strain, it can get through. For the most part, we are not taking this into consideration for lack of data that these are a predictable problem at the moment for HIV.

Blood banks errors is where most of the discussion is going to be today. Primary-test failure; this is essentially zero. Then the incidence issues, the window period. When we calculate these, we think in terms of frequency of these, so there will be an error frequency, times the prevalence--when we are calculating this out, we think in terms of an error frequency times a prevalence frequency times the change in the population.

This brings us back to this equation.

[Slide.]

Again, the change in errors is going to be equal to the change in population so that the new infectious units that could slip through the system appearing because of a new donor population are merely the summation of what I showed you on the last slide, the prevalence issues plus the incidence issues. This is just a correction factor for the length of the window period that we use.

[Slide.]

FDA is considering changing donor-suitability criteria to defer for MSM behavior within the last five years prior to donation, so we would allow people to donate if they hadn't had any MSM activity in the last five years

prior to donation.

We are going to calculate how many new individuals will join the set of donors who are not deferred by the questionnaire and, thus, have their units enter into the blood banks for testing. So we will start out by, we need to know the size of the MSM population that has abstained from MSM behavior for five years or more, and then we will multiply that by the frequency at which they can be expected to donate. That should give us the number of new MSM donors.

[Slide.]

What is the size of the MSM population that has abstained from MSM behavior for five years or more? Lynda Doll, in 1997, went to a great deal of effort to give us some very useful numbers. She came up with a population size of approximately 1.4 million MSM in USA at five years of abstention.

At what frequency can they be expected to donate?

[Slide.]

We expect them, for lack of any better evidence, to donate at a rate equivalent to the general population, namely about 5 percent. So, given an MSM population, so I thought with five-year abstention, a population size of 1.4 million, and assuming a donation rate of 5 percent, we would get a total of 70,000 new MSMs who had come to the

blood centers and have their blood drawn and have that blood sitting in the center awaiting testing.

However, some of these will already have been donating. I have a calculation here--again, we have presented this to the committee in the past--of how we calculated how many are donating.

[Slide.]

I am going to tell you a answer before I tell you how I got it so that you will know where we are going. We calculate that 0.55 percent of the newly eligible MSMs have already been donating which comes out to 0.55 percent of 70,000 which is 7,700.

What that means is 7,700 of this 70,000 that are newly eligible have already been donating so that changing the deferral to a five-year deferral for MSM behavior would result in approximately 62,300 new MSM presenting to donate blood. So that is the delta population that I have been talking about. That is the new MSMs who haven't been appearing before.

How did we get this number of 0.55 percent?

[Slide.]

What that number is is the frequency at which MSM with deferrable risk will donate. We assume that that is equal to the current frequency at which deferrable MSM donate. Of course, you could simply go out and ask 100,000

MSMs whether or not they donate, and you could generate that number from that kind of survey.

We don't have that, but we do have another way of calculating it. I believe Alan Williams was the first one who actually suggested this. We can simply take the number of MSM currently showing up to donate, which we can calculate from REDS by a frequency number from REDS and divide it by the size of MSM population.

We know from the REDS study that 0.57 percent of men who present to donate have deferrable MSM history. And we know that 4.5 million donors are male. So the number of MSM who currently donate will be 0.57 percent times that 4.5 million number.

The MSM population with deferrable risk is 4.7 million. It is only an accident that these two numbers are so close. So the current donation frequency of MSM having deferrable risk equals the number showing up to donate divided by the number of MSM in the relevant population which is this number divided by this number. That is how we get the 0.55 percent number.

[Slide.]

So, to reiterate, the critical take-home here is that 62,300 new MSM would present to donate blood that have not been presenting before with a five-year deferral.

[Slide.]

Let's look at the prevalence and incidence issues separately to see how they contribute to the possible errors that might occur in transmitting infected units into the blood supply. I just calculated the change in population number. Now, I am going to go through the prevalence issues.

First, let's focus on what we calculate prevalence to be. HIV prevalence in MSM varies widely according to the geography of the United States. It varies from 6 percent to 36 percent. The average U.S. prevalence is approximately 8 percent. However, about three-quarters of these already know their seropositivity status and are expected to self-defer.

So the effective average prevalence rate nationally would be about 2 percent. As I mentioned earlier, undetectable strains, which is this term here--we just discussed the prevalence term; now we are going to discuss these three terms--undetectable strains are ignored for lack of evidence. They represent predictable threat for HIV, again, in a population size of 62,000 or so, you are safer making that assumption.

Blood-bank errors will be a major focus today. Blood-bank error rates involving release of HIV-positive units have been poorly reported but I am going to go through some data in which we can estimate what they are like. I

will get into that in a minute.

Pipetting errors or technician errors occur at the rate of 0.5 to 1.3 times 10^{-3}. This was the data that Mike Busch summarized in his task and it comes from a paper that he has published and also from data that Sue Stramer has very generously provided from the American Red Cross.

Finally, primary-test failure. Essentially, that is equal to zero.

[Slide.]

Let's go on to the test-error issues here. If we calculate out this term here, the prevalence basically times the error, since this and this are equal to zero, it is 2 percent from the prevalence times 1.3 times 10^{-3} which is the error rate and times the change in population, the new population which is this.

With just a single test, we could predict that--and, again, these numbers are pretty iffy. I am sure you are all aware of that. Blaine contacted me and, very correctly, asked for confidence intervals and I contacted him and said I don't have any. The problem is that a lot of these numbers are 1 for 3 incidence that you are picking up. So the confidence intervals are going to be very large in some of these. But it is the best we have. It is all we have to go with.

Anyway, using this approach, it is possible that

as many as 1.6 units, HIV-infected units, could slip through the system. However, the NAT test provides a minimum of twenty-fold of redundancy. What I mean by that is anything that is EIA-positive is also going to be positive on NAT. When I say twenty-fold, I am just using a loose number saying that if something is EIA-positive, at least 95 percent of those and probably a good deal more are going to be NAT-positive.

Since those are separate tests, they provide redundancy for one another. When you take that into account, the NAT reduces this introduced prevalence rate at least by twenty-fold, so we could use the number of 0.081 units, infected units, getting into the blood supply for a year. That is a worst-case scenario.

That is not a bad number.

[Slide.]

Furthermore, this number would decrease as HIV tests eliminate the effective prevalence among repeat donors from this category. All that means is, as this group newly donates, the positives will be picked up, the effective prevalence rate will, essentially, go down in that group amongst repeat donors.

The big caveat here is that this estimate was made assuming errors only came from performing tests or technician error or pipetting errors is an easy one to

visualize. Unfortunately, double-testing, for instance the ELISA and NAT, confers no protection against release errors.

Release errors have been difficult to quantify but I was very fortunate in contacting Jeanne Linden who provided me with some data from New York State. It turns out to be very interesting data and suggests that the erroneous release rate may be a bigger problem for us.

[Slide.]

This is a selection of some of the data that Dr. Linden sent to me. Over the recent time period from 1999 and 2000, out of about 700,000 donations in New York State, there were four inappropriate release of anti-HBC-core-positives from hospitals. There was one inappropriate anticore-positive release from blood centers and there was one inappropriate HCV-positive release from hospitals.

I have broken this out into hospitals and blood centers, again at Jeanne's suggestion. It is very interesting that hospitals which, in New York State, acquire about 10 percent of the blood have over 80 percent of the overall errors. They are producing errors which are disproportionate to their number.

The reason is that hospitals, being generally small, don't have automated blood-handling systems whereas blood centers do and that is a major factor in reducing inappropriate release.

Dr. Linden did not have one of the key numbers we needed from the New York data. What we want to do is we want to take these numbers and say, "Well, we got four inappropriate releases of anticore, but how many anticore-positives were there?" So we had to estimate that for the New York data.

So I used data that Alan Williams supplied from the Red Cross and was collected by ARCNET. From a period of 1-98 through 6-30-99, which is reasonably close to the New York time period, nationally, out of about 5.9 million donations, there were collected about 5,000 anti-HCV positives and about 26,000 or 27,000 anticore positives.

So, by using the ratios or the percent of units, or the percent of this 5.9 million which were either core-positive or HCV-positive, and assuming that the prevalence in New York was the same as the percent prevalence nationally, I was able to calculate how many HCV positives were in this 70,000 donations from hospitals, how many anticore positives were present in this.

Also, I could do the same thing for the numbers in the blood centers. Then I just used those as denominators and these as numerators to calculate the release-error rate. Those numbers are summarized at the end of this table.

I want to focus on the anticore data. The reason I want to focus first on the anticore data is because there

were four events measured there. When you do this calculation for these four events in hospitals, you end up with a very surprisingly high release rate of about 1.3 percent. I think we were all very surprised that it was that high.

Granted, it is a small sample and there is going to be a large confidence interval around it, but, in spite of all, even for the HCV data which had only one event, the HCV data calculates to about 1.7 percent. So it is a number consistent with the anticore data.

For the blood centers, there was only one event and that calculates out to about 3.5 times 10^{-4} as the release error rate.

[Slide.]

So, if you apply that to what we would expect for MSMs donating nationally, nationally, about 8 percent of the donations are in hospitals and about 92 percent are in blood centers, so it is not that different from New York State.

If you had the 63,300 appearing, how many units would get through? If you just use the simple incidence times the proportion of the population which would be in hospitals and the simple incidence times the proportion of the population which would be in blood centers, these are the numbers of units of HIV-positive material that would be in the blood bank.

If you multiply that times the error rate, you come up with small, non-automated blood collection systems would contribute possibly as many as 1.3 HIV-infected units into the blood supply per year if this error rate is correct.

The highly automated blood centers, on the other hand, would be calculated to contribute about 0.4 units per year, making these assumptions, for a total of about 1.7. So, to the extent that we believe the numbers I have calculated for release error rates--and, of course, there is a certain "if" associated with that, and you have seen the actual numbers. Changing the policy to a five-year deferral for MSMs could conceivably result in a total of 1.7 infectious units getting through that would not otherwise get through.

[Slide.]

What I have discussed previously are prevalence issues. If you remember, then, the other category of issues is incidence issues. That is what I am going to discuss now. Essentially, incidence issues will turn out to be a minor problem with the five-year deferral. I can tell you that is the answer.

So, using an average incidence in the MSM in the U.S. is an incidence about 3 times 10^{-2} per person years. Although the typical window period is 11 to 16 days,

roughly, depending upon the technology, following about 51 needle-stick accidents, it was discovered that about 5 percent--maybe not quite that--seroconvert after the first six months.

So, almost all of the window periods seem to be 11 to 16 days, but there is a reasonable number that are very, very long. We don't really know anything about those window periods. Presumably, these window periods were at least six months long.

We assume that they were infectious for the entire six months but we don't know that. There is also no reason to assume that all of them seroconvert in the second six months. So I have made some assumptions here and given you some ideas of what the answers would look like.

What I have done here is I have essentially assumed a 95 percent decay rate every six months. What does that mean? That means that 95 percent of all the people who have been infected, 95 percent will seroconvert every six months or another way of looking at that would be 95 percent of what is left seroconvert.

Or another way of looking at it would be, of all of the ones that have not seroconverted, 5 percent will fail to seroconvert, will still fail to seroconvert, in the next six months. This is a very loose number, but I have said, "Well, what if we are wrong? What if it were 75 percent?

What if 75 percent converted every six months," which would mean that 25 percent had not converted every six months?

That is a worst-case scenario and I really don't think the data could ever be construed as permitting that. But if you take these possible scenarios and assume a decay, with a five-year deferral rate, you would end up with less than 3 times 10^{-5} units if it were the 5 percent number.

If even if were the obviously not correct 25 percent number, you would still only be introducing 0.42 units per year. So we think that the incident issues give you a tremendous margin of safety with a five-year deferral for the obvious reason that there are almost no window-period conversions going out into five years.

[Slide.]

I should say that I have given myself a little bit of leeway in these calculations in that I took into account the possibility of donor confusion or poor memory by assuming that a five-year query was entirely ineffective except for the behavior within the last three years, which is a pretty conservative assumption. We know, certainly, that people are going to forget; "Did I do that three years ago? Was it five years ago?" And you are in the middle of an 85-question questionnaire.

But what I actually assumed was that essentially people would always remember behavior within the last three

years and defer themselves on the basis of that question. So I have been somewhat conservative in that respect.

[Slide.]

What about a one-year deferral? A one-year deferral would result in approximately 112,000 new MSM donors rather than the 62,300, or about 1.8 times as many as a five-year deferral policy. This would result in about 0.15 new seropositive units escaping interdiction per year from errors in performing tests and possibly as many as three units from errors in unit release.

I will give you a table shortly to summarize all of these numbers. Also, a one-year deferral policy poses window-period problems. Again, if there is only 95 percent seroconversion every six months post-HIV exposure, then 0.25 percent would seroconvert after the first year.

Using this formula to calculate how many infected units you would get appearing into the blood supply, you could get 3.1 from this mechanism.

[Slide.]

So, let me summarize how the story looks for HIV. Again, with tremendous caveats because you understand that a lot of this data is based on one to four incidents of something being measured. So it is hard to come up with good statistics on them. But with a five-year deferral, we would expect zero window-period errors to be introduced into

the population by adding 62,000 or so donors.

Release errors could conceivably contribute 1.7 infectious units per year from that size population and technical errors, such as pipetting errors, would introduce far less than 1.0--maybe 0.08 or less. With a one-year deferral, it is conceivable we could have as many as three window-period units newly introduced into the blood supply. Again, you realize that we just really don't know what those long-term window periods look like, so there is a big question mark associated with that number.

Release errors would conceivably contribute as many as three new units per year and technical errors would still be down well below 0.2 per year. Again, all of these numbers should decrease with time with repeat donors being weeded out for seropositivity and, thus, reducing the prevalence error.

The other take-home from my talk is that inappropriate release, primarily due to non-automated blood handling systems remains the biggest risk factor. I should say "problem. "

[Slide.]

HCV I am not going to go into nearly as detailed analysis as I did for HIV. The reason is that the prevalence of HCV in non IVDU-MSM, about 4 percent, is only about twice that of the general population, 1.8 percent.

Given the high sensitivity of the HCV ELISA and the redundancy of HCV NAT, together with the similar prevalence rates in the two populations, deferral of MSM would be only marginally effective in preventing HCV transmission.

[Slide.]

Similarly, for HBV, I don't think it is necessary to go into as detailed an analysis as we did for HIV but, to summarize it, as with HIV, essentially all of the infectees who are going to seroconvert will have done so well before three to five years. Therefore, incidence issues are of minor concern.

The real danger is chronically infected donors, long-term HBsAg-positives. In MSMs, the prevalence of HBsAg positivity is about 1 percent. This would result in about 623 new positive units presenting to the blood supply. Again, that would reduce to small numbers of HBsAg getting through.

Also, the anti-HBV core provides redundancy, as NAT does for HIV.

[Slide.]

To look at how many HBsAg-positive units could be inappropriately released, again a bigger problem, by changing to a five-year MSM deferral policy, I have come up with this analysis. It is the same one you saw for HIV. I won't go through the details. I will take you right to the

end of the story.

Making the same assumptions, small non-automated blood systems, could conceivably contribute as much as 0.64 new units per year with a five-year deferral and automated blood centers could conceivably come up with 0.2 units per year.

Of course, I don't need to remind you that HBV has a much lower morbidity than HIV. So changing to a five-year MSM deferral would introduce minimal risk of HBV morbidity from blood transmission.

[Slide.]

You have seen this slide before. I will just show you one thing. This is data that Mike presented earlier. This is pre-NAT and post-NAT residual risk broken out by error. I just wanted to show to you that the error numbers for HIV and HCV pre-NAT go down to zero post-NAT so the redundance is a real phenomenon.

[Slide.]

Again, this is similar to, a subset of the data that Mike presented on the increasing incidence of HIV and STDs in general in the MSM population. This was provided by Dr. Hansfield from Seattle. In 1997, the incidence of HIV in MSM goes from a unit of 1 to 1.7 in non-IVDU-MSMs. So that is a worrisome number.

[Slide.]

These are in your notes. These are just the contributors to Dr. Hansfield.

[Slide.]

He asked that we display them.

[Slide.]

To bring my talk to a conclusion, we have quantitatively analyzed the risks to the blood supply of changing the deferral of MSM from "since 1977" to "within the last five years." This analysis has taken into account prevalence and incidence issues, testing errors and release errors.

This analysis has not summarized projected improvements in blood banking from improved automation but does demonstrate that inappropriate release remains a significant risk.

[Slide.]

The final conclusion is that there is some scientific data to support relaxation of the current MSM deferral policy which defers men donors who have had sex with another male even one time since 1977. Also, a five-year MSM deferral policy for blood donation would harmonize with the five-year deferral policy for tissue donation.

[Slide.]

One of the true privileges of working in the FDA on an analysis such is this is the tremendous amount of

support and help I have had from many people, both inside the FDA and outside the FDA. The truth is, they did all the real work and I am very grateful to them.

[Slide.]

Finally, the question, as we proposed it, is, "Do the available scientific data support the concept that men who have sex with other men can be deferred from donating blood for a period of five years following MSM activity rather than being deferred for any MSM behavior since 1977?"

Thank you.

DR. HOLLINGER: Thank you.

Any questions of Andy at this point? Dr. Boyle?

DR. BOYLE: Just one question for clarification. All of the equation that you have up there is based upon what is effectively changing a test. The test is the question in the screening--

DR. DAYTON: Changing the question; yes.

DR. BOYLE: But the question is the equivalent of the test.

DR. DAYTON: Yes.

DR. BOYLE: Basically, all of that is based upon an assumption about what that change will do, whether or not it is 100 percent specific or, in your case, reducing it to three years rather than five years. It is all an assumption. There is no evidence; right--what the effect

That may be relevant to a transfused population who might be suppressed for one or another reason when they got a blood transfusion, I suspect.

DR. HOLLINGER: Thank you, Mike.

Dr. Dayton?

Risk Assessment Model and Proposed Policy Questions

DR. DAYTON: Thank you, Mike, for an excellent presentation.

[Slide.]

What I am going to do is take a lot of the data Mike has presented and data that other people have communicated to me or that we have gleaned from the workshop, et cetera, and try to put this into an analysis of the predicted effects of changes in the policy that we may be considering.

[Slide.]

To go back to a piece of the original diagram that I gave you, we were concerned, largely, with infectious units and potential donors getting through the test by these various mechanisms and getting into the blood supply. The question is going to be how can we quantitate this.

As I mentioned, this occurs because of various problems. As I said before, there are prevalence issues and incidence issues to approach these quantitatively. We have undetectable strains so if there is a prevalent undetectable

would be?

DR. DAYTON: Well, no; it is not all an assumption. It depends on what number you are talking about because if it is the population number, the change in population, how many new MSMs would present--that is not an assumption. That was calculated.

DR. BOYLE: No, no; the question is that if you change a question, how a person will respond to it, is based upon--

DR. DAYTON: You are getting into an entirely different--and, actually, I am very glad you brought that up because would did consider this. You get into this whole area of test-seeking behavior and reliability.

When we first started this particular analysis, one of the take-homes that came out of it very early on in 1997 was we were very worried, well, how do you account for people who are doing test-seeking behavior? How do they fit into the equation and how do you take that into these numbers of new MSMs presenting to donate.

To a first order approximation, people who are already doing test-seeking behavior are going to continue doing it. So that number does not change.

You are shaking your head and I think I know where you are going in that and I certainly agree with you. Maybe people will say, oh, now you are only deferred for five

years, and maybe they will be more likely to engage in test-seeking behavior. We simply can't calculate that number. But I think that is where you were going.

DR. BOYLE: Just one follow up. As I understand it, there is a task force that is going to be looking at the whole questionnaire and trying to put together some evidence about what works and what doesn't. My question is why is this issue presented now rather than a year from now when, presumably, the task force is looking at the questionnaire across the board and maybe you have some evidence.

DR. DAYTON: You may have some input into that decision. Actually, you will have some input into that decision. As I said, the real reason we thought it was a great time to look at it now is because of the redundancy that exists with the concurrent NAT and ELISA tests.

Also, we have learned more about blood-banking errors which are two previous concerns. So we are a mile further than we were last year.

DR. HOLLINGER: Dr. Nelson?

DR. NELSON: As a follow up, I think the real issue--you presented one side of the equation. But the other is the questionnaire and the validity of the answers to a different question. We already have some data on validity of answers to the previous question since 1977. In other words, how many men who actually had sex with men

during that period were then found to have a viral marker and then, on subsequent testing after they were found to be positive really didn't answer, or forget, or for whatever reason, didn't give a valid answer to the 1977 question.

We don't really know what effect the change will be. I think that is the big part of the equation rather than what happens to the tests in these long window periods. I think, with the current redundant test, that is probably pretty insignificant. But the real issue is how will the change in the question affect the validity of the answers that one will get with the population.

Do you agree with that?

DR. DAYTON: Yes; I agree with it very much. I think we can give you a partial answer, and part of it is the answer I just gave and part of it isn't. We feel--we don't have data to prove it, but we feel that a five-year deferral will be perceived as a much fairer mode of deferral than, basically, forever. I think that that will actually engender more compliance.

Granted, it might be harder to remember was it five years ago or three years ago as opposed to in the last twenty years. But, as I say in the calculations, we gave a slack to that in asking for five years expecting to get three years effective deferral. So we think that is going to be okay.

at

Finally, the point I made to Dr. Boyle deserves reiteration that the people who are consciously engaging in test-seeking behavior will continue to do that. They are not going to represent a change. They are not going to come into the change that results from this policy.

But, unquestionably, designing a good questionnaire and getting it to work is a major, major problem. It is just that it is not a delta that is associated with this policy. We definitely need to put a lot of homework into that questionnaire.

DR. NELSON: Dr. Schmidt?

DR. SCHMIDT: Another aspect of this, following up on these two comments, is a question of memory. I only had one surgical insult in my life. That was my gall bladder. I found out, as I took physicals after this, year after year, I couldn't remember how long it had been. I can tell you what the room looked like and how many pounds I lost before I had it, but it is not a human type of framework, I think, to know that with the exactitude.

You really came down to it at the end--you are now, when you are telling us five years is really three years. So I am not talking about test seeking or anything. I am talking about answering questions.

I almost think, and what we are talking about, calls for a change in your question to the committee which

doesn't say that they didn't have sex in five years, but, as far as they remember, they didn't have sex in five years. That is really the issue.

DR. DAYTON: I think that is fair.

DR. HOLLINGER: Dr. Simon?

DR. SIMON: Perhaps I missed it, but I also thought that one of the reasons for concern to change at this time is harmonization with the tissue provisions because we have just had that conference and I believe we are going through with--you all are going through with a rewrite of those.

That was, I thought, one reason.

DR. DAYTON: Yes; I didn't dwell on it, but I did have it there on a slide. It is a good point. The harmonization makes for less confusion and a more coherent questionnaire and a less confusing policy. So that is a benefit.

DR. SIMON: I guess one of the questions that comes to mind, and it may be that you have already hit on the answer in some of your other questions, is the agency's thought about going to five years with the permanent deferrals--that is, IV drug abuse and sex for money or drugs. Is that something that you are putting off to the whole look at the questionnaire or are you thinking about that?

DR. DAYTON: We periodically reexamine all of those issues. They are all so complicated. We certainly didn't want to wrap them into one discussion. So we keep an eye on those and, when we feel that the data supports reexamining those issues, we will very rapidly reexamine them or bring it before here, actually.

DR. MACIK: In the numbers that you have for men who continue to donate, is there any feeling for how many of those may have gone out and had themselves tested? The people who, say, had one relationship or one event and then were worried about it and went out and had their doctor do all the tests on them. In their mind, they are negative and they are going to come in and donate.

Was there any feeling to how often that would happen?

DR. DAYTON: We do have a number for what frequency of men who donate have a history of deferrable MSM behavior. We do have that number, but I am not quite sure what you are looking for beyond that.

DR. MACIK: That they went to their doctor and said, I want you to test me for AIDS and I want you to test me for hepatitis C. And so their doctor sent all the tests and the tests come back negative. Then that man shows up at the blood donation and--

DR. DAYTON: Oh; I see. So you would want to take

that number and adjust the number that I did present.

DR. MACIK: I just wonder if you have any idea of how often that would happen.

DR. DAYTON: I don't. Alan, do you know anything from the REDS study on that?

DR. KLEINMAN: I would have to say that, at this point, the data are not available in the 1998 survey. We did start to probe a little bit on donors who did proceed with those donations despite deferrable risk and get some basic rational as to why they did that. But it doesn't get as detailed as you are suggesting.

DR. HOLLINGER: A question to the committee and then there looks like there is a group forming at the back to do something to us. Steve, why don't you go ahead.

DR. KLEINMAN: Dr. Steve Kleinman. Comment for Dr. Boyle. As a member of that donor task force, one of the things that we wanted to avoid doing was spending a lot of time on questions that there was no intention to have changed by the FDA. I think when you asked why is this brought to the committee, if the committee says don't change this, the FDA says don't change this, there is no point in having a task force look at it and come up with a recommendation to change it.

So the concept is we are looking for a direction and want to spend our time just on those things that are

really potentially changeable because it is a lot of work to review the whole questionnaire.

A couple of other comments, on two parts of the model. One is the prevalence rates for HIV antibody in MSMs which you said range from 6 to 30 percent and you took a number of 8 percent. I think that is probably quite valid except the kinds of persons that might come in and now be eligible to donate would seem to me to be two kinds of people. One would be a person who was actively engaged in male-to-male sex and stopped five years ago.

But the other type of person which I think is more common would be somebody who might have experimented and had one or two experiences back ten or fifteen years ago. I would submit that it is unlikely that the rates are going to be 8 percent in that group of people.

So I think that we might be kind of overestimating the HIV risk in the people who would come back in and be eligible to donate. I wonder if you could comment on that.

DR. DAYTON: That is a perfectly fair question. What you are getting into is the whole issue of what defines MSM behavior. That, in and of itself, is a complicated field. It is very hard to decide which of those two categories--if both of those two categories are handled equivalently.

We didn't have data to distinguish between the two

so we lumped them together. But I think that where it comes out in the wash is that the really important data is the overall prevalence data and the blood-banking release errors. I would assume that the overall numbers include both those types of people that you have just described, for lack of an effective way to really factor it out.

Maybe Alan can correct me on that. He is shaking his head no. So we just don't have the information to do that.

Also, you are quite right that all of these numbers here, if I had a chance to choose reasonably a conservative number, basically conservative meaning which would bias against relaxing the policy, I generally did that. I felt, since we didn't have confidence intervals, I felt an obligation to do that basically to be in compliance with the publicly mandated and Congressionally mandated policy of zero error tolerance in this matter.

DR. KLEINMAN: I think that my last comment is that probably applies to your numbers for release errors as well because in the era where we are--obviously, the release errors were from the hospitals, but I want to remind the committee that, in the level of redundancy, there is not NAT testing taking place in hospitals so all the NAT testing is taking place with automated systems in blood centers so that, since the HIV-positive person would presumably be

positive both by antibody and by NAT, then the release error rate would apply to the NAT-tested blood centers.

So most of those units would never get to a hospital even if the hospital collected it. I guess the unit would be at the hospital, but the testing information would get back to the hospital. I guess they could still make a release error, though, even with correctly supplied information.

DR. DAYTON: Where that would come into play in the hospitals where you only have the one test and no redundancy, you would go back to the testing error number. And that would become significant. It would rise to about 1.6 nationally if all of the tests were done that way. But only 8 percent of them are under that, so you would only have 8 percent of that 1.6 percent getting through.

So you would still have a very small number, and your biggest worry would still be the inappropriate release number with the standard prevalence rates.

DR. HOLLINGER: Jeanne, would you respond to some of that, please?

DR. LINDEN: I would just like to add to that because I really disagree with something that Steve said, and there may be a misunderstanding of what the errors were that were presented in my data.

We are talking about blood collected by a hospital

where the testing may be done either at the hospital in the microbiology department, immunology, something like that, or it may actually be done by a blood center or reference lab. The results come back but they don't come back electronically. They come back by paper or, worse yet, by fax. Those can be disworded or difficult to read.

The problem is, even when you get those results, then they may not be read properly. The fact that it is positive may be overlooked. The fact that the test is pending, which means actually it was reactive and not reported, is overlooked. That is really what those problems primarily were.

Even if the NAT testing is done, it can still be misinterpreted when it goes back to the hospital. That is why the hospitals had a much higher error rate than the blood centers because of the way the testing is set up.

DR. HOLLINGER: Thank you, Jeanne.

DR. DAYTON: Can I ask a question of Dr. Linden? How difficult would it be for hospitals to change their procedures to deal with this and reduce that rate? Obviously, they are seeking to do that, but how major a hurdle is that?

Even you seemed surprised at the rather high release rate. If this is a real surprise, what can hospitals do to address it?

DR. LINDEN: It has been a problem that I have been concerned with for many, many years. My personal bias is that units collected by hospitals are much more dangerous than units collected by blood centers for a variety of reasons.

I cannot, personally, speak for the feasibility of hospitals changing their systems. I don't know if anybody here can. But, certainly, we have seen that, as the blood centers have improved their automated systems, the hospitals have not been able to do so. In fact, it has, actually, in a way, gotten worse because the old system of paper, you could mark things in red and make things more obvious.

Now, the way things are coming, they are actually, in my opinion, more error-prone, not less error-prone. So, short of having hospitals not collect, I am not sure.

DR. HOLLINGER: Dr. McCurdy?

DR. McCURDY: I think that one very important part of this equation, as far as hospitals are concerned, is to ask the question why is a hospital collecting a unit of blood. If I were in a hospital, the liability that I would assume by collecting a donor would seem to far outweigh the value of that unit of blood.

I suspect that part of it is the difficulties in getting autologous units collected and provided at a blood center. It really has to go off-line, in effect, and is a

pain in the neck.

The other thing is the question of whether intermittent shortages of blood from the blood center, or perceived shortages, push the hospital to collect "to help out their local blood supply." But I think it is important to ask why is the hospital collecting the unit of blood. If you can find out why, and it is something that is potentially correctable, that may be a better approach than trying to change how they do it.

DR. LINDEN: In my experience, most of the hospitals collect for one of two reasons. The primary one is cost. I know that it not something that this committee is supposed to deal with, but I think that is the rationale. That is not going to be easy to fix.

The other is a perceived either shortage or lack of availability from their supplier, that they feel they need to be able to collect their own blood to supplement what they get from a blood center.

DR. KATZ: I have a couple of questions, and some of it may be that I was out of the room for a minute. You cited a 2 percent prevalence rate in men having sex with men with HIV seropositivity and used that, I believe, in your calculations. That is not discounted for that number, I presume, for those that already know their serostatus and would be excluded by a different question.

DR. DAYTON: I couldn't totally hear the question, but the average effective prevalence in MSM is 8 percent. About 75 percent of them know their seropositive status and self-defer.

DR. KATZ: Okay.

DR. DAYTON: So the 2 percent has that taken into account.

DR. KATZ: The other question is probably for-- well, I don't know, Dr. Dayton. You may know. It is my presumption that underlying this entire discussion is that any consideration of relaxation would not take effect until there were licensed NAT assays. I mean, that seems to run through all the discussions of redundancy.

DR. DAYTON: I didn't specifically address the issue, but I think it is a good idea.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: That would be our intent, would be to wait for licensed NAT. Since I have the mike, let me just comment that there are a couple of drivers why we are bringing the issue. As has been stated, we have had a general program of updating the donor suitability standards which ultimately will be reflected in revised regulations. So we are trying to deal scientifically with each of the issues, and there are a large number of them which have been reflected in discussions at the advisory committee and

scientific workshops.

Secondly, it is very much in our thinking to determine the extent to which we can and should harmonize the standards for donor suitability as they apply to blood donation and as they apply to tissue donation and cell-derived product donation, which is an active area of PHS guidance and also is soon to emerge as FDA regulation.

Above and beyond that, the agency is also responding to the fact that, over the years that we have had this deferral in place, there has been a great deal of criticism of the agency, particularly by gay and lesbian activist groups and persons concerned in their behalf including, for example, college students who have had demonstrations on campuses that the current restriction appears discriminatory and even if not discriminatory, appears to be unduly strict.

The arguments that have been made are that, first of all, a post-'77 history, for a person born post-'77, is really a lifetime exclusion for even a single MSM experience, and that why aren't we taking advantage of the fact that screening test technology has improved remarkably and can we not trade off some of the exclusion based on risk history against better testing.

Then the third argument that has been made is that we are kidding ourselves asking about remote risks. We

should be focussing on recent risks. One way of doing that is to deal with a moving deferral interval rather than one reckoned from some remote time in the past.

So these have been all the drivers why the issue comes to the fore now, although I accept the comments that have been made by several around the table, that the true impact won't be known unless we understand what a revised question might do.

But I think what we are saying here is okay, let's say we revise the question and it works perfectly. On those grounds, is it scientifically sound based on the modeling of the risk, because, certainly, that is the best-case scenario. If we reject it in the best-case scenario then, as also has been said, there is not a lot of point pursuing a question which might, in fact, not work as well.

DR. DAYTON: One just modification of what Jay said. Actually, we are not expecting the new question to work perfectly. We are assuming it will work as well as the old one did.

DR. HOLLINGER: Dr. Bianco?

DR. BIANCO: Celso Bianco, America's Blood Centers. Dr. Dayton, thank you. You have created a model that tries to include every one of the major factors that would contribute to that. That is fun, actually, because we can try to plug different numbers and see what is the impact

there.

I would like just to make a couple of observations about your assumptions. Your assumption of 5 percent of individuals donating blood and that this would also apply to the gay community; one, I think that the gay community is very aware and they have, over the years, from our experience, particularly in New York, stayed away from donating blood.

But the second thing is, even in New York, only 1.5 percent of the population donates blood, so that reduces, by a factor of 3, the level of risk that you would see. The other point that I think would be very important is that there is a dataset with the Centers for Disease Control that I feel should have been part of that estimation because it is very good, the data obtained with the HIV-positive panel study.

From the beginning, or for many years, CDC has been collecting data, very serious interviews. And this was presented at a workshop on panel suitability in '98 by Kenneth Clark--actually, a copy of his slides with me--showing very nicely the changing risks of donors that are found to be positive after they donate blood.

The objective of the study was exactly that, of identifying why did people go through the screening and were able to donate. There are a couple of figures that are very

important there. One is that today, this was '97 and I believe that today this is actually more true, only half of the HIV-positive donors are males, the ones that donate successfully and we detect them as positive.

The second thing is that, among those that are males, only about 30 to 40 percent are the ones that reveal that they had risk behavior, sex with another male, in the past. Of those, 90 percent of them had had risk behavior in the past year.

So I would love to see your model include some of that data and revised estimates because I believe, just in my mind, trying to divide the numbers, that we would not see a real difference between the five years and the one year.

Thank you.

DR. HOLLINGER: Thank you.

Dr. Linden?

DR. LINDEN: One other question, thinking about your calculations and your model, you are suggesting there are 62,000 MSMs out there who would really like to donate blood and are not able to right now. So January 1, we say, okay you can donate.

You are looking at calculating the number of units that could get into the system per year, but if we suddenly made a change, this is basically a one-time thing, assuming they would all come out of the woodwork and say, oh, yes;

here I am.

In, say, 2001, they would come get tested and then, after that, presumably, a second test is going to take care of the problem with the errors because, basically, you would cull out those who are really positive and were somehow missed.

So, on an ongoing basis, do you think the number might be less and that this is really worst-case scenario of the first year you make the change? Can you just comment on that issue?

DR. DAYTON: Absolutely. I did mention that although I am not sure how to best quantify it. But, basically, as people come in and get tested and they get weeded out for prevalence, the effect of prevalence does go down, let's say, after the first year, just as you described.

But I find it is a hard number to calculate. Also, opposed to that is every year you now have another 20 percent of that population coming in. But it is a totally correct consideration.

DR. HOLLINGER: Question for Andy?

DR. BOYLE: Yes. One thing I am a little confused on after hearing this. Are you trying to establish a policy of a five-year deferral regardless of what the question is, or are you trying to establish a three-year deferral with a

five-year question?

In other words, let me phrase it differently. If you are trying to establish a five-year deferral policy, would that mean that we would be developing questions that would accurately capture that even if we had to say seven years, or ten years?

DR. DAYTON: There are a couple of things implied by your question. One is what we are asking for and two is what will happen if we do something. My analysis addressed what would happen if we did something. So the analysis I gave you said what would happen if we did the five-year deferral policy.

The question we are proposing to the committee is do you think that the data supports this new policy or suggests this new policy. At that point, you need to take into consideration the other elements you have brought in on how well the questionnaire works.

This really comes back to what Jay mentioned and what I added to, is that we expect the new question to work as well as the old one does, relatively, for what it tries to do. I think that answers your question. If not, pin me down more.

DR. HOLLINGER: Dr. Mitchell?

DR. MITCHELL: I am still trying to get clear the current number of people who test positive. Is that around

the 12 to 14 people per year?

DR. DAYTON: Do you mean the number of units that appear at the blood bank and get tested and are HIV-positive.

DR. MITCHELL: Yes.

DR. DAYTON: That number has been dwindling over the years. It is typically around 1,000. I think it is down to 800 or 900 now in the last couple of years. Then, a few years before, it was up around 1,200. That would be per the entire whole-blood industry, the 13 million or 14 million donations per year, not including the plasma industry.

DR. MITCHELL: I think your analysis is very good. It is very, very conservative, but I think that it is very good to have that kind of analysis. Thank you.

DR. HOLLINGER: Dr. McGee?

DR. McGEE: I am a little bit confused about what the final issue is. In this multiplicative model, everything has errors. None of them are taken into account. We end up with a number of roughly 2 out of 60,000.

Let me just ask you; suppose you are off by a magnitude of 5, which is not unreasonable. I could give you some scenarios. Then, would you still make the same recommendation, if you had come up with ten cases instead of two?

DR. DAYTON: I am truly not avoiding the question, but whatever we take into account, I am not in the position of making a recommendation, and we are seeking a recommendation from the committee. The reason I am doing that is because it is a very tough question to answer and I don't have an answer.

DR. McGEE: I thought you had kind of told me that things were safe as long as it was 2. Your number was 1.7-something.

DR. DAYTON: When we first started analyzing, and this is kind of historical, we didn't realize the release-error rate was going to be such a problem. If it weren't a problem, if you just looked at test condition errors, for instance, then the errors are very, very low and probably pretty safe.

DR. McGEE: The question from the floor, one of your estimates, he thought, was off by a factor of 3.

DR. DAYTON: I absolutely agree. We don't have any better estimates. I have tried to make that point very clear and I am glad you brought it up because I don't think it was clear. These are very "iffy" numbers and, unfortunately, it is all we have to go with.

DR. HOLLINGER: Dr. Chamberland?

DR. CHAMBERLAND: I have a question for the at least two statisticians that I know are on the committee.

Is there a way to work with this model building into it some range of errors for each of these variables so that you can come out with I would assume a range? You are not going to come out with a point estimate--or a point estimate with some sort of a range. I think the point you raise is a good one because even though it may not be a FDA's intent to do this with coming forward with a very low number that would seem reassuring but there are no confidence intervals, there is no error range around these estimates.

Is it possible that work that into it?

DR. McGEE: You start with 1.4 million. It is probably done on a small survey, who knows what 95--the error is to that, but these multiplicative things, you can derive the standard errors as you go.

DR. DAYTON: One of the reasons we have not dedicated ourselves to actually pinning down all those numbers, because you could do a statistical analysis--the errors associated with many assumptions are probably going to be even greater than what the statistics tell us. It would be helpful to know the statistical numbers and what confidence intervals they represent.

But I can almost guarantee you that many of our assumptions are going to introduce even bigger errors such as how well is the questionnaire going to work, how well does the questionnaire currently work, what is the behavior,

how do you define MSM behavior?

It is a daunting task, but you are quite right that, in theory, it is doable. But it is a heroic undertaking.

DR. STUVER: I think beyond just the statistical error that might exist, so you get a 95 percent confidence interval based on that, you can do some kind of sensitivity analysis where you change your estimates given what variable numbers there might exist from different sources of data just to get a range, a sensitivity range, as opposed to purely statistically related to that error.

DR. McGEE: Some of the numbers in here are pure guesses.

DR. STUVER: Exactly.

DR. CHAMBERLAND: This very well may, and should, come up in the committee's larger discussion, but I think why we are more or less stuck with this is that this is the approach FDA has chosen to present this question to the committee. It is largely through a mathematical presentation.

There have been supporting epidemiologic data and this NAT testing data, all of which I think is very relevant and germane and we need to discuss, but this has primarily been funneled to the committee, at least in the FDA's approach, through this mathematical model which I think, at

best, we could say might be incomplete or could be amplified.

DR. DAYTON: When we began to reexamine this in 1997, we began to assemble a lot of data about behavior, MSM behavior, risk behavior, prevalence, incidence, et cetera, et cetera. It soon became clear to me that at least I felt the only way I could bring kind of a structure to the decision-making process is to actually say, "All right; we are going to change the policy. What changes is that going to introduce?"

And that necessarily leads into this kind of analysis. I think all of the weaknesses of that analysis that have been pointed out are truly weaknesses. Again, as is so often the case in this situation, we need to make tough decisions, science-based decisions, and our decisions are often necessarily running ahead of where the data is ready to take us with a lot of assuredness.

DR. HOLLINGER: We have two final questions and then we are going to take a break. Dr. Simon and then Dr. Kleinman.

DR. SIMON: I am certainly not capable of discussing the statistical issues but it seemed to me that Dr. Dayton's analysis was framed so that it would sort of a worst-case scenario, in which case, hopefully, it has been biased--you say that is not the case.

DR. McGEE: That is not the case at all.

DR. SIMON: Because that is the way I interpret it, as being biased as sort of the worst thing that could happen, what would that give you?

DR. DAYTON: I see a lot of nodding heads here. That was our intention, but the only way we could approach that is, given a choice of two numbers, we chose the worst-case scenario number. But, again, that is not the same as doing a good statistical analysis.

DR. McGEE: You did what you said. You picked one of two numbers. But the second number also had error involved in it so there was a worst-worst case, then, if you will. So this is what they thought among a bunch of point estimates. Each period gave them the biggest answer. But that is not the same at all as a sensitivity analysis or as looking at the pure error in the model.

DR. HOLLINGER: Dr. Kleinman?

DR. KLEINMAN: I just wanted to comment, though. Someone suggested a sensitivity analysis which I think is a good idea, but on a very cursory level, it seems like the model is most sensitive to the release-error information. I think that release-error information--again, it was driven strongly by the hospital-based release and we really don't have a lot of data.

We have data from one year from New York State. I

really do think that is high and I really think you would have to have a release error now on two tests. Even if that hospital was sending its testing out, it would now get an HIV antibody test result back and it would get a NAT test result back, and it would have to take the opportunity to misinterpret both of them for that unit to get out.

So I don't think the release error adequately accounts for redundancy. I think, clearly, at least in your analysis today, it was most sensitive to the release error, and that is what jacked the numbers up. So I really think it might be nice to have an overall standard-error statistical analysis, I bet if you do that, the range is going to be somewhere from zero units a year to 10,000 units a year, or some huge number that won't help you in decision-making.

So I think we have to work, just as we do with lots of blood-safety decisions, with the best data that we have and, if there are large errors, then we have to use common sense and we have to use the impressions of informed individuals.

So I don't think we can go beyond that. Again, I think that you have taken the most conservative numbers and you are even taking a five-year deferral which, I think, goes well beyond what the scientific data indicates would be necessary.

DR. HOLLINGER: We are going to take a twenty-minute break and meet back here again at 4:25, and we will have the open public presentation at that time and then go into discussion.

[Break.]

DR. HOLLINGER: We are going to have the open public presentations. There are four of them that I know of. The first is Dr. Katz for the AABB.

Open Public Hearing

Presentation

DR. KATZ: I wanted to take a brief opportunity to add my kudos to Dr. Hollinger for his performance as chairman of the committee, most particularly the almost metaphysical ability to change questions, an activity I tried to engage in during my tenure and was never successful at, and to note to the committee that I am very aware of the difficulty of the issue that you are being forced to deal with and just to say that I am glad it is you and not me.

The American Association of Blood Banks is the professional society for over 9,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,200 institutional members including independent and Red Cross blood collection centers, hospital-based blood banks and transfusion services as they collect, process, distribute and transfuse blood and components and

hemopoietic stem cells.

Our members are responsible for virtually all the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety and availability of the nation's blood supply.

Since 1977, the AABB has advocated that the deferral period for male-to-male sex be changed to twelve months. Modifying the deferral time period for male-to-male sexual contact to twelve months will make that deferral period consistent with the deferral period for other potentially high-risk sexual exposures and will improve the clarity and consistency of the donor questions.

The potential donor will be directed to focus on recent rather than remote risk behaviors and should have better recall for answers to the screening questions. Retention of a specific deferral for males who have had sex with other males is based upon extensive scientific data that document a significantly higher prevalence and incidence of HIV and hepatitis B in this population.

The 1977 time frame for questions concerning male-to-male sex was implemented at a time when the data regarding HIV transmission were more limited and HIV serologic tests were less sensitive than the current assays. It is now possible to use a large body of scientific

evidence concerning the natural history of HIV infection and serologic testing to reexamine the appropriate time intervals for such a deferral.

Studies by many investigators--much of that you have heard today--demonstrate that FDA-licensed and required HIV laboratory screening has reduced the HIV seronegative infectious window to an average of 16 days. In clinically, asymptomatic individuals, HIV infection will result in the development of HIV antibody for p24 antigen in less than one year in all cases.

In healthcare workers exposed to HIV-infected blood by needle-stick injury, the interval from exposure to seroconversion was less than six months in 95 percent of cases. In two cases, the intervals were 213 days and between eight and nine-and-a-half months and, parenthetically, some of that analysis was done with assays less sensitive than those currently used in blood-collection facilities in the Year 2000.

HIV NAT performed in minipools under IND has further reduced the seronegative infectious window to approximately twelve days and, as we have heard from FDA today, any change in the donor deferral policy in this area awaits licensure of NAT.

Accordingly, with regards to Dr. Dayton's presentation, we have just a few comments that were not in

our written statement but that do not alter our bottom line. First of all, the number of gay donors entering the blood supply was estimated to represent 5 percent of that population, approximately, and we believe this represents at least a three-fold high estimate based on donation histories in the general population.

As Dr. Bianco told you in New York, approximate 1.5 percent of age-eligible donors actually donate. We have heard no data to suggest that gay men would donate more frequently. Current incidence and prevalence data on HIV seropositive blood donors demonstrate that less than half of those donors in the HIV donor study are, in fact, male and approximately half or less of those admit to MSM behavior.

Finally, the seroconversion outlyers that are referred to in the healthcare worker studies, once again, in part and in general, rely on earlier generation testing.

Accordingly, the AABB respectfully encourages the committee to recommend to FDA a twelve-month deferral in lieu of dating questions back to 1977. We believe this modification should have no measurable detrimental effect on the risk of transmitting HIV through transfusion or the safety of the blood supply.

Thank you for your attention.

DR. HOLLINGER: Thank you, Louis. Any questions of Dr. Katz? Dr. Dayton?

DR. DAYTON: Not a question, but just a response. I appreciate you pointing out that the rate of donations by MSMs, as measured, is three-fold lower than the number we were using. That may, in fact, be the case.

However, there is also the consideration that it is known very widely that MSMs are strongly discouraged to donate for any MSM behavior since 1977 which means, basically, any MSM at this point. That probably results in a lot of self-deferral. One presumes that word will get out. If we change a policy to a five-year deferral, one presumes that the word would get out and that the donation rates would increase.

So I think what you pointed out is very valid and, again, we used conservative estimates. But even if you accept your numbers, there is an error in the other direction that we have to worry about as well.

DR. HOLLINGER: Thank you.

The next presentation is by Dr. Adrienne Smith of the Gay and Lesbian Medical Association.

Presentation

DR. SMITH: Thank you. I am a little hoarse today but thank you very much for allowing me to speak. I really have enjoyed this afternoon's scientific discussion. It is very interesting.

I just want to make a brief statement. On behalf

of the Human Rights Campaign, the Lambda Legal Defense Education Fund and the Gay and Lesbian Medical Association, we urge that you carefully consider advising the FDA to alter the guidelines excluding male donors who have had sex with another man even once since 1977 as has been discussed a number of times.

First and foremost, we stand united in our belief that the integrity and safety of the nation's blood supply must be preserved and maintained. Any change in the guidelines governing the donor deferral must be based upon current medical expertise and up-to-date testing technology, just as licensed NAT would provide.

We are not supportive of any change that would meaningfully increase the risk exposure to recipients of blood and blood products. At the same time, the committee's action should be guided by a fundamental public-health principle that would ensure a simultaneous commitment to both safety and fairness.

That principle is like risks should be treated alike, which is just what Dr. Katz was, I think, alluding to. This maxim exposes the central flaw in the current donor deferral policy which tolerates a wide range of risks associated with heterosexual sex while imposing a zero tolerance attitude towards MSMs regardless of the risk associated with individual behavior.

For example, under the current policy, a man who engaged in one act of oral or anal sex with another man in 1978 and had been celibate ever since then would automatically be deferred while a woman who has had unprotected anal sex with multiple partners over the past year with no knowledge of the personal histories remains in the donor pool.

Similarly, a man who had oral sex with another man in 1979 would be excluded whereas a woman who had unprotected anal sex with the same man thirteen months ago would be allowed in the donor pool. A more rational policy would address donors who engage in risky heterosexual behavior with partners whose histories are unknown and consider the status of MSMs whose behavioral histories do not present any meaning risk to the blood supply.

By focusing on the source of the risk rather than the size of the risk, the current policy stigmatizes gay men. The donation of blood as well as other life-saving products such as organs is viewed by many as a civic duty and a responsibility.

At a time when the demand for blood and blood products is outpacing the availability, healthy gay and bisexual men are repeatedly turned away from donating blood despite messages from mass-media campaigns appealing for donations.

In addition, many gay men are shocked to learn that they are automatically deferred when eligible blood donors are typically described as being healthy, at least seventeen and weighing at least 110 pounds.

Gay men often first find out that they are eliminated automatically as donors when they are turned away at a blood drive which is frequently at the place of employment, a local community center or at a church. Our organizations have heard from many men who have encountered stigmatization by being singled out because of their sexuality despite the fact that they consistently practice safe sex or are in a long-term monogamous relationship.

Rather than reaffirming the current blunt-instrument--namely the questionnaire--we ask the committee to consider a revised panel questionnaire that focuses on more refined and specific behavioral criteria like recent sexual histories that include unprotected anal sex or a significant number of sexual partners over the prior year. Such an approach would allow blood banks to have reasonable distinctions within the MSM donor pool and would weed out heterosexuals whose behavioral histories would create a meaningful risk for HIV and other blood-borne pathogens.

We also urge the committee to encourage the development of pilot projects to test the effectiveness of different types of donor questionnaires. Furthermore, this

committee's decision would reflect development in testing technology that has dramatically reduced the risk of both window-period donations and prevalence-related infections due to test error.

Given these developments, the committee should consider moving the current lifetime deferral ban on MSMs to a time period that reflects the impact of these developments in medical technology on blood safety. Moreover, the introduction of NAT testing will reduce the risk of infections due to test error by adding another round of testing to the collection process.

Finally, while we understand that the Blood Product Advisory Committee deals solely with the regulation of blood and blood products, we hope that any decision made by this body will not have an adverse impact on decisions made elsewhere within the FDA on the donation of other biological products, namely reproductive tissue.

Given the availability of quarantine and retest procedures, the relative risks associated with reproductive tissues are separate and distinct from the issues before this committee today.

I wish to thank you for your time and consideration.

DR. HOLLINGER: Thank you, Dr. Smith.

Any questions of Dr. Smith? If not, the next

speaker is Dr. Haley from the American Red Cross.

Presentation

DR. HALEY: Thank you, Mr. Chairman and members of the committee. I am pleased to be here today to discuss donor-deferral policies relating to males who have had sex with males even once since 1977. My name is Dr. Rebecca Haley and I am the chief medical officer of the American Red Cross.

Red Cross Blood Services is the nation's largest supplier of components serving more than 3,000 hospitals nationwide. Last year, we collected more than 6 million units of whole blood through the generous donations of approximately 4.5 million healthy donors.

Each day, 22,000 donors visit one of the 400 Red Cross blood-donation sites. Approximately 1 million liters of plasma are also recovered each year from our volunteer blood donors and are processed into life-saving plasma derivatives that are distributed to hospitals, hemophilia treatment centers and other providers.

For more than 50 years, the Red Cross has been an innovator and a leader in transfusion medicine and research. It is within this context that I am here to comment on the MSM deferral period. The purpose of the MSM question on the blood-donor record form was and remains to identify risk behaviors that pose a threat to the blood supply.

Advances over the last fifteen years in viral testing methods have dramatically decreased the risks of transfusion-transmitted disease and extensive research has provided much more information about the early phases of HIV infection.

Nucleic-acid test, better known as NAT, is now being implemented at the Red Cross under investigational new drug status and will further reduce the HIV and HCV window period. There are two fundamental factors regarding this national public health resource, the blood supply, which must always be considered.

First, the safety of the blood supply and the patients we ultimately serve much be our number-one policy. Second, it is a public-health issue not a social-policy issues. Their worst-case estimates of the impact of modifying the MSM deferral criterion to a five-year period. At a previous workshop, the CDC suggested, and Dr. Dayton reiterated here today, that approximately 60,000 previously deferred individuals might donate blood annually.

From that particular pool, about 1,200 units HIV-positive blood would enter the system for testing each year on a CDC-based estimate of HIV prevalence of 2 percent, which we just went over, in this population. We cannot change our procedures in a way that would result in increased numbers of infectious donations in our blood

supply.

The FDA, the AABB and America's Blood Centers and the American Red Cross have, together, invested hundreds of millions of dollars and immense effort in reducing the risk to the nation's blood supply. We have created one of the safest blood supplies in the world. Introducing, theoretically, over 1,000 HIV-positive units into the system prior to testing would be expected to raise risk even considering our layers of safety from the blood-donor-record questions to the current tests that screen HIV-positive units out of the blood supply.

Modifying the MSM deferral criterion to five years would result in a small, but measurable, increase in the possibility that infectious blood might be released. If the Public Health Service could assure us that introducing previously deferred donors into the pool could be accommodated with out increasing the risk, the American Red Cross would support appropriate action to do so.

The worst-case scenarios that were presented here by Dr. Dayton would give back the realized gains by NAT in the last year. The American Red Cross supports the current FDA and AABB comprehensive donor-questionnaire review. There are no current comprehensive studies related to modifying these questions.

We believe that each of the 37 questions that

relate to donor deferral should be systematically addressed regarding timeliness, relevance and, in relation to the current science and whether these questions properly complement each other based on our current biobehavioral research.

We urge the Blood Products Advisory Committee to advance the behavioral, medical and technical research to appropriately evaluate all the questions asked of potential blood donors. We urge the FDA to fully license NAT testing as another means to reduce risk to our patients.

Until data are available to show that changing the MSM deferral criterion will not elevate the risk to the nation's blood supply, we cannot support this change.

Thank you for the opportunity to provide the views of the American Red Cross on this public-health issue.

DR. HOLLINGER: Thank you.

Any questions of Dr. Haley?

DR. SMITH: My question to the American Red Cross is, in terms of the questionnaire, would you expand the questionnaire to include other risk behaviors that are outside the MSM or the gay community, which is what our point is? Like risks should be treated alike, and, at this time, they are not.

DR. HALEY: Our questions for deferral are based on data that were presented to the FDA by the CDC. The

practices that you are talking about and the population studies have not come up with an increased risk to the extent that this risk behavior does.

So if the CDC were to come to the FDA and say, "I have a new practice and it is obvious that this is a high-risk practice, we need a question," we would be the first to accept that.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: I appreciate being recognized. I just wanted to respond to Dr. Smith. The FDA is certainly willing and interested in improving the safety of the blood supply by expanding deferrals as applicable for heterosexual risk. We simply think that it is two different issues. If we can make progress with respect to MSM risk, we will. And if we can make progress with respect to non-MSM risk, we will. So that is point one.

Second, on point two, treating comparable risks comparably, I certainly agree with that. However, there may be a subtle misunderstanding that comparable behaviors always connote comparable risks. For example, we know very well that the multiple-partner risk among heterosexuals is quite different than the multiple-partner risk among gay men for the very simple reason that gay men are at a much, much higher HIV prevalence.

So, whereas I agree with the principle, we have to

be a little bit careful not to equate the concept of comparable risk with comparable behavior.

DR. HOLLINGER: Thank you.

Dr. Nelson?

DR. NELSON: I think that the one figure you cited would disturb me, too, if there were an additional 1,200 HIV-positive prevalent cases introduced. But I think that figure was a derivative--I am not sure that estimate is correct or even near correct.

Basically, I think, and Dr. Dayton can correct me, it was based upon the 8 percent prevalence of men who have sex with men 75 percent of whom know their status, 25 percent of whom don't. But it wasn't based upon a man who has not had sex with a man in the last five years, but prior to that, as to what their prevalence would be.

I think that figure is not known. I think it is likely that it is much less than the overall prevalence, maybe far less. Am I misinterpreting Dr. Dayton's model?

DR. HALEY: Our concern is we don't know that. I think if you figured this back over time, and Dr. Dayton can comment on this, you would find the place where the risk went to baseline that we have in every donor. At that point, we are ready.

DR. DAYTON: You are correct in how we came up with that number. We didn't find data on prevalence rates

on five-year abstention MSMs so we just used the best data we could find. So you are absolutely right.

DR. HALEY: The other thing is we do have a penetrance of 5 percent in a lot of our communities that are giving blood. I know we are not New York City but we have some other places that do, actually, have that high a penetrance of donors.

DR. NELSON: Prevalence?

DR. HOLLINGER: Could you respond again to that?

DR. HALEY: I said the penetrance of donors into the available population, not prevalence. I am saying we have 5 percent of some communities who give blood. Penetrance is what we call that--of blood donation into the community of available donors. I'm sorry. I introduced a new term.

DR. HOLLINGER: Dr. Busch?

DR. BUSCH: I think it was useful that you summarized the numbers because I think I, personally, got lost in the earlier presentation in terms of how we end up with that incremental risk of potentially 1 to 2 additional infections. It does factor, from the 60,000 potential new donors who will be eligible who had remote male-male sex times the 2 percent which gives you that potential 1,200 incremental HIV-positive donations.

Then that gets multiplied by this potential error

rate, particularly driven from hospital exposure which, theoretically, according to the analysis, results in one to two additional releasable units that would add to what we are saying, or only about ten currently per year, our current risk.

So this worst-case scenario, again from one perspective, could argue that we would increase risk by 10 or 20 percent. I would agree that is almost comparable to what we have achieved through adding HIV NAT. But I really, personally, do not believe that we will see anything close to a more than doubling of our HIV-positive rate were we to relax this criterion.

I think these estimates are very conservative and, applying a 2 percent rate to the people who will become eligible, I think, 60,000 additional eligible people is an over estimate, et cetera.

But your proposal that says wait until we have the data, how do we get the data until we can do studies in the context of revised questionnaires? A proposal that says wait until there is data to address these things is basically saying don't address changing them ever because, until we have a mechanism to implement studies--the measurement is right there.

We implement it and if we don't see a significant increment in HIV prevalence rate in our donors, then it says

that there 1,200 estimate was just completely off the wall.

DR. NELSON: I would suggest that if--and I am not sure whether the committee will vote to change it, but if there are any changes in the donor questionnaire, that there really be a very active effort to look at the prevalence. If there is a significant increase, that could be detected in probably a couple of months, that level of change.

I suspect that there won't be, but that is just kind of a phase IV--it could almost be clinical trial, although you can't do a clinical trial to find a negative result. So we would have to change and see what happens, I suspect. Ethically, it would be tough to sell this.

DR. HOLLINGER: Dr. Dayton?

DR. DAYTON: In theory, we could, if somebody had the money, came up with the funding. You could support a population survey to actually survey MSMs and determine their MSM behavior, which is no small feat. The numbers we are dealing with, you probably could get some numbers, and whether that 2 percent, or 8 percent reduced to 2 percent, is realistic or not.

So I think that actually is an addressable problem, not today, obviously. But, given the daunting nature of a lot of the problems we face, I think that is one of the easier problems to solve if there were funding.

DR. HOLLINGER: Thank you, Dr. Haley.

The next speaker is Dave Cavanaugh with the Committee of 10,000.

Presentation

MR. CAVANAUGH: If it okay with you, Mr. Chairman, I will just stay here. I only have a few points, and that was a tough exchange to follow. We are kind of in a tough position, too. We are an AIDS organization. We work a lot with groups representing the MSM population and plenty of others. We know their desire to contribute to the health of their peers.

We also don't want anything in the blood that would come near the holocaust that we have already experienced or anything like it. So we are very interested in the committee's deliberations on this issue. We heard the presentation that was given three years ago by Mr. Dayton on this issue. We had presented at that meeting and felt that absolutely no change should be made without serious study.

We were very surprised at some of the assumptions that were made then and some of them have not been changed. We are pointing out, as others have this afternoon, that assumptions regarding the size of the MSM population itself, estimated at 4 million, some might say 11, the number who have abstained for five years, which was fairly loosely derived, the number who would be expected to come forward

after not being able to help their peers for so many years being estimated at only the background rate for the general population, just to name a few, would be a considerable problem.

And there are those who would give blood regardless of what the questionnaire asks them. There is deliberate response to the questions wrongly by lots of populations, but those infected, in many ways. We find that tagging and presenting data on those who turn out to have an MSM background who are caught only by virtue of an HIV-positive test underestimates the percentage of people who do that because of all the HIV-negative ones that got through.

So, pointing to response to the questionnaire in one case but not clearly looking at some of the data on questionnaire responses, even now that we have got the U.K. deferral question, now that we have the other questions dealing with long-term abstention, seems to be a missing and necessary part of this review.

We are very pleased to see the GLMA here to present some of the perspective from a scientific standpoint from the experience of the community and we wish there was more of the questionnaire research community presented here, too. We are also kind of stunned by the lack of confidence intervals, even though multiplying them does greatly increase the variability of the estimates. That has to be

done anyway.

As I said, tossing out the number 11 million and saying maybe--let's just say that the percent coming forward is the same, the percent abstaining for five years is the same, but what about the number coming forward not being 62,000 but 162,000. The HIV rates therein could be all over the map.

Now, we are concerned about identifying the group, not the behavior. Anyone, male or female, engaged in risk behavior should be deferred appropriately. We would refer you to Ms. Smith's suggestions as to how to do that. A sexual history is really what you want rather than, "Do you self-identify with a certain behavior?"

Anybody who has worked with Hispanics knows that identification of MSM behavior is very difficult. Other methods are needed rather than just tagging with a label.

Supply; to back up a little bit, the point of this exercise is to increase the supply. Supply can be increased in many other ways and much further than by admitting potentially high-risk groups. High-risk donors may carry other risks not yet identified. We need data on cumulative exposure to pathogens. We have concerns about what was presented this afternoon about HHV-8.

In general, we would encourage the committee to proceed very carefully with this. We note that the question

is worded, "Should the FDA consider." We have no quarrel with that. Consideration is actually what this needs, a much brighter spotlight on the question.

Thank you.

DR. HOLLINGER: Thank you. Any questions to Mr. Cavanaugh? Celso? I didn't have you on here, but that is all right. You can get up and speak if you want. You should have been on here. I just didn't have it before me here. Sorry about that. Dr. Bianco for the America's Blood Centers.

Presentation

DR. BIANCO: I exist. America's Blood Centers, or ABC, is an association of 75 not-for-profit community-based blood centers that collect nearly half of the U.S. blood supply from volunteer blood donors. We thank FDA, CBER, for the opportunity to make public comments before the Blood Products Advisory Committee.

ABC members urge FDA to modify the current lifetime deferral of men who have sex with men since 1977 from donating blood. We believe science supports limiting deferral to a year to make it consistent with other deferrals related to risk behavior; for example, sexual contact with a prostitute.

ABC members have expressed this position before BPAC and at FDA-sponsored workshops. The lifetime MSM was

introduced in the early '80's when little was known about the epidemiology of HIV and the screening assays required further refinement. ABC members are comfortable with this recommendation because the last 17 years of donor health history and fifteen years of laboratory screening have seen major changes.

Donors receive clear and unambiguous information about risk behavior, HIV transmission and why they would not donate to obtain an HIV test results. Individuals with one HIV-positive test in their lifetimes are permanently deferred. Medical history became more rigorous with direct questions about risk behaviors, venereal diseases, contact with individuals with infectious diseases, use of I.V. drugs, and so on.

More important, significant technological developments led to a reduction of the window period for HIV assays from an average of 56 days at the beginning of HIV testing to an average of eleven days with the introduction of NAT. There is evidence from animal models that this window is even shorter, and we heard this from Dr. Busch today.

ABC members are concerned about the unintended consequences of the current deferral criteria for MSM, lifetime deferral for a man who had sex with another man once, even once, since 1977. The question focuses attention

on events that took place more than twenty years ago instead of events that occurred within the currently known window period of days or weeks.

Donors may repress or deny these old events. The question is inconsistent with similar risk behaviors that are deferred for one year. The logic of the current deferral is difficult to justify because risk of exposure to HIV and other infectious diseases is associated with behavior, not sexual preference.

Individuals who respond affirmatively to risk-behavior questions use confidential unit exclusion, use post-donation callback, and they do not present additional risk to the blood supply because they are deferred, permanently or temporarily. I didn't put in the statement, those who do not reveal risk during medical history and have risk will not change regardless of the changes that we make in questionnaires or in what we do.

Obviously, individuals who indicate that they had a positive HIV test in the past are deferred permanently. Actually, this assumption that has been discussed and the 1,200 HIV-positive individuals that could potentially donate is an assumption that is made assuming that 100 percent of those individuals will come and they will pass through medical history, they will pass through the entire screening system, which many of them do not pass today.

So I, again, do not believe that this number--I believe that the number is at least an order of magnitude smaller than that. Medical history can be improved in order to become more effective. We are happy to note that an AABB task force with participation of ABC, FDA, ARC and other organizations is addressing this issue.

In our opinion, the change in deferral will not increase risk. Thus, we request that FDA modify the current lifetime deferral of males who have had sex with males since 1977 from donating blood to a one-year deferral.

Thank you.

DR. HOLLINGER: Thank you, Celso. Any questions for Dr. Bianco?

We have one final person who asked to speak. It is not specifically this topic, but it was earlier today and he was promised that he would be given a position. So we are going to do that. Derrick Robertson for the Hemophilia Treatment Center.

Presentation

MR. ROBERTSON: Good afternoon, Mr. Chairman and members of the committee. Thank you very much for allowing me this time to present to you. I am especially appreciative since this is somewhat off the topic which is under consideration currently.

My name is Derrick Robertson and I represent

fifteen hemophilia treatment centers across the country. We are particularly concerned about the current supply situation or recombinant Factor VIII products. This situation is reaching critical levels as we speak with centers not being able to get product as they would normally be able to.

We have centers that are down to four vials for recombinant product and they are having to take steps to switch patients from recombinant product back to plasma-derived products. We have centers that are changing treatment protocols and this is very concerning.

There are a number of events that have taken place over the past few months which we feel has contributed to this situation. Genetics Institute, who recently got a product licensed, Refracto, by the FDA has decided that they will not be able to bring that product to the U.S. market until sometime in 2001. Baxter Hyland Immuno has had difficulties in getting a new suite license and that has limited their supply.

Bayer has decided to launch its newly approved product through a direct marketing program and we are not sure exactly what the availability of the Aventis product is going to be in the coming weeks.

We are particularly concerned with the Bayer direct program which is going to be launched because we feel

that that will exacerbate the supply situation in two major ways. The program, as it has been outlined, intends to allocate to specific patients specific amounts of product to the exclusion of those that are not able to enroll due to the limited availability that Bayer may have.

This we feel might create a situation where product is allocated to one particular patient where there is another patient who would need product but is not able to get it. The second way we feel this will adversely affect supply relates to the inpatient market. Bayer direct, as proposed, does not intend to sell to hospitals and we feel that that is going to put an added burden on the other manufacturers to make sure that large hospitals have a supply of clotting factor.

As you are aware, in the treatment of hemophilia, it is extremely important to treat the bleeds as quickly as possible. We do not want to have a situation where patients end up in an emergency room or in a hospital and are not able to get immediate treatment because they do not have product.

While it might seem that the hospitals may have other alternatives to go to, over the years, the market for recombinant product has always fluctuated. One thing that has become clear is that we need all the manufacturers to be participating in the marketplace so that there is some

amount of product available for everybody.

We are concerned that if one manufacturer is not doing its part to be a part of the supply, that that will adversely affect the situation. We are concerned about what will happen if this does continue in this way. We are concerned that patients will be forced to go back to plasma-derived products which will go against a 1995 recommendation by the National Hemophilia Foundation's Medical and Scientific Advisory Council which recommended recombinant treatment, a recommendation which was endorsed by the Public Health Safety Blood Safety and Availability Committee.

We are asking that this committee look at this issue to make sure that if, indeed, there is a shortage, that this is a real shortage and that there is not product out there in the distribution channels that are somehow not getting to the patients or, if the product is tied up with the manufacturers, that the FDA work with these manufacturers to expedite this product getting into the marketplace.

I think another critical thing for the FDA to look at and understand is the decision-making process that goes into deciding how much product is coming into the U.S. market vis-a-vis the international marketplace. Understanding that will probably give a better determination and an understanding of how much product will be available

and when it is available.

We do not want to go back to a situation--even though the plasma-derived products have had an excellent record over the past many years, I think it is of concern, especially to the new patients, not to have to go back to a plasma-derived product.

Again, I thank you for your time and I am extremely appreciative for giving me this opportunity to present our position. Thank you very much.

DR. HOLLINGER: Thank you, Derrick.

We are going to move back to the topic at hand. Before we close the open public hearing, is there someone else that would like to say a word? Yes? Please give your name.

Presentation

DR. JACKMAN: My name is Dennis Jackman. I am the Executive Director for the Plasma Protein Therapeutics Association for North America. I wanted to take a moment here to address the questions about recombinant supply, Factor VIII supply.

First, I would like to state that the industry is working diligently to meet the needs of consumers and medical professionals recombinant factor VIII. We are concerned about making sure there is adequate supply to meet those needs.

We want to state that, over the longer-term period, supply has remained relatively steady or, in some cases, improved in certain months with periodic variation. We do recognize there is some variation right now during this period and we also recognize that demand is increasing. I actually have a chart that could be shown on an overhead, if we had a moment, that would show the supply for the last eighteen months. But, in any case, it shows a relatively steady situation and we know that, right now, we have a tightening situation as well.

But investments have resulted in recent increased capacity and new formulations. First of all, Baxter's Thousand Oaks facility was approved earlier. That increased their capacity by up to 40 percent. That helped the supply situation. Bayer's new formulation was approved as well--that is Cogenate FS. That has increased the overall supply of factor in the U.S. market as well.

Baxter is working diligently to try to get approval of a new suite which will also increase the supply of recombinant factor VIII. All those things combined ultimately will have a result of improving the supply situation and ameliorating the situation over the long term.

We also cannot forget that we do have high-quality plasma-derived products available as well for those patients who want to utilize them.

Thank you very much.

DR. HOLLINGER: Thank you.

If there are no other comments on the MSM topic, then we are going to close the open public hearings for right now and open this up to the committee discussion.

Committee Discussion and Recommendations

DR. HOLLINGER: Who would like to start out? Dr. Linden?

DR. LINDEN: A couple of things. One is that in the model that Dr. Dayton presented, it seemed like the vast majority of the risk was attributed to post-analytical or release errors. One way to potentially get around that would be if people could basically get pre-screened before the donation so you would have two tests rather than one.

I was wondering if Drs. Bianco, Haley and Katz could, perhaps, comment on the idea of pre-screening and whether that is anything that could be feasible.

DR. HOLLINGER: Yes; I think these are important questions. The issue would be of asking a question to individuals, have you ever had sex with another male ever---one of the "ever" questions--and then go on from there about some timing if you want, but the question is, if they have, and they fit into that time span, if there is a time span that is chosen, then one issue would be to screen them and then have them come back at another time if they are

negative for donation, similar to what, perhaps, is done in the plasma industry and other things.

So would somebody like to take on this issue because it could be an important issue.

DR. KATZ: We could talk about this for hours. The source-plasma industry has done this as part of their quality plasma program in a certain sense with a 60-day hold to make sure that people come back, a high percentage then been retested before anything is released.

Whole-blood collection these days is done in some fixed sites but lots and lots on mobiles, at corporations and elsewhere. So the logistics of a separate visit to give us a sample, be tested and then, at subsequent visits, at whatever intervals, which may be as long as six months or a year, have always been considered daunting and it has not met with great favor.

To say it is impossible I think would be wrong, but I do not think it would positively impact the adequacy of the blood supply to essentially not draw donors at their first presentation.

DR. HOLLINGER: Dr. Haley?

DR. HALEY: I think this has both merit and difficulty attached. This might be the form of the study that we keep talking about. When we keep batting back and forth, well, is this the rate, isn't this the rate, that

would certainly answer the question.

The other objection to singling out and identifying these donors as labeled or different might, certainly, be valid if we had a group of donors that we drew and a group of donors that we took a tube on in a mobile unit.

Again, with the right kind of situation, we might be able to overcome that. I think that our electronic control of donor records may be sufficient that we could probably handle, with some planning and some timing, being able to test a sample and then be able to mark a record as "MSM tested, okay."

It is certainly an interesting thought.

DR. BOYLE: Dr. Linden, I think that concept has been raised on a couple of occasions but I just want to remind you that approximately 85 percent of the blood donors are repeat donors so they are in that process. They have been screened before. They come back. Actually, one of the efforts that we have in medical history is not to torture them again with all these sets of questions in the same way that we do today every time they come back.

The second thing is, in terms of logistics, those donors donate approximately 1.5 to 2 times a year, on average, so that makes it a logistic problem. So we have about 15 percent of the donors that are first-time donors

that we try to attract into the donor base with the intent of replacing the donors in the pipeline that will get old, sick or will abandon the idea of donating.

So, essentially, the vast majority of the blood donors are repeat donors. They are continuously screened. I think that is the essence of the safety. Actually, Dr. Dayton, maybe we could divide these by 6 again because only 15 percent of what is added every year are first-time donors.

DR. NELSON: But, Celso, isn't it true that if you change the criteria for people who didn't meet the criteria before, they will all be first-time donors the first time they donate.

DR. BIANCO: Yes, but the number of first-time donors will increase from 15 to 17 percent or 18 percent. But, overall, the change in the donor base is going to be small.

DR. NELSON: No; but I think it is this population that we are concerned about; right? The 60,000 are the ones we are concerned about.

DR. BIANCO: No; it is the 1,200.

DR. NELSON: Yes; it is the proportion of the--

DR. BIANCO: That is correct. That would come in the first year. That would be part of the first-time donors. But they would be diluted again in the overall.

DR. HOLLINGER: Dr. Smith, would you like to respond to that, about how you think the gay or lesbian community would--is she here still? I guess she is not here.

Dr. Linden?

DR. LINDEN: On a different issue, the issue that Dr. Nelson raised about the prevalence in the people, men who haven't had sex with another man in five years versus the overall population, could somebody from FDA or CDC comment? My recollection is that, at the CDC meeting a few months ago, there were data presented on remote risks and my recollection is it was still quite high.

Was that consistent with the figures that you used, Dr. Dayton, in your model or am I completely misremembering that meeting?

DR. DAYTON: Maybe somebody else went to that meeting because I was not there. Anybody else from FDA?

DR. LINDEN: Dr. McCurdy agrees with my recollection.

DR. SIMON: I don't have the exact numbers, but I think they were pushed, the CDC speakers were pushed, if there was a group with remote risk that had lower prevalence. I think the issue was they didn't have such a group, they had no group in their studies of MSMs that had the kind of extremely low prevalence, but they didn't have a

sizeable group, as I recall, that was remote enough, I think, to answer this question.

DR. NELSON: I think this group with the remote--sex with another man--can be very heterogeneous. Two sort of outlyers, if you will, were, a), an adolescent or young adult who is experimenting and does not continue having sex with me. Another type of population would be one--a person who is in prison or is an all male situation where sex occurs. I would suspect that the risk would be different in those two.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: I can't recall specifically those data from the Atlanta meeting, but we do know that persons with remote risk of intravenous-drug abuse have a markedly higher prevalence of certain markers including hepatitis C than persons negative for that history.

So there is every reason to believe that, for chronic blood-borne infections, remote risks do matter.

DR. NELSON: But I am not sure about the adolescent. I think that is a different situation.

DR. HOLLINGER: Dr. Chamberland?

DR. CHAMBERLAND: Mine was more of an overarching comment following Dr. Linden's query about trying to, I guess, sort of evaluate certain parameters in the model that FDA has developed. Again, certainly with deference to the

statistical consultants that sit on the committee, if FDA wants to continue using this model as a framework for the discussion, and I think that is a very valid thing to do--I am not being critical of using a modeling approach, but my sense is that what you can do in these sensitivity analyses that have been put forward is that you can actually use them to assist you in determining which factors in the model exert the most influence on outcome.

If you could pull out of the model--I think, right now, there is a lot of confusion--not confusion, but people are bringing up a lot of questions about either the derivation of these estimates, their reliability, et cetera. So if you could do a sensitivity analysis of each of these factors in the model and maybe, as I said, it could point you in the direction as to what is influencing this risk estimate the most, maybe that at least could pare down whatever studies or research that you might need to pursue to get a better handle on it.

It has been presented as a large black box, but maybe it is actually just a couple of parameters that are really going to drive this.

I will, as I said, defer to the statisticians to help me clarify that, perhaps, a little bit better.

DR. McGEE: Personally, I think the whole analysis is driven by two numbers, the 1.4 million--this is my

intuition and you can disagree if you like--and the other is this assumption of prevalence and then the proportion who self-defer. So they decreased from an 8 percent prevalence to a 2 percent who would actually go in and donate.

You can see immediately that if it were really three-quarters who came in, you would multiply the risk estimates by 3. So I think those two numbers need to be pinned down.

DR. HOLLINGER: Dr. Simon?

DR. SIMON: I will just try to say a couple of words to kind of bring together the industry point of view. I guess, as you have gathered, the blood bankers are divided between the position brought to us by the American Red Cross of not changing and sticking with a deferral of anyone since 1977 and the other group has suggested the one year which gets to the like risk being treated like, and that is the 12-month period to cover all your various windows with the testing.

I think the FDA has tried to come in between those two, and I would actually speak for that approach, or at least for the approach of the question, because Dr. Epstein, I think eloquently, spoke to this issue at the CDC conference about the differences between incidence risks and prevalence risks and the concern about drawing from a high prevalence population.

So, from that point of view, one would want to go beyond the twelve months which we apply for the incidence risks to something that would also pick up the prevalence. I think the five years is a reasonably good compromise that I think, intuitively, should protect us safetywise.

From the point of view of the plasma industry, I think there is less feeling that this is going to make a significant difference in our number of donors. But I believe the plasma industry would go along with the change to five years. Of course, as has been pointed out with the applicant donor program and the inventory hold, we have dealt with almost all of the potential release problems, so that issue doesn't figure in in terms of test error. I think one can be more reliant on the test results to pick up any window case.

So I think if you put the whole thing together, and I know there has been a lot of talk about Dr. Dayton's model--I accept that it is flawed, but I think the problem is it is hard to get much better in terms of numbers or in terms of data that can support a position. I think, given all the data presented by Dr. Busch, I think the model, taking some conservative estimates, the weight of all the information that we have indicates that safety will not be significantly impaired at all by going to the five year.

I would speak for that as I think a reasonable

approach to the issue. I think it would achieve the concordance between the tissue regs and the blood regulations which I think would be very useful, to have a single standard.

I think that it preserves safety and moves us along in the right direction and, perhaps, some small number of individuals who do not present a risk would now be able to donate and contribute.

DR. HOLLINGER: I would like, for just a minute, if I could, get a feeling from the committee at this stage so I see sort of where we are a little bit. I am not going to shut off discussion but I would just like to know. I would like to know how many on the committee here, at least at this point, are in favor of a change in the current--I am not going to deal with five years, four years, three years, two years, one year and so on or anything like this, but how many people here on the committee so far feel that there should be a change in the question from having sex even once back through 1997.

I would like to see how many are in favor of at least making a change in that question. If you would just give me a feel.

[Show of hands.]

DR. HOLLINGER: Okay. So a fair number. It looks like the majority are. I wanted to start with that because,

if so, then--I don't want us to get bogged down in maybe five years or three years or one year as the question. The question states one thing, but it looks like the majority of the committee are certainly willing to have this question changed.

Now I would like to sort of open it up either way, with comments for and against, but other things, too. So I am going to start with Paul McCurdy and then come back here with John.

DR. McCURDY: When this issue came before the committee in 1997, I was in favor of making a change, thinking that either two or five years might be quite acceptable and would not result in an issue.

In the meantime, however, the HHV-8 situation has come to the fore and it is my belief, at this point, that the HIV question and all the modeling that has been done on that is basically irrelevant, that the issue now is HHV-8. As Dr. Pellett said at the close of his presentation, we just don't know about that.

There have been a couple of statements made, one of which is that the absence of evidence is not evidence for absence. I think the data that do not indicate transmission are really relatively few on which to base a decision.

I think that another situation, my recollection is that the approach that he took to whether or not HHV-8 could

be transmitted by blood carried about the same amount of evidence that rang very, very similar to what was presented in 1982 and 1983 about what turned out to be HIV infection and blood transfusion.

Finally, I think HHV-8 poses the greatest risk for immunocompromised patients. I think it is worthwhile considering that there is a rather small class of patients that are routinely immunocompromised and for whom an infection with HHV-8 could be devastating, and that is the premature infant who receives, often, a number of donor exposures as a result of various different testing procedures and their immature hemopoietic system as well.

So I am opposed, at the present time, to any change until we have settled, or at least gathered considerably more evidence about what HHV-8, what the risk and what the situation is with that.

DR. HOLLINGER: Once again, along these same lines, Paul, again, and perhaps, Mike, you could again help me with this, the highest prevalence is in what groups, again, so far--I know there is a lot of data that still needs to be done, but, so far, where does the highest prevalence seem to be located?

I know you talked about injection-drug users and so on, but--

DR. BUSCH: HHV-8 seroprevalence rates run around

20 to 30 percent in most studies of gay men with much higher rates in HIV-infected gay men. I think a couple of points; one is, as Phil pointed out, it is the HIV-infected gay men in whom people can detect viremia. You need to have immunosuppression as well as HIV, HHV-8, infection not only to manifest disease but to have viremia.

So, at least in the studies that have been done, you can't detect circulating virus in HHV-8 seropositive gay men who are not HIV infected. I disagree with Paul. I think HHV-8 is a very--one, I think the evidence is pretty compelling that it is not transfusion-transmitted from the epidemiology that, at a time when there was high prevalence not only of HIV but HHV-8 in the donor pool, there were high rates of HIV transmission to hemophiliacs and to recipients, and yet there is no KS.

There is no HHV-8 infection in these individuals who acquired HIV from transfusion. I think that broader epidemiology is much more powerful than the limited number of direct transmission cases that have been studies which only number about 30. So I think the epidemiology is, to me, strongly against transfusion transmission of HHV-8.

In addition, the storage effect is a major impact on non-transmission. Again, the attributable risk of male-male donor pool changes--if there is HHV-8 in the blood supply and 1 percent of our donors are infected, we would be

screening the blood supply for HHV-8.

The contribution of male-male sex-donor prevalence is small because they represent a small fraction of the donor pool, if there is a problem which, personally, I don't think there is.

DR. HOLLINGER: Mike, you are saying that it appears to be mostly in the PBMCs or PBSs; is that correct?

DR. BUSCH: It is a b-lymphocyte-associated virus.

DR. HOLLINGER: Would leukoreduction make a difference?

DR. BUSCH: Yes; it certainly would. If there is a transmission effect, it would make a difference. Again, only a small fraction of HHV-8 seropositive people are circulating virus and those tend to be immunosuppressed HIV-infected people.

DR. McCURDY: The only thing is that HIV is transmitted by virtually any blood component and any of the derivatives that was not virally inactivated whereas HHV-8 would probably be transmitted only by white-cell-bearing components and those that are relatively fresh, primarily, perhaps, platelets, for example, which are fairly fresh and are not inactivated, or they do have white cells.

DR. HOLLINGER: Do we know if there is any in platelets? I hadn't heard anything that says that HHV-8 is found in platelets.

DR. McCURDY: It might be found in the peripheral blood mononuclear cells that are in platelets. There are fewer in the current platelet concentrates, particularly those that are obtained by pheresis but, on the other hand, I think they are there.

DR. HOLLINGER: Dr. Boyle?

DR. BOYLE: Thank you. Let me tell you what concerns me, and I have no objection to changes in the questionnaire that would make it better. This morning, we heard a presentation where we were presented a lot of information which made a fairly easy choice about changes in the safety system. In that case, it was the testing standards.

This afternoon, we are presented with another change and another aspect of the safety system with donor--in this case, it is donor screening--and, although there was quantification of what could be quantified, the core assumptions were just that; assumptions. There was really no evidence.

So I was a little disturbed about being asked to choose between something that we could say with a fair bit of assurity was between the size of a bread box and a barn. But that doesn't bother me as much as the two pieces which is if we are starting to move down the road towards non-evidence-based or differential-evidence-based decisions on

things like donor screening, and I hear presentations that some people in the industry would like to move to a one-year standard and there is a lot of research literature that says past-year prevalence of risky behavior is way under reported, that I get very, very concerned that we will be deciding that issue down the line without the evidence put forward.

Moreover, the statements that I hear that we don't have this information, we couldn't get this information--I'm sorry; it is a lot cheaper and easier to test reliability and validity of survey instruments than it is to do a lot of these biological markers that you are dealing with.

I am just concerned where we are going. So, in the beginning, until we got to a certain point, I was probably just going to abstain for lack of information. Because I don't think there is enough information to make a decision at this point in time because what I am concerned with as a direction, I will oppose this.

DR. HOLLINGER: Thank you, John.

Dr. Chamberland?

DR. CHAMBERLAND: A couple of things. When you asked us if we were open to considering changing the MSM deferral question, I did indicate yes because I am open to that. However, just a couple of thoughts about the information and what we know to push us in one direction or

another that we have at the moment.

I will reiterate that I think, because FDA has chosen to use a model-based approach for the committee to consider, that I, for one, would like to see the model expanded or amplified in some of the ways that the other committee members have spoken to and to see if there can be any more statistical rigor or robustness brought to the model, or at least point us in a direction, as I said, of what factors seem to be influencing it because I do think that people are sort of responding to this, your bottom line, which is this very, very low, one or less than one, additional unit or donation that would enter the supply annually.

So I think it would be actually a more fair estimate if we had at least some range of what that might be and the parameters around that.

Be that as it may, I think all of us that have heard the data this morning about the nucleic-acid-testing data I think have to have a lot of confidence that, with the advances in testing that we have seen, that contributions to safety have been tremendous in that my gut tells me that, even if this deferral period was going to be changed in some way, it would not really--the testing is that good that we probably are going to cap the incidence-prevalence arguments that have been put forward could probably be adequately

addressed.

An additional concern that I have, though, is one that Paul McCurdy started to articulate. I use HHV-8 sort of as an example or a bookmark or a flag, whatever you want to call it. My personal feeling is that it is uncertain if HHV-8 is transmitted in the blood supply based on what we know.

I think it is possible. I do, though, agree with Mike Busch that I can't believe that it is happening in any large extent, that it is something that we would have picked up by this time. But that doesn't preclude that it may happen occasionally, and I can't quantify that in any way.

But I think, clearly, there are more studies that can be done. I think HHV-8 is just kind of a reminder out there that certain risk behaviors would not--changing the deferral to a floating five-year exclusion would not necessarily protect the supply, the blood supply, from other infectious agents that we know about, don't know about.

Most of our discussion today is focussed on those that we know about and have really good tests to detect. It is a bit of a gamble because you don't know which population is going to be affected by the next emerging agent. It could be, as it was, pig farmers in Malaysia that experienced significant morbidity and mortality or other agents, so it is a bit of a crap shoot.

In totally agree with the other comments. It is very crude to say it is the MSM population. We all know it is a subset of the MSM population as it is a subset of heterosexuals, et cetera.

Unfortunately, the questionnaire that we have been using is just very crude at getting at that. I do think it is amenable to study but I think, John, do not--I don't think that this task force that had been put together, which is very good--it doesn't have resources and tools to set up the very careful studies that would be needed to be done if you wanted to evaluate different ways to ask a question or do population-based surveys of MSMs and find out additional information.

I am open to changing the question, but I, personally, don't have all the information at hand to do it.

DR. HOLLINGER: Dr. McGee?

DR. McGEE: I just wanted to say that my indication that I wouldn't vote was not that I wasn't interested in changing the question but that nobody has offered me a set of criteria that I could use to judge how to make that decision.

If I just accept the FDA, we get a 20 percent increase in the risk. I think somebody threw out that number. That is a sizeable increase in risk for a minor increase in the donor pool. At any rate, nobody has offered

me yet what I would consider a criteria that I could base judgement on.

DR. HOLLINGER: Dr. Mitchell?

DR. MITCHELL: I think I approach this from, well, several points of view. But the main thing is that the current criteria of having MSM contact since 1977, on its face, seems very discriminatory and it seems very arbitrary. And so I feel very strongly that it needs to be changed.

Now, the question is what does it need to be changed to? I think that a lot of the things that we were presented today were, again, very, very conservative, very, very high estimates of risk. Again, we know that in the overall blood-donation population, that the risk is much lower than the overall population for a number of different conditions.

I would expect that it would also be the same for the MSM population. We know that, again, if somebody is not practicing male sex on a regular basis, or in five years, or have been abstinent--anybody who has been abstinent for a number of years is going to have lower risk than the general population of sexually active people.

So I think that, even using the 2 percent estimate is much, much too great. But the question is what should the number be, and I certainly don't have that number. I think it would be difficult to get that number.

Part of what I am basing this on is also the 1997 presentation and other presentations from the REDS study. I wish that we had had more data on the population from the REDS study. As I remember, the population that did donate, in fact, were people who did not consider themselves to be gay or bisexual. Oftentimes, if they were men, they were married and there were a number of women.

So I think that if you change this, you are not going to get the higher-risk population. I think that a one-year time period is a reasonable time period and I think that that will turn out to be a reasonable time period.

I don't think that we have had the evidence to support that--I don't know that it has been specific enough, the things that were presented today, to make that determination. But I think that a two- to five-year--to me, the weight of the evidence is clear enough that a two- to five-year deferral would be reasonable.

DR. HOLLINGER: Ms. Knowles?

MS. KNOWLES: I support the change, but I think this goes hand-in-hand with updating the panel questionnaire and really focusing in on behavior irregardless of sexual orientation because of exactly what you just said, Mark. I mean, there are people who are engaging in high-risk behaviors who may not self-identify as being MSM.

DR. HOLLINGER: I need to just take a moment.

Colonel Fitzpatrick also sent something, a comment, and he asked if we would read it into the record and I need to do that. So if you will bear with me while I read his comments, I would appreciate it.

This is on this issue here and I presume, if he were here, he would have said this very thing. It says, "While the statistical data supports reduction, I am concerned about the logic for requesting it. One of the reasons offered by the FDA is to bring deferrals for semen, tissue and blood donors into agreement. There are a number of other deferrals for high-risk behavior. I.V. drug use even once; that is a permanent deferral. Sharing needles even once, such as for steroids, which is not a high-risk population; permanent deferral.

"Yet we only ask about the following behaviors for the past twelve months. 'In the past twelve months, have you received blood, blood products or a tissue transplant including any you may have donated for yourself?' like an autologous. 'In the past twelve months, have you had a tatoo, ear or skin piercing or acupuncture?' 'In the past twelve months have you had an accidental needle stick or come in contact with someone else's blood?'

"In the oral questions, we ask about sex with a prostitute in the past twelve months, but also ask, 'Have you ever taken money or drugs for sex?' It seems to me that

we have either deferred permanently or for one year for high-risk behavior. MSM is a known high-risk behavior and, while there those donors who have changed their lifestyle, they are relative few and the REDS data confirms these donors are not always truthful and some still donate to get tested.

"Will the next step be accepting a male in a monogamous relationship for the past five years with another HIV-negative male? Changing the deferral to five years, based on the statistical model provided, may seem like a reasonable risk but, to me, it says we should change all the other deferrals from one year to five years.

"I would like to see the same model run on each high-risk behavior so that we can determine the relative risk of each high-risk behavior before making a recommendation. The FDA has used theoretical models to eliminate donors who spend six months or more in the U.K. when there has never yet been a recorded transmission of mvCJD through human transfusion.

"This seemed to be a political and scientific response to an unknown problem that could not be easily quantified. Reducing the MSM deferral to five years has a real increase in risk, albeit small. These two policies seem contradictory. We are to accept a theoretical model which indicates the real risk of accepting one additional