The first phase is to make a large enough study to determine the prevalence with a small confidence interval, to make it big enough, and

then compare, in this study, the overnight storage versus immediate sampling right after donation. The second phase was the determination of the effect of the diversion of the initial flow.

[Slide.]

We used, as measurement, the BacT/Alert system of Organon Technika. This is a culture system, aerobic and anaerobic bottles and screening for the carbon-dioxide production as a measure of bacterial growth. We do confirmation with normal culture later.

We made a special four-bag system with an additional sample bag to do the sampling for Organon.

[Slide.]

So this is the machine. It is automated and you can have these bottles with bar-code labeling.

[Slide.]

Now, about the system. This is not the diversion bag you have seen before. This is the bag which was used to draw a sample from the whole-blood bag after storage overnight or immediately, within three hours after drawing the blood. These two spikes here are for entering the bottles of the BacT/Alert.

This is the system where we have--it is not a top-and-bottom system but the older system where we have the segmental here. The plasma is in there and the buffy coat

is put in there. And then the segmental is put back on the red cells. But the sampling for this study was done on the whole blood.

[Slide.]

We wanted to validate first if the introduction of this sample bag did not introduce any flaws in terms of Factor VIII content in the plasma because you could imagine that the extra Y piece at the beginning of the tubing would influence the possibility of clotting.

We would look at the component preparation outcomes and quality-control data whether or not this bag influences--these were all normal. We also looked at cells, countings, to see whether the sampling bag was a representative of the whole-blood unit.

[Slide.]

We cultured all samples for seven days in the BacT/Alert at 35 degrees, and when it had a positive signal, of course we did a culture on blood agar and looked further for confirmation in typing of the agent. Standardized disinfection is used in The Netherlands, usually with isopropyl alcohol or iodine, most of the time, one disinfection, not two. We had an aseptic transfer to the BacT/Alert in the laminar-flow cabinet.

[Slide.]

The determination of the prevalence of the

bacterial contamination--we wanted to have a 95 percent confidence interval resulting in not more than half a percent of diversion so that we have a narrow enough measurement to be precise enough.

We tested overnight, this group, too. And we tested also freshly.

[Slide.]

Group I, where we tested within two hours or three hours after donation, this was 9,219 units tested. Twenty-seven units were positive which gives you 0.3 percent with a confidence interval with what is a acceptable. Group II was also about 9,000 units tested, also have the prevalence of about 0.39, 0.4 percent, with a confidence interval which is largely overlapping, as you see.

So this difference was not significant. This was giving us some confidence, at least, that overnight storage would not heavily influence bacterial growth in the product. So the overall prevalence of whole-blood contamination was, then, 0.3 percent, 0.34 percent, with a confidence interval of 0.25 to 0.44 percent.

[Slide.]

So what did we find? In group I and in group II, predominantly staphylococcus sp. and Propioni bacterium sp. And we had some other agents, but, as you can see, most of the bacteria that we cultured were skin-related. This, of

course, is an outlier where you could say, how does this come into the blood but, probably, came from the skin as well. This is, at least, the estimation of our bacteriologists.

[Slide.]

SO we have a similar distribution of species in both groups, either freshly sampled after donation or after storage overnight of the whole blood. It may be skin-associated and not pathogenic agents and this Peptostreptococcus case is probably rare.

[Slide.]

So this is what we conclude, which is merely not more than the results, but we could elaborate for that a little bit longer. We think it is a little bit lower than we have previously seen in the literature. It is mainly skin-derived bacteria and we have no direct effect of overnight storage.

What has to be discussed and has to be studied yet in the system is that when we do overnight storage and then when we take out leukocytes by buffy-coat removal or by general leukodepletion, does this give us a better sterility of the product. But that has not been studied yet.

[Slide.]

For phase II studies, we would address the question which was also put here by Dr. Wagner's studies and

the Bruneau study from France, whether the skin plug is introducing bacteria in the product.

[Slide.]

So we also used a new bag where we have a sample site at the beginning and the materials and methods were similar to phase I. The modified bag, with the sample site, was validated as a in phase I.

[Slide.]

This was the setup. It is the same setup as before but here you have a Camposampler which allows you to take one tube of 10 milliliters and then the blood is going further. Now, the discussion of whether this is open or not has been debated in Holland but, to be honest, the blood typing sample has always traditionally been taken from the whole blood by this needle so you could argue--be more precise maybe by not using this.

I am not sure. This was at least in the experimental setup. This is the sample bag for the culturing and these are the two needles for the bottles.

[Slide.]

So the aim was to measure of prevalence of bacterial contamination in whole-blood units, the outcome of what you want, after diversion of the first 10 milliliters.

[Slide.]

Here you see the results as compared to phase I.

This is the phase II study, 7,115 units tested, of whole blood tested and the prevalence is 0.21 percent. As you can compare this with the prevalence in the original study where there were 18,000 done, it is not so big a difference.

But the difference was significant and you see there is an overlap of the confidence interval. But if you do other statistics, there is a reduction of infectivity.

[Slide.]

If you split up the second group, within three hours sampling or overnight storage, there was no significant difference as well. So this was the same as in the phase I study.

[Slide.]

So, after diversion of the first 10 milliliters, the prevalence was lower and it was significant. This was mainly due, by this group, which included the overnight storage although in the larger study, we could not find a difference of infectivity in the overnight storage group versus the fresh-sampled group.

[Slide.]

This is what we found. This was, again, the data of the phase I study, and this is the data of the phase II study where the first 10 mls have been taken away. This is 18,000 samples and this is 7,000 samples. So this reduction is significant but it is not to that amount as it shows

here. There is no real difference in the Propioni. So the main difference in infectivity by taking out, in practice, in the clinical situation, the first 10 ml is due to a reduction of the Streptococcus sp.

[Slide.]

So the majority of the bacteria were identified as Propioni which were not affected by the intervention and a significant degree of the prevalence was due to the Staphylococcus sp.

[Slide.]

What we would like to discuss is that we find kind of confirmation on practice but which was studied in a model by Wagner, which was also studied by Bruneau but Bruneau did not test the final product, the whole-blood product. What we did not know yet is why only reduction of the Staphylococcus sp. is due to the small numbers or is there something really going on.

We had a discussion about plugs versus flaps. I am not sure whether this is scientific but the idea was that a plug might get into the blood and that would be one occasion, so you might take that out with the first 10 milliliters, but if it is a flap, it still would get you bacteria into your product.

[Slide.]

So even after introduction of this preventative

measure, if you count the 0.2 percent, if you take that into account, that 0.2 percent of the single units were infectious, then a platelet pool of 5, which is stored in Holland at 20 degrees for five days, you would have a 1 percent chance of having a contaminated product.

So this is even after the intervention. So if you bring the intervention bigger, with taking out 30 ml or 40 ml, we feel that probably you would gain some effectivity but you would not take it away.

[Slide.]

We conclude, actually, this can be significantly reduced. We have said that before. What we did not find in our study was Gram-negative bacteria. We don't know why that is; maybe that food is healthier, although you might doubt it lately. So the majority was skin plugs.

[Slide.]

My conclusion would be, and actually that has been supported--it is not on this slide because it is very actual--our medical advisory board concluded from this study that it is nice to take away the first couple of milliliters of the product by drawing the blood but it is better to culture the platelet products, and we are very glad to announce that we have got agreement from the Minister of Health to test all platelets for bacterial contamination before release.

Thank you.

DR. NELSON: Any questions?

DR. KLEINMAN: One thing I didn't understand. When you showed the data from the diversion and you showed the 95 percent confidence intervals, they overlapped.

DR. VANDER POEL: Right.

DR. KLEINMAN: And you said, well, this doesn't look significant if we look at it this way, but if we look at it in some other statistical fashion, you make--

DR. VANDER POEL: Chi square. That was significant.

DR. KLEINMAN: I am not sure which to believe as to this. It didn't look like a big difference to me, nor did it look statistically significant by confidence intervals. I think your other point was well taken, your last point, that since the pathogenic bacteria are not these bacteria, in general--they are the Gram-negatives. Since you didn't have any, you really haven't been able to document that your intervention will be effective to stop the serious clinical problems, just that it will reduce the number of Staph species.

DR. VANDER POEL: Exactly. But the Gram-negatives, of course, would not be taken out by taking out the first--

DR. KLEINMAN: Exactly.

DR. KUEHNERT: Matt Kuehnert, CDC. I just had one question and one, perhaps, clarification. I guess I might have been confused by one of your slides. It was the second study that showed Klebsiella pneumoniae. The last time I checked, I thought it was a Gram-negative. I just wondered if that was excluded for some reason or not.

DR. VANDER POEL: It was the overall interpretation to state that the majority were skin flora and that there were not so much Gram-negatives as reported in the literature. That was the statement.

DR. KUEHNERT: Oh; okay. I'm sorry. I thought it said no Gram-negatives. Thanks for that. The other was that I am not so sure that you can concluded that these were all necessarily skin flora. For instance, Peptostreptococcus is a common oral flora and might suggest that it could represent transient bacteremia. So those were just my two points. But a very interesting study.

DR. WAGNER: I just wanted to make one comment. Steve Wagner from the American Red Cross. Based on what is reported in the literature, from 30 or 35 percent of the cases that transfusion-associated bacterial sepsis is caused by Staphylococcus species.

DR. VANDER POEL: That's right.

DR. NELSON: Thank you.

We have the open public hearing

DR. NELSON: First is Dr. Rebecca Haley from the American Red Cross.

[Slide.]

DR. HALEY: With our studies that I am reporting on here today from the American Red Cross, I have tried to pull the salient parts out of three different studies.

[Slide.]

We have both studied extensively the clinical surveillance through the Medical Office of cases that have been reported to us of bacterial contamination and the trends are monitored constantly so that we can see if there is anything going awry or if it is pretty much as it has been. And there are laboratory studies from the Holland Laboratories, Dr. Wagner's study that was already highlighted in the first presentation in this section. We will see if we can find a couple of different things to talk about that are helpful.

[Slide.]

In Dr. Wagner's study, he drew six tubes of whole blood sequentially from a bag with a port that is painted with Staph aureus and a final sample of 40 mls of blood was withdrawn into a transfer pack to see if there were still bacteria remaining. Then, at the end, a tube of whole blood was withdrawn from the uncontaminated port of the original

bag and each sample was cultured. The total colony-forming units for each sample were listed.

[Slide.]

Steve, this is an art class where everybody interprets your findings. This is our interpretation. What happened was there was whole blood in this bag. This port was painted, was contaminated, and all six of these samples were drawn. Then a 40 ml sample was pulled down into this bag.

Then, through the uncontaminated port, a sample was drawn and cultured. The very interesting thing is yes, there was contamination in all of these tubes that went down by quite a bit as was reported before with each sequential tube that was drawn.

This tube that was drawn at the end was still sterile. So that tells us that the Staph aureus were not carried into the whole-blood bag but it suggests that they were carried on a core that the needle made through this medication port and then carried into the successive bags.

[Slide.]

As was reported before, I tried to do a simpler representation. This is, I think, a 16 to 1 reduction. This is about 70 to 1. This is about 100 to 1 reduction of the number of bacteria as we go from tube 1 to tube 5. I chose tube 5 because we now draw five tubes in order to do

our testing. Our thought is if we could draw a sufficient amount of blood into this diversionary pack, seal it off and then go from there, I think we could make significant in-roads into the bacterial-contamination problem.

[Slide.]

This is the second go-around. The clinical reporting of the investigation, or the outcome of Steve's slides, was that the first tubes collected were heavily contaminated. Successive tubes had fewer bacteria and this appears to be an effective method for reducing the bacterial load although it doesn't completely get rid of it.

[Slide.]

In the clinical reporting, according to 12 CFR 606.170, we write that into our supply contracts and we tell our hospitals, if you find something wrong with a unit of blood that you suspect may have hurt your patient, please let us know and we will investigate that with you.

We included this stipulation when we participated in the BaCon study

[Slide.]

But what I would like to show you now, the questions that we had were how frequently does it happen, or I will talk next about how frequently it has happened, that we know about, and how often does bacterial contamination cause problems and how often is it just found incidentally

when it is not directly associated with a problem and how important is the source of the culture, and do the organisms give a clue as to their source.

[Slide.]

Let's go back and pick up our fiscal-year data. We started keeping these records at Headquarters, apparently, on July 1, 1991 and so Fiscal Year '92 would be ending on June 30 of 1992, and so on, for five years. These are the deaths that we had reported to us that we, in turn, reported to the FDA.

If you think that things were really getting good in 1996, I will have to tell you that there were four deaths in 1997. So it all sort of evens out. In those five years--I did not pull down these slides from this set, but there were about 30 million red blood cell distributions--we don't know; we expect that the majority of those were transfused--and that there were about 300,000 apheresis platelet transfusions each year and about 300,000 platelet-pool transfusions each year for approximately 600,000 platelet transfusions each of those years.

Beginning in '92, the predominance was on the pooled-platelet transfusions and that gradually switched over so that there is a slight edge for the apheresis platelets but the time you get to the end. On the third study that I review, the BaCon study, you will see that the

apheresis platelets have an edge.

[Slide.]

We are assuming here that the Gram-positive cocci, which I will represent in yellow in the following slides, and Gram-positive rods, probably came from the skin and that the Gram-negative rods were probably carried in from the blood stream or may have come from the skin. We really don't know.

[Slide.]

These are the reported apheresis platelet transfusion adverse reactions during these five years. During this time, we had three deaths and here are the organisms that were causing death. As you will see, only one of these three happen to be a Gram-negative rod. The other two were Gram-positive cocci.

The ones that were causing septic illness, again, you have only one Gram-negative rod but, of the organisms that were reported in cases that turned out where the patient did not run a 2-degree centigrade rise in temperature, did not require any intervention and, although the units were positive, the blood cultures of the patient were not positive. So these were suspected transfusion reactions that really didn't turn out.

You will notice that with the apheresis products, we talked about a diversionary bag. You will notice the low

number of problems in this column compared to the others that you will see.

[Slide.]

Then, when we go to platelet pools, you will find that we have, again, a wider variety of organisms and, again, we had Gram-positive as well as Gram-negatives that caused death. Now, here the Gram-negatives begin to move out and cause many more problems, particularly in the sepsis area, the Gram-negatives really showed up. But we still had our representative Gram-positive cocci and, over in the sort of garbage column, it is predominantly skin organisms that apparently came along for the ride but, according to our clinical reports, did not cause serious problems.

[Slide.]

With the red cells, now, all of the fatal organisms are Gram-negative rods. The Yersinia enterocoliticas happened fairly early on in this period. We have seen many fewer of those in recent years and I don't know if people are not hanging around farm animals as much or if red blood cells are being used earlier in their dating period and these haven't had a chance to grow up. But that certainly has abated.

But, again, the serious incidences are predominantly Gram-negative rods although a great deal of consternation, trouble, blood cultures and so forth, were

done because of Gram-positive supposedly skin contaminants.

[Slide.]

Now we will go another study which followed. By the way, because of the information we had collected that I have just shown you, I went over that in a conversation, in a scientific conversation, with Dr. Sue Cookson from the CDC, and then she was replaced by Dr. Matthew Kuehnert. We tried to look at that information to see if the BaCon study was worth doing.

So the BaCon study years were '98 and '99 and 2000. These were calendar years. During this time, with, again, a distribution of 17 million red cells, about 1.2 million platelet pheresis units and an estimated 700,000 platelet-pool transfusions, we had bacterial sepsis events. Now, by the definitions of the BaCon study, we got rid of that long column on the right where the symptoms were not serious and the bacteria usually turned out to be what looked like contaminants. Then we, of course, captured the death events.

[Slide.]

Again, trying to color-code for you, the red-cell deaths, again, were Gram-negative rods. The platelet-pool deaths, one of those was a Staphylococcus aureus and our Clostridia, down here, are problematic in that they were not either of those a lock. In one case, the unit was never

cultured. It was thrown away. The patient had a reaction after receiving blood but, on autopsy, had ulcerations in the colon. So we don't really know that it came from the blood unit.

In the second Clostridium case, the unit was culture positive. The patient was not and the bag from which the culture was taken was pulled out of the trash. So we don't know exactly. But I put those up because they certainly were serious reactions.

[Slide.]

What is the size of the problem that we see laid up on our doorstep? We had three fatalities in platelet pools, which was one in 235,000; platelet pheresis, the deaths we had were one in 298,000; and the red cells, one in 6 million. That is about one in 65,000 of septic events for platelet pools; one in 54,000 for the platelet pheresis; and one in 1.5 million for red cells.

[Slide.]

If you like that in numbers per 100,000, as Dr. Dodd is trying to teach me to do, we have it by the alternative method on the next slide.

[Slide.]

In summary, a diversion of an initial sample would be likely to decrease the number of bacterial-contamination incidents observed. Sepsis incidents could be reduced

significantly, we hope, and fatalities may not, however, be significantly reduced and the American Red Cross is working with the supplier to try to have a sample-first system in by the end of 2001.

[Slide.]

Our recommendations are that sample diversion is an incremental safety step for blood transfusion particularly with platelet concentrates and should be adopted. Research to detect bacterial contamination should be pursued. A method capable of finding Gram-negative rods would be of great value. Effective pathogen inactivation could also be helpful.

Now, I will comment, Dr. Simon, on the questions. On the design, we certainly agree there should be a closed system diverted by unidirectional flow. We support that. The volume of blood diverted should be sufficient to get the samples for testing. That may also be very helpful in saving some units where the unit stops bleeding at the end, so that may help offset some of the cost.

Are the European studies sufficient? I think that what we know from the studies in the United States and the studies in Europe, that even without definitive proof, if we could get a system where this wouldn't hurt anything, it would be more than worth trying. What studies are needed? I think the studies that are needed would be studies for

effectiveness of this method if it were introduced.

Thank you.

DR. NELSON: Thank you.

Are there questions for Dr. Haley?

The next speaker is Dr. Mark Popovsky from Haemonetics Corporation.

DR. POPOVSKY: Mr. Chairman, ladies and gentlemen, good afternoon. I am Mark Popovsky. I am the Corporate Medical Director of Haemonetics Corporation. I don't have any slides. However, I have a text that I would like to share with you.

Thank you for giving industry the opportunity to speak on this topic today. Haemonetics would like to comment on two aspects of this issue. First, our experiences to date with implementation of a pre-donation sampling pouch on all of our currently marketed apheresis, platelet and red-blood-cell sets; secondly, our input on FDA's recommendation that the initial donor blood volume collected be diverted for all blood products collected.

Currently, all Haemonetics apheresis platelet and red-blood-cell kits have a sample pouch attached to a Y-connector on the donor needle. I brought an example of that with me today. This is the Vanna White portion of this program. Actually, you can pass this around to show the committee.

We implemented the sample pouch on all our platelet sets back in the late 1980s. This implementation was driven by customer request to provide a more user-friendly and easy method than a post-donation second venepuncture to obtain donor blood samples to determine the donor's platelet count.

Limited studies were performed to investigate whether use of the pre-donation sample pouch had the added benefit of reducing the frequency of bacterial contamination observed. The results were inconclusive indicating that large numbers of collections would have to be tested for bacterial contamination before the benefit of diversion of the initial blood volume collected could be absolutely confirmed.

Our apheresis red-blood-cell sets have included a pre-donation sample pouch since early 1997. This implementation was in response to a concern that the saline compensation provided to the donor during the apheresis procedure could "dilute" the donor's blood potentially resulting in false-negative results in the donor's infectious-disease screening results when obtaining the donor blood sample post-donation.

The feedback from blood centers that have implemented the use of the pre-donation sample pouch on our apheresis sets has been very positive. Our customers use

the sample pouch as intended; that is, they obtain their donor blood samples pre-donation.

We recently worked with two major blood-collection facilities to implement our apheresis red-blood-cell sets. Whole-blood phlebotomists were primarily involved with this implementation and conversion of the staff from post-donation to pre-donation donor sampling was completed without major issues.

However, if the recommendation for pre-donation sampling is extended to all blood collections, Haemonetics foresees that there may be logistical issues to overcome when implementing us of the pre-donation sample pouch in mobile collection settings; for example, lack of access to hand-held heat sealers or other sealing mechanisms used to hermetically seal the sample pouch.

Haemonetics has brought several examples of its pre-donation sample pouch and is more than willing to answer any questions from the BPAC members or the audience after the presentation.

As you know, Haemonetics has served the blood-collection industry for many years and we actively support all efforts to enhance the safety, quality and availability of the nation's blood supply. We believe, with this record, and our long experience with pre-donation sample pouches qualifies us to give input on a proposed FDA recommendation.

We concur with FDA's belief that diversion of the initial blood volume collected in blood donations offers the potential to reduce the bacterial contamination of blood products as suggested in two recent studies already quoted today, one by Dr. Steven Wagner and the French National Blood Agency.

In addition, as a secondary benefit, the diversion of the initial blood volume may insure adequate amounts of blood for donor-qualification testing thereby reducing the amounts of discarded blood products due to insufficient samples collected post-donation.

We believe, however, that a recommendation that the diversion of the initial donor blood volume collected should be focused on platelet donations rather than all blood donations. The rate of bacterial contamination of platelets is approximately one in 2,000 to one in 3,000, whereas the rate of bacterial contamination in red blood cells is on the order of one in 40,000 to a much lower number, depending on whose data one interprets.

Moreover, cultures of contaminated products have shown that the bacteria found in contaminated platelets are typically skin flora while the bacteria found in contaminated red cells are indicative, usually, of a systemic infection in the blood donor.

Therefore, it is reasonable to conclude that the

implementation of diversion of the initial blood volume collected may, indeed, reduce the incidence of bacterial contamination of platelet products, but it is likely to have little or no effect on reducing the rate of red-blood-cell contamination.

In addition, the cost-to-benefit ratio of adding a pre-donation sampling system for all whole-blood and red-blood-cell donations may not be justified. As part of any recommendations, FDA should clarify whether it is the intent to use the diversion of the initial blood volume for pre-donation testing. If this is the case, we believe it raises some concerns regarding the type of systems used to withdraw the samples from a pre-donation volume and how to maintain a closed system.

We believe that pre-donation sample-collection systems should be designed so that the method of collection of the blood-donor samples does not compromise the sterility of the collection system; i.e., the sampling technique and sealing mechanisms used to insure a closed system.

If a guidance document results from the committee's recommendations, we suggest that FDA clarify this requirement in the guidance document. Also, if FDA decides to move forward with the recommendation to implement systems for diversion of the initial donor blood volume collected, FDA should allow blood-collection device

manufacturers to implement such systems per the least-burdensome provisions of the FDA Modernization Act of 1997; that is, those blood-collection device manufacturers that do not seek to claim that the diversion of the initial donor blood volume collected reduces bacterial contamination should be able to implement their systems under a special 510(k) or NDA supplement, CBD 30, or similar regulatory pathway.

Additionally, blood-collection centers should be able to add implementation of such systems to their biologic license applications through the annual reporting mechanism. This would best serve to assure rapid and smooth adoption of this recommendation.

In conclusion, we believe that industry must strive to continuously improve the quality and safety of blood products. Haemonetics supports those regulatory initiatives which move us towards that goal.

Thank you for your attention.

DR. NELSON: Thank you, Dr. Popovsky.

Any questions?

DR. MITCHELL: You talked about the cost of implementation of a system like that. It seems to me that it is just a change and so I would not expect that there would be a significant amount of cost for moving toward something like that.

DR. POPOVSKY: Significance is all relative. Compared to, perhaps, other changes, the cost of other, let's say, donor-screening tests, no; it would probably be considerably less expensive. I think, just in the context of the environment that all of us are working in in terms of managing costs with the constraints that we have, I am putting that forward for consideration. But, no, not in relative terms.

DR. MITCHELL: But you are saying there is a cost, it is not just a change in--

DR. POPOVSKY: Yes; if, in fact, a manufacturer is not already doing this, then, if you are going to make a change in the assembly, absolutely; there is a cost associated with that. Sure.

Other questions? Thank you.

DR. NELSON: The next speaker is Dr. Guillaume de Saint Martin from Macopharma.

DR. DE SAINT MARTIN: Mr. Chairman, ladies and gentlemen, my name is Guillaume de Saint Martin. As you can probably hear, I am coming from France. First, I want to thank the organizing committee to give me the opportunity to present the Macopharma experience with diversion of the initial collection.

[Slide.]

I will especially describe the system we have

developed called the Bactivam.

[Slide.]

The agenda of my talk is quite simple, first, to give you basic information on Macopharma you probably don't know, some background and bacterial risk, and then present you our system, the Bactivam, its design, use and some developments we have recently made on it.

[Slide.]

Macopharma is a French company producing a wide range of blood bags, leukodepletion filters and specific bags for inclusion bags, cryobags and also viral-inactivation sets.

[Slide.]

Here are some figures concerning our company. We have now an international organization and we are selling in about 35 countries. Our product strategy is to develop in-line systems to make transfusion practices more secure.

[Slide.]

This start-up product is a good example of what we can provide. It includes an in-line whole-blood filter, an in-line sampling device on the left side of the picture, with a needle product, also, you can see on the left.

Let's focus now on this donation line.

[Slide.]

The fact is that there are more and more

discussions around bacterial contamination of blood components.

[Slide.]

Among all the studies, all the different studies which have been carried out on this topic, this is one we have participating in. It was first presented in Oslo in the ISBT in 1998 and recently published in Transfusion. Dr. Bruneau's conclusion is that excluding the first 15 milliliter of blood may reduce the rates of bacterial contamination in blood donation.

[Slide.]

Following this study, most of our French customers thought to use our sampling pouch around the summer of 1998.

[Slide.]

In September, 2000, nearly all French blood banks were using such a system and the French Blood Agency gave this guideline; the use of a sampling pouch should improve security in transfusion.

[Slide.]

Today, we can say that we have, in Macopharma, a great experience in routine use of Bactivam around Europe in countries such as France, Belgium, Portugal, Switzerland with more than 4 million systems which have been used.

[Slide.]

I now want to describe for you a bit more in

detail our system.

[Slide.]

First, you can see the Bactivam, itself. It is a blood-collection pouch which is 42 ml volume.

[Slide.]

Then the Vacuvam--we call it the Vacuvam, the barrel--is preconnected to the system. This holder is kept for more security.

[Slide.]

Then you have a clamp on the dry tubing coming from the Y-connector through the Bactivam. Something which you cannot see on the picture is that there is also a clamp on the donation line--I mean, after the Y-connector.

[Slide.]

Then you have a breakaway cannula to prevent any anticoagulant to go into the Bactivam.

[Slide.]

Then a specific Y-connector which has been designed to prevent any disturbance of blood flow during the donation.

[Slide.]

And then what we call the Secuvam, which is a needle protector specifically designed to fit in the Vacuvam after use.

[Slide.]

The use of our system is quite simple, secure and friendly. First, you close the donation line using this clamp. Then you proceed to venepuncture. You break the cannula which is here somewhere and let the Bactivam fill itself.

[Slide.]

Once the volume needed has been reached, then you close the clamp. You open the clamp on the donation line and you proceed to normal donation. We recommend to seal the tubing between the clamp and the Bactivam.

[Slide.]

Then you remove the cap of the Vacuvam, of the vacutainer, holder. Then you hold the Bactivam upside down with one hand to trap the air which is in the Bactivam. Then you proceed to something with the other hand. There is no need to purge the system. There is no anticoagulant. There is no more air as the bag is upside down.

[Slide.]

At the end of the donation, you remove the needle and you cover it with the Secuvam. Then, this needle and Secuvam can be introduced into the inside of the Vacuvam for more security; no risk of any injury.

[Slide.]

Then the donation line is thrown away.

[Slide.]

Here is a picture which gives you a better idea of the handling of the Bactivam.

[Slide.]

More and more countries are interested in such a system. In addition to reduction of bacterial risk, there are a lot of other advantages which are mentioned by the customers; first, the elimination of the loss of blood donations due to lack of sample. Another advantage is the better quality of the blood sample which is taken before rather than after donation.

These are the countries we are working on which are especially interested with Bactivam.

[Slide.]

We are still working on some more studies, first in England with the National Blood Service, with national validation of the system, and also in Spain where we will undergo a study in the near future to see whether the diversion has any effect on the bacterial contamination of the platelet concentrate which is prepared from whole blood.

[Slide.]

We are still improving the product with a new permanent one-way clamp, first, to be sure that the donation is made in a closed system. We are also working on a new breakaway cannula to make it more visible and easier to break.

[Slide.]

I thank you for your attention.

DR. NELSON: Thank you.

Are there comments or questions?

DR. SCHMIDT: Question. What is the significance of "vam?" You have Bactivam, Vacuvam, Secuvam. Is that some--

DR. DE SAINT MARTIN: Yes. That is because one of the names of our companies, of our sister company, is Vamaco. So that is the reason why.

DR. NELSON: Thank you very much.

DR. DE SAINT MARTIN: Thank you.

DR. NELSON: Our next presenter is Dr. Steve Binion from Baxter.

DR. BINION: Thanks to the committee for listening and I guess thank you to FDA for inviting us to talk.

[Slide.]

I will try and make this brief. I know it is late in the day.

[Slide.]

As presented to us, the issue on the table is the possibility of diversion of the initial volume of blood for sampling purposes. I am simply going to focus on the feasibility question.

[Slide.]

The literature, or at least these two reports from the literature, have already been reviewed. It is worth pointing out that this sampling technology is available on blood-pack units outside the U.S. Also, last November, there was an industry-government representatives meeting that was hosted by AdvaMed. It included representatives of manufacturing companies, CBER and NHLBI.

General issues regarding this topic were discussed.

[Slide.]

Just to point out, as was actually mentioned previously, this sampling option is already available on a variety of apheresis instrument disposables that are currently in use in the U.S. From Baxter's perspective, we do currently produce blood-pack units with an integral sampling pouch which are distributed in Europe.

[Slide.]

Here is a photo showing the setup of the Baxter system for diversion of the initial sample. The vacutainer access port is not open to the atmosphere until the breakaway cannula is opened after the bag is filled. So, basically, the sample pouch is filled. The line is then sealed off and the product can then be collected.

The main point is that sealing the tubing after sample collection maintains a closed system with this blood-

pack unit.

[Slide.]

I think these topics have already been commented on. Obviously, there is a change, or perhaps several changes, in the collection process, but this method of sample collection doesn't affect the collected product.

[Slide.]

In terms of additional issues, and certainly these were identified at the CBER-industry meeting last November, fundamentally, communication of CBER expectations and requirements needs to be a key next step and, certainly, rapid implementation of this technology, if it is desired for introduction into the U.S., would be facilitated by identification of least-burdensome approval requirements for manufacturers.

[Slide.]

Finally, in summary, current technology supports implementation of sample diversion for whole-blood collection. As mentioned, it is already available on apheresis instrumentation. Manufacturing capacity is adequate to address U.S. needs. Finally, the critical input that is needed by manufacturers at this point is the communication of CBER regulatory requirements for implementing this technology.

Thank you for your attention. If there are any

questions?

DR. NELSON: Thank you very much.

Are there any questions for Dr. Binion?

Next, the American Association of Blood Banks, Dr. Louis Katz.

DR. KATZ: You have a pre-prepared statement in front of you, so I will abbreviate. We believe that the technology is feasible, has a reasonable probability of having a beneficial effect and, under those circumstances, should be strongly considered for implementation.

I think the major issue that we are dealing with now has to do with whether we require any extensive revalidation of our testing techniques based on changes in sample collection. I think that will be dealt with with the manufacturers and CBER.

DR. NELSON: Thank you.

Dr. Celso Bianco from America's Blood Centers.

DR. BIANCO: Also, you have our statement from America's Blood Centers. Just to highlight some of the points. We expect that, while the idea is very attractive, we would like it to be introduced carefully in the sense that these bags be appropriately tested, we receive adequate training materials and technical supports, and we are sure that the manufacturers will take good care of that.

The proposed scenario is that the side pouch will

be used as a source of specimens, so it must hold enough for testing, as this was pointed out by FDA, and we did a survey of our members. We actually were surprised by the variety of procedures that they use, the order of the tubes that they collect and the sizes of the tubes that they collect.

But we believe that the majority of our members would be served by a pouch of 30 to 35 mls of blood. But, according to this same survey, there is no consistent approach to the sequence of tubes collected. Some centers collect first the dry tubes for serology. Others collect first the EDTA tubes for NAT and red-blood-cell typing.

Currently, the sequence is irrelevant because venous blood is only exposed to a short segment of tubing. With the proposed collection system, the technician must seal the tube in between the needle and the pouch, initiate blood flow into the collection bag prior to the start of sample collection in order to prevent obstruction of the needle by clots.

This may affect the sequence of specimen collection, which tubes should be collected first, the specimen for NAT, the dry tubes, the anticoagulated tubes. We hope that this will be clearly addressed in the package insert and training materials.

We also request that CBER consider allowing the collection of an alternate sample obtained from a different

venepuncture site on the same donor at the time of collection in case the feeding of the pouch or the collection of samples from the pouch are unsuccessful.

We also believe that the package insert and training materials must acknowledge that there other sources of accidental contamination of transfusable blood and blood products that are not associated with the venepuncture of the donor.

6 p.m.

Thank you.

DR. NELSON: Thank you very much.

Questions?

Next is Dr. Jeff Miripol from Terumo Corporation.

DR. MIRIPOL: I have been asked by Dr. Katz to keep things short or I die.

[Slide.]

I will show you two overheads and I am going to give you a real sample. By the way, I am Jeff Miripol. I am General Manager of the transfusion business in the United States for Terumo Medical Corporation. We do supply blood bags, blood-collection systems, to a wide range of blood centers in the United States, both the American Red Cross and the various ABC centers as well.

First, what I would like to do is, very briefly--we have been talking about the Wagner article. I have to make sure that you saw Dr. Friedman's name and my name, too.

This is the article that Dr. Wagner's group demonstrated that one could reduce the amount of bacteria in a model system and demonstrate approximately a one-log reduction.

[Slide.]

Once again, this is the original model system that we used, again as described by Dr. Haley and others. Once again, what Dr. Wagner and his group did was the sample sequentially the blood coming off the sampling system to demonstrate that, from tube 1 through tube 6, you saw a reduction in bacteria in the system.

Again, as Dr. Haley so nicely pointed out, the original whole-blood bag at the top or saline bag--Dr. Wagner's group did two sets of studies, both with saline and with whole blood. That unit was not contaminated so the contamination came from the sampling process, putting the needle through the painted-on bacteria on the membrane.

[Slide.]

Very simply, the system that we have talked about with FDA, and I have a sample here, is, frankly, a very simple system to use, we believe, and very much like the present system that we supply to a lot of blood centers, again, the idea being that you sample first--in this system here, we have, actually, what we call a large CLIKTIP at this point. This is the line going to the collection bag. This system keeps this closed in a positive fashion so no

blood can go to the bag until you have actually done the collection of whole blood from the donor into the diversion bag.

Obviously, one of the things we wanted to insure is that this bag is the right volume. Again, Dr. Bianco indicated about 30, 35 mls. There has been some indication that it may be necessary to have as much as maybe 38 to 42 mls. But whatever that volume is, this would be a fixed volume.

Then we have again, another breakaway cannula over here. The concept, very simply, is you collect the sample of blood in here, the 30, 35 mls of whatever. You seal this off with a metal grommet seal or a heat seal or whatever. And then you can attach a luer adapter and tube holder to the this female adapter at this point, break this CLIKTIP and sample your tubes.

This can be done subsequent to opening this CLIKTIP. Again, once you have closed this off, this has now been a closed system, you now break this CLIKTIP and, again, you are collecting blood directly into this unit.

So the phlebotomist can, after they get this sample, close this off, break this CLIKTIP and then start to take the sample tubes. That is very simply the system. I brought a prototype with me which I will pass around. But I wanted to at least let you have something that you can touch

and feel.

So, once again, your collection needle with the needle safety device as well, the large what we call CLIKTIP going to the primary bag and then, again, the sample pouch with the female luer adapter which is broken. You put the male luer adapter with the tube holder on that end and you would be taking your samples this way.

Again, thank you for the opportunity to speak to you and to demonstrate the system. Thank you.

Any questions?

DR. NELSON: The final person who has requested to speak is Dr. Matthew Kuehnert from CDC.

DR. KUEHNERT: Hi. I will be mercifully brief. I just wanted to expand on Dr. Haley's comments. I appreciated her mentioning BaCon. I just wanted to round out her comments since it was a collaborative study involving not only the American Red Cross but also AABB and the Department of Defense.

In fact, it turns out that exactly half of the cases were American Red Cross and half were not. It worked out mirroring the distribution of the blood supply. But, basically, again, to emphasize, we looked at cases that were absolutely attributable to sepsis in the recipient, so they were definitely pathogenic organisms. We did this by confirming positive culture on the blood bag in the

recipient by blood culture and then doing pulse-field gel electrophoresis on the two organisms to make sure they were the same.

Basically, what we had were a ratio of platelets to red-cell units of about 4 to 1, so the majority were absolutely platelet units. About 60 percent were Gram-positives but 40 percent were Gram-negatives. More importantly, almost all the fatalities were due to Gram-negative organisms.

So I certainly echo the sentiment and the conclusion that most fatalities are due to Gram-negative organisms and that, in multiple cases, we link these episodes to donor bacteremia. So this intervention is not likely to affect those cases but it may reduce overall contamination. It is probably not going to reduce overall--most fatalities.

The other point I wanted to make was our data also show, and the study has been submitted for publication, that the cases associated with fatality were associated with units that had very short storage time, which, I think, suggests either a large organism load or rapid growth or, most likely, the presence of endotoxin.

One approach might be to consider either selective screening for Gram-negative organisms or some sort of screening test for endotoxin. So, in sum, I think the

measure being proposed is an important first step but I think a combination approach is going to be what is most effective.

Finally, I think that the most critical thing is that this can be evaluated. I am not so sure that we will ever be able to tell whether it works or not unless we evaluate it. So I just want to close on that note.

Thanks.

DR. NELSON: Thank you.

I don't have your name on the list here, I'm sorry. But maybe you could introduce yourself.

DR. E. NELSON: I am Ed Nelson from Pall Medical. We are a blood-bag manufacturer, like Terumo and Baxter, and supply centers in the U.S. and Canada and Europe.

I wanted to mention that we have done a similar study to Dr. Wagner's which was done by Dr. Figueroa at UCLA and presented at AABB I think three or four years ago and demonstrated the same sort of effect with the 7-ml sequential alloquots taken, that the vast majority of bacteria were found in the initial two or three alloquots, and tapering off at the fourth or fifth alloquots.

So it seemed reasonable to us to take this approach to remove the initial sample of blood prior to collection.

[Slide.]

This is an example of our current system being used daily in the U.S. and Canada and Europe. This is the current sampling system where we take the sample after collection. So you take the collection, seal off the tubing here below the Y, and then hook up the vacutainer holder and use the vacutainers to get the samples directly from the donor.

We had initially considered trying to use this same system for pre-donation collection. However, concerns were raised, obviously. If you just hemostat here, you would be essentially opening the system, going in and out with your vacutainers. Also, the question was raised whether, during the storage of the units prior to use, anticoagulant could migrate up into this area and then be collected in the first tube and, thereby, possibly dilute the sample and give us a false negative.

So I just wanted to show the current system that is under development.

[Slide.]

As you see, we have added a few components to the system. It still includes the same Y-sampling needle for attaching the vacutainer holder and the vacuum tubes. It includes a diversion pouch for collection and segregation of a sample volume. Our marketing people have done research and they say this should be 45-ml size, capable of holding

up to 45 ml.

There is a sample line, a pinch-clamp here, to facilitate actual permanent sealing. On this end, there is a breakaway closer to do two things; one, to prohibit any anticoagulant from migrating up here and diluting the sample and, also, as Jeff mentioned, to keep blood from migrating down this way and thereby ending up in the collection bag where you don't want the initial blood to go.

So, to use this, you make your phlebotomy, fill the diversion pouch, use a pinch clamp and then permanently seal up here by the Y, open the breakaway closure and start the collection. And then you go in and use your vacutainers to collect the samples out of this pouch.

We have made this tube a little longer to facilitate the manipulation of this while the blood collection is going on to try to get it away from the donor's arm a little bit. So that is basically the system that is under development.

In this same area, Pall is currently also developing a bacterial detection system for platelet products which we actually think will have greater potential to reduce the incidence of morbidity and mortality associated with transfusing platelet products.

That's all I have. Thank you.

DR. NELSON: Thank you.

Questions?

I think that is--unless Mike Busch wanted to say something. [Laughter.] It is rare that he doesn't.

Open Committee Discussion and Recommendations

DR. NELSON: We were given three questions by the FDA. I don't know, Jay, whether you wanted somebody from the FDA, or should I just read them.

They are in your packet. I will read it while they are putting it up.

The first; are the FDA's proposed criteria for the design of the collection system adequate to assure the safe diversion of the initial volume of blood with possible reduction of bacterial contamination. These criteria include: a), a closed system; b), diverted blood is separated from final product by unidirectional flow; and, c), volume of diverted blood is sufficient, i), for all required testing, and ii), to potentially reduce bacterial contamination.

Is there committee discussion about this issue, these questions?

DR. SIMON: Everybody wants to go to dinner, I guess. I guess we are not expected to get into a long issue of whether this is the way to go and a value of this versus detection systems at all, but this is if FDA has presented to them a diversion, are these the appropriate criteria. Do

I have that kind of correct?

DR. VOSTAL: Yes. I think if we are presented the criteria, or if we were presented a product, should we apply this type of criteria to the product. That would be the first question. The other question is whether we should actually recommend this for general use.

DR. SIMON: So if you should go beyond just approve the product that comes to you but whether you should also go and push it as a--

DR. VOSTAL: Right.

DR. SIMON: So, both; okay. I mean the criteria seem appropriate that you have got under No. 1.

DR. NELSON: One issue that with some of the--I guess Celso raised the issue of some anticoagulated, some plasma, some serum, some--you know, et cetera--whether or not the systems presented would do that. However, I think it is a reasonable criteria and that is what we are asked.

DR. MIRIPOL: I wonder if I might just speak to that very briefly. Right now, most blood in the United States is--obviously, it is collected first in the bag but then it is sampled and, typically, in many of the systems now, it is completed unanticoagulated when it is sampled. So, at the present time, most of the testing is done--again, they add the specific tubes that are required so that blood coming from the donor is unanticoagulated. This would be