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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGIC EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

57TH MEETING

Thursday, December 11, 1997

8:10 a.m.

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Paul R. McCurdy, M.D.
Mark A. Mitchell, M.D.
Jane A. Piliavin, Ph.D.

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P R O C E E D I N G S

DR. SMALLWOOD: Good morning and welcome to the 56th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. At this time, I will read the statement of conflict of interest.

Statement of Conflict of Interest

DR. SMALLWOOD: This announcement is made a part of the record to preclude even the appearance of conflict of interest at this meeting of the Blood Products Advisory Committee on December 11th and 12th, 1997.

Pursuant to the authority granted under the Committee charter, the Director of the FDA Center for Biologics Evaluation and Research and the Lead Deputy Commissioner, FDA, has appointed the following individuals as temporary voting members: John M. Boyle, Norig Ellison, Margaret Kadree, Chris Mathews, Paul R. McCurdy, Mark A. Mitchell, Jane Piliavin, and David Stroncek.

Based on the agenda made available and all reported financial interests as of this date, it has been determined that all interest in firms regulated by the Center for Biologics Evaluation and Research, which have been reported by the participating members, present no potential for a conflict of interest at this meeting.

The following disclosures are presented: Dr. John

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Boyle reported that he and his wife are unpaid trustees on the board of directors for the Immune Deficiency Foundation. The Foundation receives unrelated funding from several regulated firms.

Mr. Corey Dubin has an agency-approved appearance determination dated December 11, 1996, regarding his suit with several regulated firms.

Dr. Jerry Holmberg has an agency-approved appearance determination regarding the use of test kits from regulated firm in relation to his official government duties. In addition, he provides technical expertise on platelets for an NIH contract with the American Red Cross. Dr. Holmberg consulted in the past with a regulated firm on unrelated products and which he received a fee.

Dr. Rima Khabbaz's employer, the Center For Disease Control, has unrelated credas with two firms which could be affected by the general discussions.

Ms. Katherine Knowles reported that her employer, a nonprofit organization, provides AIDS training to blood bank employees. Ms. Knowles participates in the teaching of this course. She receives no personal remuneration. In addition, her employer received unrestricted grants from regulated industry. Ms. Knowles is not involved in the solicitation of these funds.

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Dr. William Martone is a Federal Government employee detailed to the National Foundation for Infectious Diseases, a nonprofit organization. The foundation received a donation and nine grants from regulated firms. The grants and donations are unrelated to the committee's discussions, and Dr. Martone receives no personal remuneration from these grants and/or donations.

Dr. Paul McCurdy is employed by the National Heart, Blood, and Lung Institute. As part of his official government duties, he reviewed proposals submitted to the cord blood program for the collection, process, storage, and transplant of cord blood, stem cells from two firms that could be affected by the committee discussions. Also, his wife is a consultant to a small regional blood bank in the State of Illinois.

Dr. David Stroncek reported that he is a Federal employee who served as a co-principal investigator on an unrelated grant which was awarded to the University of Minnesota. The grant ended in June 1997.

Copies of appearance determination statements addressed in this announcement are available by written request under the Freedom of Information Act.

In the event that the discussions involve any other products or firms not already on the agenda for which

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an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

In regard to FDA's invited guests and speakers, the Agency has determined that because the services of these guests and speakers are considered essential, any information provided by them will be included in the public record to allow meeting participants to objectively evaluate any presentation and/or comments made by the guests and speakers.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

At this time, if there are any declarations to be made, I will entertain them.

[No response.]

DR. SMALLWOOD: If not, I would like to move ahead by introducing the members of the Blood Products Advisory Committee.

I would like to introduce our newly appointed Chairman, Dr. Blaine Hollinger. Dr. Hollinger, if you would raise your hand.

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Seated next to Dr. Hollinger -- and I will go to his right in introductions -- Dr. Rima Khabbaz. Dr. Joel Verter. Dr. Jerry Holmberg. Dr. Jane Piliavin. Dr. Norig Ellison. Dr. Paul McCurdy. Dr. Kenrad Nelson. Dr. Jeanne Linden. Dr. David Stroncek. Dr. William Martone. Ms. Katherine Knowles.

I would also like to announce that at the end of the fiscal year ending September 30, there were several vacancies that became available on the Blood Products Advisory Committee. As our usual procedure, we try to fill those vacancies timely, and unfortunately, we were unable to complete that process at the time of this meeting.

Therefore, to enable us to proceed with this meeting, we needed to have a quorum of members, so we did identify individuals who will be participating in this meeting as temporary voting members.

I would also just like to introduce to you Dr. Mark Mitchell, who just arrived. Dr. Mitchell, if you would raise your hand.

As you will note on the roster that is available outside, if you didn't pick up one, we have identified the temporary voting members. Also, tomorrow, we will have the services of Dr. Margaret Kadree and Dr. Chris Mathews, as well as Dr. David Gates. These individuals are members of

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advisory committees from our other centers. Dr. Kadree is from the Center for Devices, as well as Dr. Gates, and Dr. Mathews is from the Center for Drugs. They serve on those advisory panels, and they will be assisting us in tomorrow's deliberations.

We hope that by the time of our next meeting, tentatively scheduled for March 12th and 13th, 1998, that we will have a full committee here.

At this time, we will proceed with the agenda. Dr. Hollinger, the Chairman, will preside over the meeting.

Excuse me. Mr. Corey Dubin, who is listed on the roster, is absent for this meeting due to illness. Thank you.

Welcome and Opening Remarks

DR. HOLLINGER: Thank you, Dr. Smallwood.

I want to welcome the new members to the committee, as well as the previous members. It is always nice to see you again.

We have a full agenda today. The first item is some committee updates of some things we have discussed in the past, mostly to just keep us abreast of what is happening from the FDA standpoint.

There is really nothing to vote on this in general, it is just mostly for information.

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Could we start with the first presentation, I think something on fibrin sealants, an informational update, please. Dr. Lynch.

Committee Updates

Fibrin Sealant - Informational Update

DR. LYNCH: Good morning.

I would like to update you on a product for which the review cycle is nearing completion and for which I anticipate the committees will recommend approval to the Center Director in the near future.

Please note that the final action on this product will be the Center Director, so my remarks should not be construed as announcing any sort of final action on behalf of the Agency.

[Slide.]

The product in question is a fibrin sealant under the trade name Tisseel, that is produced by Immuno-AG of Vienna, Austria.

[Slide.]

This product has four components: a sealer protein, which is basically fibrinogen, this is produced from human plasma; thrombin also derived from human plasma; bovine aprotinin, and calcium chloride.

The first two of these materials are provided in

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dried form, the latter two are solutions.

[Slide.]

The sealer is applied by reconstituting the sealer protein with the aprotinin solution, the thrombin with calcium chloride. The two resulting solutions are placed in a dual-chamber syringe, and they are mixed together as they are expressed from the syringe.

When mixed, the thrombin cleaves the fibrinogen to form fibrin, which results in the clot. The purpose of this is to control bleeding, that is, provide hemostasis, and also to seal tissues together. Its primary application is in the surgical field.

[Slide.]

Manufacturing. The sealer protein basically entails producing cryoprecipitate, which is washed, then dried to a very narrowly specified water content, and then it is treated with a vapor heat method at two temperatures: 60 degrees followed by an 80-degree temperature at elevated pressure.

This is a viral inactivation step following which the product is formulated, sterile filtered, filled and lyophilized. The thrombin component is produced by activating a currently licensed product called FEIBA. This has been already vapor heat treated. Following activation,

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it is also formulated, sterile filtered, filled, and lyophilized.

The aprotinin is produced from another currently licensed product called Trasylol. This is a protease inhibitor intended to inhibit the activity of plasmin. The final licensed U.S. product is reconstituted, reformulated, sterile filtered, and filled. This is provided, as I said before, as a solution.

The calcium chloride is a simple salt solution, which is terminally sterilized in the final containers.

[Slide.]

The vapor heat treatment step has been validated using a number of marker envelope viruses. Notable among this list is hepatitis A virus, which is a non-envelope virus that is known to be rather difficult to inactivate by a variety of methods.

In all cases, the method has proven effective in removing all detectable virus. The numbers for the fibrinogen and thrombin components are shown. Notably, there were no seroconversions during the clinical trials and there have been no reported transmissions under European pharmacovigilance.

This product, a very similar product is available in Europe, has been so for a number of years, and has

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achieved a relatively admirable safety profile.

[Slide.]

I want to describe the clinical trials that support the licensure of this product. The pivotal trial involved cardiovascular surgery, primarily CABG patients. There are two additional supportive studies involving surgeries of the spleen and liver. These were primarily trauma patients, and colon surgeries involving resealing colonostomies.

[Slide.]

The cardiovascular study initially enrolled 489 patients, however, there were a rather large number of exclusions for a variety of reasons listed on this slide. The endpoints of this study, the primary endpoint was hemostasis within five minutes.

The design included a provision for crossing patients over at the end of a five-minute period if the treatment failed. The controls of this study were any other approved or standard hemostasis technique.

The secondary endpoints included postoperative blood loss and reoperation rate.

[Slide.]

This is an example of the results. I am not sure that you can read that. Because of the number of exclusions

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from this study, the data were analyzed by both intent-to-treat and per-protocol method.

This slide shows group A with the fibrin sealant treated patients, group B are the controls. The slide indicates the number of patients for whom bleeding stopped within the five-minute period, those where it did not, the number of patients with missing data points, and patients with no bleeding at all.

As you can see, in the treatment arm, 159 patients out of 193 achieved hemostasis within five minutes as opposed to 75 out of 172 in the control arm. This was a highly significant result in a Pearson test, and indicated that the product was effective as an adjunct to hemostasis.

[Slide.]

The second study, the spleen/liver study, was an historically controlled study. Controls had conventional surgery within a year of the treatment arm. Treatment again was with fibrin sealant. 240 patients were enrolled out of which 128 were actually treated, and there were a variety of endpoints that were identified in the study.

The bottom line was that the study demonstrated a significantly decreased rate of splenectomies in patients with damage to their spleens.

[Slide.]

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The third study involved resealing colonostomies, 120 patients, roughly half were treated with fibrin sealant. Endpoints were a variety of complications, abscesses, need for reoperations. Among these complications were leakages of the colonostomy itself.

Again, the controls were patients with conventional hemostatic methods applied during the surgery.

Out of the endpoints identified, there was a significant reduction in leakage at the site of anastomosis was demonstrated.

[Slide.]

One of the problems with a product like this is the fact that it does comprise multiple components. In order to demonstrate that each of these components contributes to the effectiveness of the product, a series of preclinical studies were undertaken using animal models.

I will talk about the number of studies involving rabbits, and these were designed to demonstrate the contribution of the fibrinogen, thrombin and aprotinin components, and originally factor XIII, which is a component of the European product, which is not proposed to be included in the U.S. version of this product.

[Slide.]

This is an example using heparinized rabbits with

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a liver abrasion study, which produces small-vessel bleeding. The endpoint in this study was time to hemostasis, and the treatment of the animals included the fibrin sealant alone as the entire product, fibrin sealant without the aprotinin component, without the factor XIII component, thrombin alone, thrombin plus aprotinin.

Here, the times to achieve hemostasis are listed. Obviously, thrombin alone did not work as well as fibrin sealant, but there was relatively little difference between the fibrin sealant with and without aprotinin or factor XIII.

[Slide.]

A second study, similar, used heparinized rabbits, but which had been treated with streptokinase. Here, the contribution of the aprotinin component could be shown, but leaving out factor XIII did not greatly reduce the effectiveness of the product.

So, the result of these and similar studies suggested that factor XIII was not an essential component, but aprotinin could be under circumstances where there was a high fibrinolytic state in the animal.

However, the relevance of the model, the streptokinase rabbit was questioned, so another series of studies were undertaken to validate that model.

[Slide.]

The studies were designed to demonstrate the comparability of the fibrinolytic activity in this last rabbit model with human cardiac surgery patients undergoing extracorporeal circulation.

This was determined from clinical data compared to the fibrinolytic state of the animals in the study and used to decide whether or not the studies were relevant and, hence, whether or not the aprotinin made a contribution.

[Slide.]

The conclusions were in the course of determining the fibrinolytic state of the patients, the time course of that state was determined, and it was quantified by a direct measure of fibrin lysis and hydrolysis of an artificial substrate.

The pharmacodynamic curve that resulted was compared to that in the rabbits, and the optimum dose, which was in fact used in the study I described before, was determined to be comparable to the fibrinolytic state in human patients. In order to confirm this conclusion, a final study was undertaken using tPA-treated rabbits.

[Slide.]

This was a liver resection model using tPA instead of the streptokinase. Three time points in the course of

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action of tPA were examined that were intended to represent application in the human during ECC immediately after disconnection and some time thereafter.

The treatment arms were the product with and without aprotinin. I don't think I have any data on this.

[Slide.]

The outcome of this study was a significant difference in blood loss between the product with and without aprotinin, aprotinin reducing blood loss during the first two hours after surgery.

The sum of these studies is that efficacy of this product has been demonstrated as a topical hemostatic agent, as an aid to surgeries involving the pancreas and as a tissue sealant in colostomy patients.

The components, the contribution of each component has also been demonstrated via these preclinical studies, and this is deemed acceptable since the overall efficacy of the product does rely on human trials.

The other issues that remain are the results of an establishment inspection that was conducted in November of this year, the firm was found to be in substantial compliance with current Good Manufacturing Practices, and the corrective actions that will be required before licensure are fairly straightforward.

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Also remaining to be finalized is the labeling of this product. This is currently under examination, discussion with the firm. As Dr. Weinstein described last March I believe the acceptance of an endpoint, such as five-minute hemostasis, has been conditioned on drawing final product indications narrowly to reflect the results of the clinical trials actually undertaken and completed.

Are there any questions?

[No response.]

DR. LYNCH: Thank you.

DR. HOLLINGER: Thank you.

The second update is on HIV-1 Group O Antigen.

Dr. Hewlett.

HIV-1 Group O Antigen - Update

DR. HEWLETT: Good morning.

[Slide.]

I am going to be presenting the committee with an update on the HIV-1 group O issue, which was last discussed at the Blood Products Advisory Committee meeting in September of 1996, as a result of the identification of two cases of group O in the U.S. causing some concern regarding HIV screening of the blood supply.

[Slide.]

By way of background, HIV-1 group O was first

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reported in 1994 as a highly divergent HIV-1 strain isolated from patients of West Central African origin. Two major strains were identified at the time, the ANT-70 and the MVP-5180. Since then, a third strain, BAU, has been added to the list.

These viruses share a 65 to 70 percent DNA sequence homology with HIV-1 group M viruses, and 55 to 60 percent homology with HIV-2. Due to their degree of diversity from group M viruses, they were referred to as the HIV group O, where the O stands for the outlier group of viruses as opposed to the standard group of viruses.

From a diagnostic point of view, these viruses posed a challenge since some licensed recombinant and synthetic peptide-based assays were not 100 percent sensitive for group O detection.

[Slide.]

In response to reports on HIV group O, FDA took a couple of actions. First, this issue was brought to the Blood Products Advisory Committee, which identified the need to modify tests for enhanced sensitivity for group O without compromising group M sensitivity and to include group O specimens in clinical validation studies.

These recommendations were transmitted to industry in meeting with sponsors. In 1996, the first case of group

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O was identified in the U.S., and FDA requested manufacturers to expedite development of modified tests for group O sensitivity and to include a group O consensus antigen sequence for a group O claim.

[Slide.]

In December 1996, upon identification of another case in the U.S. of group O, bringing it to a total of two cases, there was an increased concern over screening of the blood supply.

FDA sent memoranda to blood and plasma establishments recommending temporary deferral of donors who were born in or lived in certain Western Central African countries where group O is prevalent, and of persons who traveled to, and received a blood transfusion or a blood product made from blood or had sexual contact with persons from these countries since 1977.

The list of countries, which are not on this slide, are Camaroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, and Nigeria.

[Slide.]

Currently, FDA's efforts are aimed at assembling a panel of specimens for evaluation of test kits for group O sensitivity, and we are continuing to work with manufacturers to expedite the submission and review of

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applications.

To facilitate licensing, FDA has agreed to permit the use of repository specimens and in-house testing as a clinical site for clinical validation studies in lieu of de novo clinical trials. This information was transmitted to industry in a letter dated July 1997.

[Slide.]

The most recently identified issue in group O in regard to diagnostics is the question of what antigens would provide optimal group O sensitivity, and this is, in fact, the reason for the update.

As mentioned before, manufacturers were requested to incorporate a group O specific antigen, either a consensus or a representative sequence to obtain a group O claim. The regions that have been most frequently and commonly used, both in the research setting and I believe in some European tests, are the C2B3 region of the GP-120 and the immunodominant region or the IDR region of the GP-41.

For group M strains, the IDR region appears to work reasonably well due to the degree of conservation and immunogenicity of these epitopes, however, recent data indicate that both the V3 and the IDR region may be more variable in group O viruses, and that overall diversity may be greater in group M than in group O viruses.

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[Slide.]

This slide actually is difficult to read, but I am just going to point out the key observation here. This is the amino acid sequence alignment of the C2V3 region. This is taken from the Los Alamos database and the group O consensus is based on 45 available sequences.

The point I would like to make here is that there is more variation amongst group O viruses than the group M viruses. It should be noted also that the V3 is a hypervariable region in the HIV genome, but it is highly immunogenic, so it has been used for diagnostic purposes, but its more common use I believe is in serotyping of the klates [phonetic], so although this has been used in a research setting, particularly for group O detection, it tends to be not favored as much as the IDR region for diagnostic purposes.

[Slide.]

However, when you look at the IDR sequence for the group M and the group O viruses, and this data set is actually again from Los Alamos and represents a very limited data set for group O, in fact, there are only about five isolates here, and the consensus is based on nine available sequences.

This information was made available to us last

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year at the time that we enunciated the position that we would like manufacturers to use a consensus sequence, and the point to be noted here is that based on this limited information, you can see that there does not seem to be a great difference between group M and group O, that this was information that was available about a year ago, however, during the past year, there have been a few reports and there is a fair amount of unpublished data, and this in fact is a published reference.

This is a paper from Lutz Gurtler's laboratory, which has been studying group O diversity since it was first identified in 1994. What this involves is this is sequence information of the gp41 immunodominant region of 25 group O isolates, some from Camaroon, some from France.

The point that I would like to make here is that as you sequence more isolates, you are beginning to see greater diversity, and another point is that the substitutions that one sees are not conservative amino acid substitutions.

I would like to point out two instances. The first is the replacement of leucine residue at position 516 with a lysine, and another leucine with a phenylalanine residue.

So, what we are seeing is that there are

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substitutions being made or that we are seeing among group O isolates that indicate to us that the diversity even in the conserved regions may be greater for group O viruses than group M viruses.

[Slide.]

The current consensus opinion of experts in the field is that sensitivity for group O detection requires the use of group O specific antigens due to sequence diversity between groups M and O.

I think there is also a fair amount of agreement that at the present time, there may be no adequate consensus group O sequence for screening assays for all anti-HIV group O specimens, however cross-reactivity of antibodies between group O antigens indicate that perhaps using a mixture of group O sequences may reduce the risk of false negative group O test results.

[Slide.]

Finally, the current scientific perspective in this area seems to be that there is an evolving understanding of HIV-1 group O diversity due to increasing sequence information that is being accumulated by sequencing additional isolates as they are identified.

This suggests that perhaps using a mixture of antigens of representative group O strains may offer more

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sensitive detection of variants than a single consensus peptide sequence. Alternatively, sequences of greater length or longer proteins having multiple epitopes may also be more useful.

[Slide.]

Finally, the message in all of this is that it is important for industry and the FDA to continue to be aware of HIV diversity in designing screening assays for HIV.

I would like to also acknowledge some of the investigators in the field who have contributed information and expert opinion to this discussion. They are Lutz Gurtler from the University of Munich, Francois Simone from Paris, Betty Korber from the Los Alamos Laboratory, Sushil Devare from Avid Laboratories, and Wouter Jansen at the WHO Collaborating Center for AIDS in Belgium.

Thank you. I will take any questions.

DR. HOLLINGER: Any questions of Dr. Hewlett?

Dr. Hewlett, it looked like on the IDR region in the con-0 group, that the consensus 0 was made from how many isolates, I mean initially?

DR. HEWLETT: Initially, it was from nine isolates.

DR. HOLLINGER: Nine, but it looks like the consensus needs to change. I mean there are some in there,

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I noticed just quickly taking a look, there are a bunch of r-amino acids in one section, which makes up the vast majority, which would then change a little bit the consensus.

DR. HEWLETT: Yes, that is exactly the point. I think at this point, investigators who are studying the sequence diversity feel that there is really no good single consensus sequence for group O, unlike with group M, you can actually come up with an acceptable consensus sequence particularly in the IDR region, which is highly conserved. That may not necessarily be the case for group O, and I think that is the emerging picture in the field.

DR. HOLLINGER: And they still may be detectable even with that variation.

DR. HEWLETT: Possibly so, yes, I think more studies need to be done in that area, but I think the point really is that we need to be aware and to sort of maintain a watchful eye in regard to emerging diversity in HIV group O.

DR. HOLLINGER: The next update is on Creutzfeldt-Jakob Disease Guidance Document. Robin Biswas.

Creutzfeldt-Jakob Disease Guidance Document - Update

[Slide.]

DR. BISWAS: In previous FDA guidance memoranda to industry regarding precautionary measures to reduce the risk

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of transmission of Creutzfeldt-Jakob Disease by blood and blood products, FDA recommended that persons who have received human pituitary-derived growth hormone or dura mater should be deferred and that blood products intended for transfusion or for manufacture into injectable therapeutic products from such persons should not be used.

The FDA took this step because of reports of CJD in recipients of human pituitary-derived growth hormone and in recipients of dura mater grafts. In the case of the dura mater recipients, it was those dura grafts which had been processed together in pools, in batches, which was associated with recipient CJD.

[Slide.]

Now, in July 1996, FDA's special advisory committee, the Transmissible Spongiform Encephalopathies Advisory Committee recommended to FDA that it is not necessary to withdraw plasma derivatives if the plasma pool from which those derivatives are manufactured contains a unit from a dura recipient who received unpooled dura, that is, dura that had been processed singly on its own.

The reasons supporting this decision are that CJD risk from a single donor of dura mater is infinitesimally small, and no transmission of CJD to recipients of unpooled dura mater has been reported.

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[Slide.]

The FDA is therefore in the process of drafting a guidance memorandum in which it is recommended that blood products from a dura mater recipient may be used if it can be documented that dura was not pooled, was processed singly, and also that an autopsy of the dura donor's brain demonstrates that it is free of changes suggestive of TSE.

[Slide.]

Now, the FDA is also recommending that all human pituitary-derived hormones, that if the donor received any human pituitary-derived hormone, that the donor is deferred and all products intended for transfusion or for manufacture into injectable therapeutic products should be withdrawn, and the reason for this is that there have been reports of human pituitary-derived gonadotropins being associated with CJD in recipients.

Thank you very much.

DR. HOLLINGER: Any questions? Yes, please, Dr. Nelson.

DR. NELSON: Is melatonin a human-derived, pituitary-derived protein, because this is commonly used?

DR. BISWAS: Well, I am not an endocrinologist, Dr. Nelson. I don't know the answer to that. I believe that it does come from the pituitary, from the hypothalamic

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region, but I really don't know the answer to that.

DR. NELSON: It is very commonly used by travelers like Blaine and I. I have not used it, but --

DR. HOLLINGER: I am asleep. I don't use it. Does anybody know the answer to the question? It is an interesting question, Kenrad.

Yes, Dr. Holmberg.

DR. HOLMBERG: Yes, I have several questions. How will the donor know whether he or she has received dura mater from a pool?

DR. BISWAS: How will the donor know whether -- well, the donor may not know, but the answer to that question is, is that the blood collecting centers are asking donors that question, and I guess that presumably one would expect that a donor who had an operation would remember that he or she had such a operation.

Jay, do you want to add something to that?

DR. EPSTEIN: But that is going back to the medical record. What is going on is that the donors are deferred on the presumption of a dura mater transplant and then an investigation is done of the medical record. Generally, the origin of the graft is traceable back to a supplier, and the suppliers are queried.

Now, in the U.S., there never has been a practice

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of pooling of dura mater in processing, so if it's a U.S. source, that question is resolved. That, of course, doesn't resolve the question of an autopsy record, which also has to be pursued. So, the bottom line is that there has to be an investigation. Donors rarely know.

DR. HOLLINGER: The other question, maybe, Robin, you could update us a little bit, there was a question always about where this is transmitted through blood or blood products, but I thought there was some recent information, at least in hamsters or something, that very high concentrations of blood was able to transmit CJD or something of that nature. I thought I saw that presented at one of the meetings recently, a hemophilia meeting maybe.

Jay, do you know?

DR. EPSTEIN: Yes. There is a series of experiments that are ongoing, that involve a mouse-adapted TSE model. What is done is an endogenous infection is created in the mice and then the morbid mice then have samples taken from the blood, which are inoculated into target or readout mice.

In that experiment, there was one instance of one mouse in which a high dose inoculated mouse, the blood was taken and then transfused into a target animal, and one out of some large number of recipient animals did come down with

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TSE. I think this was mouse CJD that was being used.

DR. HOLLINGER: It was very high doses, too.

DR. EPSTEIN: Well, two points need to be made. the inoculum was very high dose, but there is always high titer in the mouse at the time of disease, but that high titer is in the brain. The titers that have been determined in the blood are low, of the order between 0.1 to, at most, 10 infectious units per milliliter of blood.

These same studies investigated the partition of the infectivity, comparing the whole blood, the plasma, the buffy coat, and plasma fractions, and infectivity was readily recoverable from blood buffy coat and plasma. It was also present in cryoprecipitate, and it was not detected in those experiments from further plasma derivatives, such as albumin, fraction V, fraction IV.

But again just to repeat the point, when whole blood from an ill animal that had been high dose inoculated was transfused to a set of target animals, one target animal came down with TSE, indicating for the very first time in an animal model system a transfusion-transmitted TSE from infectivity in blood by a quote, unquote "natural infection model."

Now, there are many artificialities of the experiment that are being pursued. One of the main concerns

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is whether high dose inoculation of the source animal results in a carryover of the inoculum, which stays in the periphery, and that that was the cause of the infectivity that was transmitted, and that is being pursued in a variety of ways.

DR. HOLLINGER: Thank you for that update.

Yes, Dr. Holmberg.

DR. HOLMBERG: In regards to the pituitary-derived hormone question, I noticed that the references here in this draft document are 1990 and 1992. What was the Agency's reasoning in not making this a more generic question back in 1996?

DR. BISWAS: Those reports came from Australia, and I believe at the time, there was just one report, and I think that the reason for that, we just weren't aware of that particular report.

DR. HOLMBERG: I have one more question. Actually, it is a comment. In regards to the document again, I noticed that we are now going a little bit more restrictive when we go with the human pituitary-derived hormones.

What if now we find information on a post-donation answer, and the document does not state notification of the consignee?

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DR. BISWAS: We are in the process of developing that document. I would think, though, that that at the present time, we would certainly want to be informed if there is some post-donation information.

DR. HOLLINGER: Dr. Linden.

DR. LINDEN: Sort of in followup to Dr. Nelson's question, is there a generally available list of pituitary-derived hormones generically and/or by brand name, because I don't think blood banks, let alone donors, would really know what is covered under that.

DR. BISWAS: Is there a list of pituitary-derived?

DR. LINDEN: Right, or could that be generated by the Agency?

DR. BISWAS: I think it could be, yes.

DR. HOLLINGER: Dr. Epstein.

DR. EPSTEIN: We are really only aware of gonadotrophin, and it has really only been ever generated outside the U.S. Our main focus was on human pituitary-derived growth hormone, because that was the product made in the U.S. to which U.S. citizens might have been exposed.

However, we do recognize that other hormones were made worldwide and that, you know, a donor could conceivably have received it abroad, but we are really only aware of

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gonadotrophins as being other human pituitary-derived hormones for which patients might be at risk.

As far as melatonin is concerned, I don't believe that it is of human origin.

DR. HOLMBERG: I have one more question concerning basically it is a housekeeping issue, and in the draft document, it also says that once a facility implements this, they should notify the Agency.

Will that now go away with the requirement for the annual report in the reorganization of government? Will the facility report that in the annual report versus notifying the Agency when they implement this?

DR. BISWAS: Exactly how that is going to be done, I don't know at the present time. As I said, this document is under development.

DR. HOLLINGER: We will move on. The next update is on patient notification initiatives, and the initial discussion will be by Dr. Weinstein.

Patient Notification Initiatives

DR. WEINSTEIN: I would like to update the committee on continued efforts by the FDA to encourage the development of better notification procedures to inform consumers about withdrawals and recalls.

The FDA attended a meeting about notification

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issues hosted by the International Plasma Products Industry Association, or IPPIA, on November 7th. The meeting was attended by representatives of the Centers for Disease Control and Prevention, plasma derivative consumer groups, and the plasma fractionation industry.

At the meeting, FDA discussed a number of initiatives that we have undertaken to improve patient notification. These measures include providing easy access to information on the Internet and 800 telephone numbers.

The notification system provided by the FDA, however, should only be viewed as a secondary means of notifying consumers about recalls and withdrawals. Manufacturers have the responsibility always to notify consignees and to notify end users, when appropriate, about recalls.

The FDA has the responsibility to oversee that notification is carried out. FDA is in the process of assessing what regulatory actions are necessary to ensure that there is adequate recordkeeping and an effective mechanism to identify and notify product recipients of health hazards.

This may involve improving the ability to track product by lot number to the final recipient. Labeling is being considered that would facilitate recordkeeping and

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tracking. An example of this kind of labeling would be tear-off labels that contained the lot number and other information.

At the IPPIA meeting, emphasis was placed on notification procedures that would inform recipients actively rather than on demand by them. One method of active notification that was endorsed by a number of manufacturers and consumer groups involves the creation of a voluntary registry of participants to be held by a third party.

The third party would receive information about recalls and withdrawals, and inform registrants rapidly by telephone or by other means of communication. One way to encourage the use of this system would be to place the telephone number of the third party on the product container. Information could be provided to the consumer about the voluntary notification system in a package insert.

While this voluntary system would not supplant the manufacturer's requirement to have a recall strategy in place to effect product retrieval, it could act as a valuable supplement to this plan.

The FDA is looking forward to learning more about the details of this plan and to actively engage other members of the Public Health Service, such as the CDC, as

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well as consumer groups, health care providers, distributors, and manufacturers to further enhance this initiative.

DR. HOLLINGER: Thank you. There are several speakers on this. I think the next person to speak is Mr. Bablak from the IPPIA.

MR. BABLAK: Good morning. My name is Jason Bablak, and I am Director of Regulatory Affairs for the International Plasma Products Industry Association.

I would like to take the next several minutes to update the committee on progress made by the plasma products industry in the area of patient notification.

As part of the ongoing dialogue between consumers, FDA, and industry, we presented a notification proposal to this committee last March.

In that presentation, we discussed several initiatives to improve patient notification including the creation of an industry web page that would contain recall information posted by all our members. That site can now be found at www.ippia.org, and we intend to have the recall section up and running over the next several weeks.

Since March, we have expanded our original proposal to include an active form of consumer notification which has been successfully utilized by our individual

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members in past recall situations.

Our proposed system will expand on this idea to create a voluntary registry of interested parties who will automatically receive notification whenever a recall or withdrawal is initiated. Our intention to develop this type of system was highlighted at a meeting held on November 7th, where consumers, industry, and the FDA discussed issues, concerns, and innovative ways of improving the consumer notification system.

At that meeting, it became clear that patients do not always receive notification of recalls or withdrawals through the current regulatory system. Our members feel a strong sense of responsibility for the safety of our therapies, and therefore IPPIA agreed to address the elements offered by the coalition of consumer groups and develop an industrywide active patient notification system.

I am pleased to announce the following consensus principles which reinforce and confirm our commitment to the development and implementation of a patient notification system that will, at a minimum, reach the chronic users of plasma-based therapies.

It is important to note that this new system will complement, not replace, existing responsibilities under the current regulatory framework.

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The industry consensus principles include: There is an immediate need for an enhanced patient notification system that reaches the treating physician, consumer, and end user. The notification system needs to be industrywide and have one point of access.

The system must assure patient confidentiality. Consumer participation in the system must be voluntary. The system should provide rapid access to recall information including direct physician and patient notification. The system should be operated by a third party.

An advisory panel consisting of consumers, physicians, and industry should be constituted to assist in the development and implementation of the notification system.

In order to implement this system as expeditiously as possible, IPPIA commits at this time to submitting a system design proposal for competitive bidding no later than February 27, 1998. We will work within this time frame to develop the actual framework of the notification system, secure non-member participation, and establish the advisory panel.

While we are excited about the accomplishments we have made towards improving patient notification, we also believe that additional measures must be taken to continue

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this progress. The system we have described today will only reach the chronic users of our therapies.

In order to reach the more occasional user, we must address the deficiencies in the current recall system that prevent effective tracking of lot numbers and impede timely notification through the chain of distribution.

We stated in our March presentation, and we still believe today, that only the FDA, through its rulemaking authority, is able to correct these defects.

Thank you for this opportunity to share our progress in the area of patient notification. We look forward to our partnership with consumers, FDA, and other interested parties in the development of an enhanced patient notification system, and we hope this cooperation will lead to additional opportunities for us to work together in the future.

I would be happy to answer any questions you have on this subject.

DR. HOLLINGER: Dr. Piliavin.

DR. PILIAVIN: What do you mean by a third party and what would be in it for this third party to be willing to do this?

MR. BABLAK: Basically, we would contract with an organization that would have the capability of doing this

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sort of notification, and they would actually run the system.

DR. PILIAVIN: Who would pay them?

MR. BABLAK: Industry would pay them.

DR. PILIAVIN: Thank you.

DR. HOLLINGER: There are several consumer groups that had asked to speak to this issue today -- oh, one statement representing all. Okay. Mr. Tom Moran. Thank you.

MR. MORAN: Good morning. I am Tom Moran, President of the Immune Deficiency Foundation. I have the privilege today of speaking on behalf of a coalition of consumer organizations representing regular users of plasma derivatives including the Alpha-1 Foundation, Alpha-1 National Association, the Committee of Ten Thousand, and the National Hemophilia Foundation.

We wish to offer the perspective of the substantial customer segment on industry plans for a patient and physician notification system for plasma derivative withdrawals and recalls.

First, let me remind everyone of the reason we are discussing this issue. Today, there are tens of thousands of regular users of plasma derivatives, along with the overwhelming majority of their prescribing physicians who

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are never notified of plasma product recalls or withdrawals.

Everyone agrees that this situation must change. Until it does, IVIG in distributors' warehouses, alpha-1 protease inhibitor on the pharmacy shelf, and anti-hemophilic factor sitting in consumers' refrigerators will be infused into patients days and weeks after withdrawals or recalls are announced. This fact is a matter of public record.

FDA and this committee have received testimony on this point, Congress has been alerted to this situation, industry is aware, the consumer organizations themselves know this to be the case. This circumstance is a disaster waiting to occur.

If a pathogen representing an immediate health threat would slip through current safeguards, what would we say to affected individuals and parents who would ask why we did not solve this problem?

To break this logjam, the consumer organizations I am representing today brought forward a proposal to FDA and to industry offering a voluntary consumer and physician registry as a means for industry to notify patients and physicians directly.

We are very encouraged that industry has responded to this initiative. We are aware that some companies,

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including American Red Cross, Baxter, and Bayer, have developed patient and physician notification programs on their own, consistent with the consumer organization proposal. Further, they have shown restraint in postponing implementation or in postponing the promotion of these programs in the interest of developing an industrywide system.

The IPPIA has taken the initiative and has assumed responsibility for pulling manufacturers and brand owners of plasma derivative products together to implement an industrywide system early in 1998.

The coalition of consumer organizations congratulates industry and the IPPIA for these activities and reaffirms our strong desire to assist you in designing an efficient and effective notification program.

Specifically, the coalition wishes to recognize IPPIA for convening a broadly attended meeting on November 7, 1997, to begin designing a specific system. We also congratulate IPPIA for their subsequent activities in gaining consensus among its members for the principles outlined and for the principles outlined in the IPPIA presentation.

The coalition endorses these principles. We encourage IPPIA to take the following steps:

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1. Fully involve non-IPPIA plasma derivative brand owners, including the American Red Cross, Novartis, and the Genetics Institute in the design of an industrywide patient and physician notification system.

2. We encourage IPPIA to immediately consult with the coalition members on the selection of consumers and physicians to serve on the advisory panel outlined in the IPPIA's statement of principles.

3. We encourage IPPIA to attempt to accelerate the February 27, 1998, time line for specifying the system design. The coalition members commit to participate in an advisory panel meeting as early as possible, perhaps even the first full week of January 1998, if this would assist the process.

In conclusion, with respect to the issue of patient and physician notification, we have the potential to demonstrate how the public benefits when plasma product consumers, industry, and regulators work together to identify and solve problems.

Thank you.

DR. HOLLINGER: Any questions? Yes, please, Dr. Mitchell.

DR. MITCHELL: I am concerned that people may get notified of too many products that don't affect them. Is

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there a way that you are looking at trying to make the notification specific to the product and also to the geographic area where people may have received?

MR. MORAN: I understand that the system is under construction now or under design right now, but in the meetings that have been held, there is a provision or an ability for an individual consumer to specify either the type of product or the individual brand that that individual is on, so as to limit, if you will, the notices that that individual would receive.

Part of the process, this is how it is envisaged at least at this point -- keep in mind also that there will be an advisory panel consulting with IPPIA to design the system -- but it is envisioned that an individual, when they enroll, in addition to providing a means of communicating with them, can also specify or target the type of notices and the products for which they receive notices.

DR. HOLLINGER: Mr. Moran, how many withdrawals and recalls occurred in the last year of plasma derivatives, can you give me some idea of numbers? I mean is this a small amount, is it large?

MR. MORAN: Well, it is a substantial amount, I don't have the precise -- perhaps someone from FDA maybe could help with this. I wouldn't hazard a guess.

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DR. HOLLINGER: Anybody?

DR. WEINSTEIN: Including withdrawals due to CJD, there would be something on the order of 5 to 10, I would say.

DR. HOLLINGER: Five to 10 withdrawals or recalls?

DR. WEINSTEIN: Combined figure, something on that order.

DR. HOLLINGER: Thank you.

DR. MITCHELL: So this is not the same as withdrawals of blood, whole blood. You are saying that there are only 5 to 10 a year, and I guess I am not sure that I have seen more than that, but I thought that there was -- I know that there is at least a large number of withdrawals of units of blood, but you are saying that this is very different from that?

DR. WEINSTEIN: This is referring to the plasma derivative industry, right.

DR. HOLLINGER: Does that include something like the albumin withdrawals because of contamination or something?

DR. WEINSTEIN: CJD.

DR. HOLLINGER: Thank you.

The next topic is a very important topic. It is the donor deferral policy regarding men who have had sex

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with another man, even one time, since 1977.

We will start with a discussion of this by Dr. Dayton, who will give us some background and introduction to the issues.

**Donor Deferral Policy Regarding Men Who Have Had
Sex With Another Man, Even One Time, Since 1977**

Background and Introduction

[Slide.]

DR. DAYTON: I am Andrew Dayton in the Division of Transfusion-Transmitted Diseases. You just heard the topic announced.

[Slide.]

Currently, men who admit to having sex with other men, even once, since 1977, are deferred from donating blood. Now, as part of an FDA-wide effort and thrust to update our regulatory guidelines, we have decided to reexamine this deferral criterion and judge whether or not current knowledge warrants altering it.

To give you a little bit of background, this issue has been debated really ever since the beginning of our knowledge of the epidemic.

In the early 1980s, as the nature and extent of the AIDS epidemic were only beginning to be perceived, it

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was recognized that the high risk groups, such as intravenous drug abusers, prostitutes, and men who have sex with other men were a danger to the blood supply, and donor education was instituted to avoid donations from high risk groups.

In December of 1984, the policy was formally revised to, amongst other things, defer males who had sex with more than one male since 1979. In September of 1985, the MSM -- we will use that abbreviation quite a lot, that is men who have had sex with men -- the MSM high risk group was redefined to include men who have had sex with another male even once since 1977, which was then understood to predate the earliest HIV infections in the United States, and which even in retrospect, predates the widespread emergence in the U.S. of the HIV epidemic.

[Slide.]

The FDA's historical concepts on donor deferral include what is listed on the slide here, lifetime deferrals of individuals who belong to groups with a high risk of HIV infection and temporary deferral of persons with recent high risk exposure to these groups, but who are not otherwise members of a group at high risk for HIV infection.

[Slide.]

These are homemade slides as you can tell. It is

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part of the FDA effort to do more with less.

The current criteria that result in permanent deferral based on HIV risks were described in an April 1992 memorandum from FDA, and include the following: persons with clinical or laboratory evidence of HIV or AIDS infection, men who have had sex with another man, even one time, since 1977, past or present intravenous drug users, persons with hemophilia or related clotting disorders who have received clotting factor concentrates, and men and women who have engaged in sex for money or drugs since 1977.

[Slide.]

Additionally, the following criteria result in a 12-month deferral: persons who have had sex with any person meeting the above or previous descriptions in the preceding 12 months, persons who have had or have been treated for venereal diseases in the past 12 months, and persons who have received a transfusion in the past 12 months. Also, blood donors are deferred based on a risk history for malaria, CJD, and hepatitis.

Well, over a decade has passed since the institution of the 1977 MSM deferral policy. There has been growing awareness here within the FDA that the accumulation during this time of new knowledge of the dynamics of HIV infection and the dynamics of the HIV epidemic might warrant

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reconsideration of this policy concerning deferral of men that have had sex with another man.

Many have vociferously opposed the policy on the grounds that it is discriminatory and degrading, as well as outmoded. Although the Agency is sympathetic to these concerns, the country has made it clear through its representatives that any threat to the safety of the blood supply is intolerable, and it is incumbent upon us to protect, above all else, the health of recipient patients.

[Slide.]

This slide gives you an idea of the complexity of the policy considerations surrounding this particular policy. There are semantic considerations, which I am not going to go into. There are considerations concerning patterns of male homosexual behavior, issues concerning test-seeking behavior and inaccurate responses to the blood donor questionnaire.

There are incidence issues and we were wondering what happens with incident rates as a function of exclusion category. By this, I mean if we were to change the exclusion category to men who have had sex with men in the last five years, or, in other words, we would admit people who had had sex over five years ago, but not since, or perhaps a one-year exclusion category, do the incidence

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rates change as a function of exclusion category.

Also, prevalence issues, do they change as a function of exclusion category?

Finally, we have to consider human errors in testing in blood banking, if units are mislabeled or switched accidentally, even at a very low rate, they could conceivably contribute to infectious units entering the blood supply.

Undetectable strains, are there strains of HIV that simply aren't -- HIV in particular -- that simply aren't detected by current testing, and what about newly emerging pathogens and non-HIV pathogens.

It became clear very early on in internal policy discussions that we needed a way to really focus our thinking. Of course, what we are asking the committee is for guidance on deciding whether to and/or how to change the current policy, and to help the committee and ourselves focus on the important issues and sort things out, we are proposing that a decision be based on a model that I have devised that focuses on the number of infectious units that could enter the blood supply solely as a result of changes in the deferral criteria for MSMs.

[Slide.]

Now, it is going to be very hard with these slides

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to really read the numbers, and unfortunately, your material doesn't have the numbers on it, but you do have an outline in your premeeting material of the mathematical model.

I think if you can read some of the fine print on that, as I talk, and I will try to explain very carefully what is going on, and it is really quite simple. It may look complex, but it is actually quite straightforward.

Where are we going with this? Well, we want to know how many bad units, how many infectious units could conceivably enter the blood supply as a result in the change of policy, and that number is going to be calculated over here on the righthand side of the model.

And where do we start? Well, we start by asking if we change the policy, how many new MSMs will appear at the door to donate, and we all calculate this in this upper table up here, and of those people who newly appear to donate, how many are going to work their way through the system and potentially contribute infectious units to the blood supply.

Now, there are two tables here, and I am going to tell you that one of them will drop out of the consideration, but I want to discuss it with you because it is important to know that the issues that it covers can be, not overlooked, but they basically drop out of

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consideration.

The upper table here, as I just described, was designed to calculate or to look at the numbers of people newly appearing at the door to donate, so if you had a five-year exclusion policy, those people who abstained from having sex with another man for six years or more than five years, would now newly be able to show up at the door.

Now, we had set up the lower table here, and you needn't worry too much about the details of the lower table, to take account of test-seeking behavior and inaccurate responses. To be mathematically correct, you do need this table under certain situations.

Now, what we have wanted to do with this table was to say, well, what percent of the people in these exclusion categories will be giving inaccurate responses and, hence, getting past the questionnaire and into the screening stage.

However, the short answer to this table is that the people who will be giving inaccurate responses or who would be giving inaccurate responses under a new policy are already giving inaccurate responses, they are already being tested. They are already getting to the screening stage.

So, changes in our policy will not show a reflection in changes in people showing up that is at all perturbed to a first order approximation by the category of

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people who are giving inaccurate responses.

Another way of saying that is if we were to look at the five-year exclusion category, we might say, well, of the people who are excluded, the people who have had sex within the last five years, a certain percentage are going to want to be tested anyway, and they are going to exhibit test-seeking behavior or otherwise give an inaccurate response.

But those people are already doing that, so that group does not contribute to considerations of what is going to happen if we were to change the policy, and the reason I dwell on this is because so many of our internal discussions had initially focused on test-seeking behavior and how it would affect the policy, and what the organizational effects of the model have told us is that for considering changes due to changes in policy, we can ignore the test-seeking behavior question, which vastly simplifies the overall equation.

Now, let me go back and focus on this top table. In the lefthand column, as I said, we are putting in the numbers of people which newly present due to changes in policy. This line here is the numbers of people that would show up with a five-year exclusion policy, and this number here is what would show up with a one-year exclusion policy

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as examples.

With a five-year exclusion policy, we calculate -- and this is really Lynda Doll -- we calculate 58,000 people would show up, and about 112,000 people would show up with a one-year exclusion policy.

Where do we get these numbers from? Simply put, we took calculations of known male homosexual behavior and what percentage of the population exhibited or pursued MSM behavior, and there is data on what percentage of those have abstained for various time periods. We used those to calculate how many MSMs fell into the exclusion category in the overall population.

We then figured that of those people who were no longer excluded, they would appear to donate at the same rate that is generally followed by the U.S. population, which is 3 to 5 percent per year.

Then, we subtracted from that the number of people that we calculated were already donating, and this is where actually you take into account the truth-seeking behavior. That is how we end up with those numbers. Lynda Doll will go into that in more detail later.

Now, you have these people showing up at the door to donate blood, and these are the people that would be allowed through the questionnaire. Now, how can they

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contribute to infectious units entering the blood supply?

Well, there are really basically two ways that these people could contribute. One would be if they are in a window period of infection, a period after infection, part of which at least they are infectious, but during which current tests don't pick them up. Basically, this is an incidence phenomenon.

There is another way that they can contribute infectious units to the blood supply, and that is basically a prevalence phenomenon. If we know that a certain number of them -- and I will go through the numbers in a minute -- if we know that a certain number of them are infectious, then, we can calculate how many new infectious units, not people now, but infectious units are getting through the questionnaire and to the test screening assay.

Well, the test is supposed to be perfect, why would they go past that point? Well, an implicit or rather explicit assumption of the FDA is that even though the tests, as far as we can make them, are 99.999 percent or even higher sensitive, there is always the possibility of human error, such as a unit being switched in the blood bank or mislabeled, and there is also the possibility of undetectable strains.

Now, let me discuss these two issues, incidence

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and prevalence, separately. The first issue I want to discuss is the issue of incidence or window periods. Down along at the bottom of this incidence column here, I have written the yearly frequency at which you would see window period donations on a per-unit basis.

If there were no exclusion policy, in other words, if all MSMs could donate, and basically, that means a zero year exclusion policy, and that frequency is about 4×10^{-4} , which is based on an incidence rate of about 1 percent per year in this population, and sometimes you will see numbers that are higher than that, even 2 and 3 percent, and on the length of the window period divided by the number of days in the year, and that is the standard way of getting that number there.

Now, very few infected people will seroconvert after a year. As a matter of fact, with needle-stick injuries, 95 percent of needle-stick injuries who are going to seroconvert, seroconvert within six months, or another way of looking at it is 5 percent will seroconvert after six months.

We assume that another 95 percent of what is left will seroconvert in the next six months, so after two, six-month periods, or one year, or the period of one year exclusion, the number of window periods which would get

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through would be reduced by a factor of 0.05, 5 percent squared.

That comes out to a number like 10^{-3} . I haven't written it out here, but if you multiply that 10^{-3} number times this 10^{-4} number, you are dealing with 10^{-7} or 10^{-6} number, meaning that, let's say, 10^{-6} of these units might get through to the blood supply based on window period considerations. That turns out to be less than a tenth of the unit certainly for the five-year exclusion policy.

So, for the most part, these policy changes which we have considered would not have terrible consequences in terms of window period donations, largely because of the small number of people donating, and it is generally felt that there are basically no seroconversions after a year, but these are the closest we can come to, to real hard numbers to calculate for you.

Well, of more danger we think are the prevalence issues. Again, we have this number, 58,000, or 100,000 down here of new MSMs showing up and getting through the questionnaire. Now, how many of these will be infectious units?

The prevalence rates in the MSM population in the U.S. vary widely. We have been using a figure, an average national figure of about 8 percent, so that about 8 percent

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of those would be infected. However, the effect of prevalence is considerably less.

If we used an 8 percent figure, we would multiply the 8 percent times the 58,000 over here to get the number of units which would get into the testing stage, and then would be subjected to error problems, but we have to reduce that 8 percent because a large percentage of the MSM population has been tested, and we calculate or we know from a couple of sources that approximately 75 percent of HIV-positive MSMS already know that they are positive through testing, and we fully expect them to self-defer, there is no reason for them to exhibit test-seeking behavior.

So, instead of an effective prevalence of 8 percent, we are using an effective prevalence of about 2 percent. So, if you do the calculations, this means that if you started out with 58,000 MSMS newly coming in to donate with the five-year exclusion policy, you would get about 1,200 infectious units getting through the questionnaire and appearing at the testing stage.

Is that number a problem? Well, it is difficult to answer that. The way we would normally like to answer that for this model would be to multiply that times the error rate plus the undetectable strain rate and get an

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answer.

Undetectable strains are basically nonexistent at the moment. Really, group O is the biggest threat. The numbers we are considering for undetectable strains are less than 1 in 10^6 , so the undetectable strain part of the equation drops out. That leaves the error rate.

Well, I have saved the worst for the last. The error rate is very difficult to determine. Numbers anywhere from 10^{-6} , which is a good number, to 10^{-3} , which is a bad number, are floating around.

Certainly, if 10^{-3} was the error rate, you would get 1.2 units sneaking through here, which we don't want.

Well, I can't give you an answer as to what the error rate is, but I can suggest another way of looking at it which I think you will find helpful, and that is basically to make the assumption -- and which I have already stated this is an explicit assumption of FDA policy -- we don't know what the error rate is at this stage, but we worry about it. We assume that it's significant.

So, then if we want to take the standpoint of looking at this from changes in policy, we look at the current policy and what its effects are. Currently, in the U.S., about 1,000 units a year test positive for HIV. That means under current regulations, about 1,000 units get

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through the questionnaire and get to the screening process.

If we were to institute a five-year exclusion policy, we would now have 2,200. We would more than double the number of infectious units which get to the screening assay stage.

We are not making a recommendation based on this number, but I think it is clearly problematic. For the one-year exclusion policy, it would be 2,000 new units entering the testing stage, which would triple the number of infectious units getting to the assays.

Now, you would take this double or triple risk, and the benefit you would get from it would be a less than a 1 percent increase in the blood supply, and I will just let that number stand for your consideration.

We have done a very thorough analysis as you have just seen of the HIV story. The hepatitis story is still not as well worked out, but I am only going to summarize that along the lines of similar thinking.

[Slide.]

These slides are hard for me to read even at my desk, so don't feel bad. It is not just because they are small, it's complicated.

Now, this was courtesy of Mike Busch, so you can ask him the tough questions. The incidence rates for MSM

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populations, for the hepatitis are not as well worked out. So what Mike suggested was a way of calculating the incidence rates based on relative prevalence rates in the populations of MSMs and current donors.

[Slide.]

To make a long story short, we take those numbers and we can generate this table for HBV. Again, we are starting out with the same number of people appearing at the door. Once again, without going into details on the number, the incidence issues become very small. The window period issues contribute less than a unit a year from these numbers. So, the window periods for the hepatitis HBV drop out.

Now, a prevalence rate may be significant. We have quoted a 25 percent prevalence here based on anti-core testing. That does not mean infectious, and you will have to bear with me on that, but it still means excludable, and we calculate that maybe 14,500 units would get through to the screening assay, past the questionnaire using the five-year exclusion rule.

[Slide.]

For HCV, again without going into the numbers, the window period issues or the incidence issues drop out and become less than a unit per year. Using a prevalence rate

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of 1.5 percent non-IVDUs in this population, we calculate that maybe 900 units would appear from a five-year exclusion policy.

[Slide.]

To summarize that, and I have to warn you that the middle line here is not the correct numbers, here, I have listed the new infectious units that would appear using a five-year deferral category, the increase above current, and over here I have listed the approximate current units.

For HIV, we have discussed these data in detail. We get about 1,200 new units a year, and we already see about 1,000. For HBV, instead of using these numbers here, we are calculating that maybe 700 to 1,000 new infectious units would appear -- the confusion here is because these are core numbers -- versus about 6- or 7,000 units that are currently being tested positive, and all of these numbers are a little bit soft, but again you are talking about a 10 percent increase for a 1 percent increase in benefit.

For HCV, we are calculating about 900 new units up here over a much larger number of currently infectious units.

[Slide.]

So, the numbers certainly for HIV are problematic. One compromise which is suggested -- now, we are not

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proposing this as a policy, but we are throwing this on the table as the kind of issue that may want to be discussed -- is basically to have a two-phase testing scenario whereby if we reduce the exclusion time to five years or one year, whatever, the people who are newly admitted would first go through an HIV test before they could donate, but they wouldn't give a unit, and then at a certain time period afterwards, they could come back if the first test was negative and donate as would anyone else, and then be tested again of course.

This would basically have the effect of dropping the prevalence problems to zero. I suspect that this would be a very complicated thing for collecting centers to do, and I am sure we will get some comment on that.

[Slide.]

So, in conclusion, test-seeking behavior and inaccurate response issues have minimal effect on policy consequences, at least this particular policy that we are looking at, and that is a very important thing to realize.

Secondly, window period or incident infection considerations also have minimal effects on policy consequences.

Prevalence considerations may contribute significantly to policy consequences, particularly for HIV,

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which is the one for which we have the best numbers, and which has always been the one of the biggest worry.

The quantitative contribution of human error to infectious units entering the blood supply critically affects policy consequences, and there is a misspelling on the slide, but however, this number remains to be adequately determined. Certainly, we would like to see a lot of future research on this particular number, and we do encourage that.

We should not forget that the MSM population any way you look at it is a group that is at high risk for HIV infection and for many other diseases including HHV-8, which I have not discussed, but which Mike Busch will go into in detail in his talk.

We have really not been able to take into account newly emerging pathogens, but in a high risk population in which many sexually transmitted diseases are so highly prevalent, we certainly have to worry about the general phenomenon of other newly-emerging pathogens becoming highly prevalent in this population.

Now, the benefit of reducing the MSM exclusion criterion to even one year would be less than a 1 percent increase in the blood supply.

Finally, I should remind you that the risks we

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have discussed, the risks that are introduced by the newly included categories if we were to change the policy or to reduce the years of exclusion would decay after the first year, basically because of repeat testing issues.

So, what I have presented is probably the worst case scenario for about the first year, and then risks would go down after that.

I could read the committee questions at this point, what you have before you, or since we are getting a little bit late, should I read those at this point, would that be helpful?

DR. HOLLINGER: I think we will go ahead and wait.

DR. DAYTON: Okay, because I will read them before the committee discussion, so I will open it up to questions now.

DR. HOLLINGER: Dr. Nelson.

DR. NELSON: I am still a little troubled by the issue of an inaccurate response of time. There are a number of studies that have shown that people's memory for when an event occurred, that is, the last time a man had sex with a man being the year.

The assumption you made was that that would not be an issue and would be 100 percent accurate and as accurate as the question not having had sex since 1977, and I

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question that. I don't think that that -- I think there is likely to be more inaccurate responses given the time of one year or five years.

Five years, you know, if it was five years, that is certainly a long incubation period, but if it was one year, it's conceivable that there would be people that would inaccurately report unintentionally, maybe even intentionally, but most unintentionally just by lapse of memory.

DR. DAYTON: Well, these certainly are worries. We have tended to view them as second order of perturbations as opposed to first order of perturbations. I agree with you, I think cutting it to a one-year policy would be taking a big risk.

The other thing I should point out is that these are somewhat small numbers subtracted from fairly large numbers in calculating how many people are going to appear, so it is hard to say which way these numbers would go if we were able to accurately determine how many people are going to give inaccurate responses along these lines, but they would not change the numbers we see by factors of 2 or 3, for instance. That is our best estimate, but this is an estimate, I don't have hard data, and basically, you are right.

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DR. HOLLINGER: I want to remind the committee that there are several talks here today, so let's right now, at this point -- we will have an open discussion later on, on other things -- so let's limit the questions to the specific presentation today.

Dr. Verter.

DR. VERTER: I had two questions about the assumption. One, maybe you can just clarify for me. The first one is from what I read last night, what we were provided, it wasn't clear to me, the estimate of 95 percent seroconverting within six months, is there a confidence interval on that probability?

DR. DAYTON: That is a group down at the CDC, and they have something like a cohort of 50, and two of the samples went out past six months, so I don't know what the confidence intervals are, but that is as much as is known.

When you are getting out to those numbers, it is tough, but on the other hand, it does square with the common wisdom in the field that basically, you don't get anything after a year.

DR. WEINSTEIN: Six months is the upper bound of the 95 percent confidence interval. There is the median seroconversion is under three months. I think it was 2.8 in the published study, and six months is the 95 percent

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confidence limit upper bound.

DR. VERTER: The other question was does anyone have any data that of the 5 percent, the estimated 5 percent that don't seroconvert within six months, do they all seroconvert eventually?

DR. DAYTON: Well, we don't have data on that. As I said, there were two samples that seroconverted after six months, and what can you do with a study of two samples.

DR. NELSON: There has been a recent report in Clinical Infectious Disease of an AIDS patient that never seroconverted, and that is almost unique, but cases have been reported.

DR. HOLLINGER: Dr. Martone.

DR. MARTONE: It seems that you predicate some of these calculations based on the expected prevalence in the population of MSM. When you did that approximation, did you take into account the MSMs who have been tested for HIV and tested negative?

DR. DAYTON: I did not take into account the ones that had been tested and tested negative, but I did take into account the ones who had been tested positive and therefore self-excluded.

DR. MARTONE: So, what is this 2 percent who don't know, is that 2 percent of MSM who have never been tested?

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DR. DAYTON: That would be 2 percent of that MSM population, just as the general MSM population is likely to show up at the door.

DR. MARTONE: So, what would these calculations be if the screening question were have you in the last year had a HIV test which was negative?

DR. DAYTON: I don't know, I would have to think about that.

DR. HOLLINGER: Dr. Tabor, do you have a response?

DR. TABOR: The issue of those with HIV infection who don't seroconvert, if there are any, may not be significant because of the presence of antigen testing, but I think the message from Dr. Dayton's analysis is that the major risk in this situation or the major risk to focus on in this situation are those people who get through the first screening, which is the questionnaire, who are, in fact, infections, and who for some reason are not excluded by the second screening, which is the laboratory testing.

As he showed in his table, the major area that we have to focus on there are those whose infectivity is not detected because either there is a laboratory or other human error in the testing facility or because of new strains.

DR. HOLLINGER: Dr. Mitchell.

DR. MITCHELL: I guess that was my question. Is

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that what these numbers are? It doesn't seem to me that these numbers are the number of units that will get into the blood supply.

DR. DAYTON: You are absolutely right, and the reason we can't give you that number is because we don't know the real error rate.

DR. MITCHELL: But do you have an estimate of that?

DR. DAYTON: I would give you an estimate of that if I had a good error rate, but I just don't. Do we know how many units, and basically looking back throughout the year, how many have gotten into the blood supply through errors? We know that it is small.

The problem is when you are dealing with numbers like 10^{-3} to 10^{-6} , and you only have 1,000 positives per year, you are dealing with very small expected numbers of events.

DR. STRONCEK: The high risk individuals are at high risk for multiple things, not just one, so to make an assumption about errors in isolated tests, I don't think you can do that, because if one test is falsely -- you miss it, you might pick it up on another one.

So, I think you have to really be real cautious about these kind of calculations, and I think we really have

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to look at the experience of the blood centers, and it is my experience that there hasn't really been a lot of HIV slipping through, past all the screening we do, all the screening tests and getting into the blood supply.

DR. DAYTON: Let me address one point you made. Regardless of how many other infectious disease the units test for, if it is switched or mislabeled in the blood supply, it is still going to get through at that error rate.

DR. HOLLINGER: Dr. Khabbaz.

DR. KHABBAZ: I realize you went quickly over the hepatitis B calculations, but if I got your numbers right, you had the incidence, the number for incidents for five years and one year was the exact number that I saw for HIV. Given that you have a different window period duration and different rates, I don't understand that.

DR. DAYTON: I couldn't hear the question. What exactly are you asking?

DR. KHABBAZ: The incidence that you showed for hepatitis B seemed similar to the HIV one, and that got me confused given that with hepatitis B, you have a different, longer duration of a window period, and the rates are certainly different.

DR. DAYTON: Mike, do you want to comment on that?

DR. BUSCH: Just to say I am going to walk through

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those numbers later in detail.

DR. HOLLINGER: Jay, do you have a burning question?

DR. EPSTEIN: No, just to clarify. Rima, what is in the table and what was cited is the frequency at which a window period unit would be collected, which is dependent both on the incidence and on the window period. So, the fact that the two estimates come out close is because there is more than one variable operating.

In the case of HBV, you have a higher population incidence and you have a longer window period.

DR. HOLLINGER: I think we will move on to the next speaker. Dr. Lynda Doll is going to talk on sociological and epidemiological information.

Sociological and Epidemiological Information

DR. DOLL: Good morning.

[Slide.]

I have been asked to cover an awful lot of data this morning, so bear with me if you will. What I am going to try to do is talk about the characteristics of current and potential MSM blood donors.

[Slide.]

Related to that, I have five different kinds of data that I am going to present. First of all, I am going

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to present data on trends in the annual HIV seroprevalence rates of blood donors, as well as the behavior risks found among blood donors who test seropositive. This is from the CDC study of seropositive blood donors that has been ongoing for 10 years.

Secondly, I will describe the characteristics of HIV seropositive male blood donors who report same sex contact.

Thirdly, I am going to compare those characteristics of infected MSM blood donors with the MSM blood donors that were identified through the REDS study.

Fourth, and Andy already alluded to this, I am going to walk you through estimates of the number of potential new MSM blood donors who may present to the blood donation centers if the exclusion criteria were changed.

Finally, I am going to end by giving you some data on trends in the epidemic among MSMs in the United States. These data may provide you with information on the characteristics of the pool from which new MSM blood donors might be drawn.

[Slide.]

The first data I am going to show you are, as I said, from the CDC study of HIV seropositive blood donors. Information is collected on infected blood donors from 15

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U.S. blood centers, and that has occurred from May 1988 through the present.

The rates I will be showing you this morning are from 1988 through December of 1995. In order to be eligible, donors must have been 18 years or older at the time of interview. Donors are enrolled after they have been notified and counseled about their sero status and with their consent, they are asked to respond to a series of standardized questions assessing their risk behaviors.

Then, these reported risk behaviors are categorized into the same hierarchy of risk behaviors that is used for CDC's AIDS surveillance system.

[Slide.]

More than 19.2 million donations were screened for HIV antibodies during the study period that I am referring to. Of these, 2,980 confirmed seropositive units were identified, for an overall prevalence of 15.4 per 100,000 units.

Now, if you look at the trends in annual HIV seroprevalence, you will notice notable decreases over the study period. The overall prevalence among all donors, which is shown with the orange line in the center, has decreased significantly since 1988, from 23 to 8 HIV-positive donations per 100,000.

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This decrease is particular striking among the male donors, which is the blue line on top, which decreased, this prevalence decreased from 31 to 10 positive donations per 100,000. The prevalence for female donors, indicated in this case by the bottom line, was much lower, as you can see, than it was in the male donors.

HIV prevalence decreased by two-thirds in male donors across this time period, and only by about one-half in females over the study period.

[Slide.]

What this slide shows are the trends in prevalence of exposure categories or risk behaviors reported by HIV seropositive male donors. I am going to try to focus these data primarily on the male donors, since I am going to be giving you an awful lot of data.

For prevalence calculations here, the numerator was the number of donations by a positive donor reporting a given exposure, and the denominator was the number of donations for all donors of that particular gender.

For example, in 1988-89, which is the first and most left point on there, there were 225 HIV-positive male donors reporting same sex contact out of the total of 2,226,000 donations by males in that particular year, and giving a prevalence of 10.1 per 100,000 donations.

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The most significant change among the HIV seropositive male donors was in those men who reported sex with men. The prevalence of this group -- and that is in the red line -- the prevalence of this group dropped from 10 to 3 positive per 100,000 donations over the time period that I am referring to.

In the same time period, the prevalence of those not reporting a risk, which is the green line, also decreased, but it decreased much less rapidly. In 1991, the prevalence of HIV positives not reporting a risk, which we call NIRs, was higher than that for men reporting same sex contact. I don't know if you can see where the green line is higher than the red line there.

The prevalence of heterosexual exposure, as well as injecting drug use, are the two bottom lines. They are much lower and they did not change significantly over time.

[Slide.]

While there has been significant decreases in the prevalence of HIV among potential donors over these time periods, I think it is very important to note again that we are still detecting HIV-positive donations, and these pie charts show the same risk profiles, but only for the year 1995 for each of the genders, and again I am going to emphasize here just the males on the left.

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Although pre-donation questions should defer donors with known risks, such as men who have sex with men, it is quite clear that these individuals continue to donate blood. Of the male HIV seropositive donors identified in 1995, the N here is I believe 81, 53 percent of them were men who had sex with men.

[Slide.]

I am going to move on here and what I am going to do is talk only about the men who have been identified who have reported having had same sex contact in a recent time period, and the years I am going to use here are 1993 to 1996. The N on this slide, in this group of individuals, is 174, although you will note a few places that N will change over time, because some of the questions were not asked all the years.

What I would like to do now is just describe some of their characteristics. Again, this is only for the 15 blood centers in the study, 1993 through 1996. As you will notice, the majority of the MSM blood donors were in the ages 18 to 49, and nearly 70 percent were men of color, 13 percent were married at the time of donation, and over 50 percent were not homosexually identified, despite reporting recent same sex contacts. This is a relatively unique population of men.

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[Slide.]

The next data report on the sexual behavior contacts of these individuals. As you will note, nearly 70 percent of those men had sexual contact with another man in the last year, and nearly 60 percent had had sexual contact with another man in the last six months.

Remember that all of these men responded to the health historian at the time of donation that they had not had sexual contact with another man since 1977. In fact, 48 percent reported unprotected receptive or inserted anal sex in the last year.

[Slide.]

What I have done on this slide now is list a series of just a few selected reasons why these individuals indicated that they had donated blood, despite the fact that they were ineligible for donation.

Thirty-one percent indicated that they donated in order to have their blood tested for HIV. Over 60 percent indicated they had donated at a work site, and around 50 percent indicated that they felt pressured to donate by either fellow workers or the blood bank, the folks who were running the blood drive, et cetera; 38 percent reported concerns about privacy during that donation process, and finally, I think it is important to notice that only 13

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percent used the CUE to ensure that their blood was not used for transfusion.

[Slide.]

Now, what I am going to do now, just in a single slide -- and I apologize for these slides, they were put together relatively rapidly at the end -- what I am going to do right now is basically compare and show you just a little comparative data from the REDS study, the men who reported sex with men in the REDS study.

These data are from 1993. The data I have been presenting are all seropositive men. These men are primarily uninfected, but I assume there are some in here who are infected, and the N here is 105.

One of the things I was looking at, first of all, was how many of these men had actually reported recent same sex contact. If you remember, in the seropositive men, 70 percent had indicated recent same sex contact in the last year, whereas, this group reported 31 percent had recent same sex contact.

We don't know how many of these men had recent unsafe sexual contacts. We do know, however, that in this population, 31 percent had initiated a new relationship with another man during the last year, and this is known to be a time in which a lot of unsafe sexual behavior occurs.

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Interestingly, we do not have data on the sexual identity of these men. Again, if you remember, in the slides I just showed you, among the seropositive men, the majority of them are not gay identified or homosexually identified. We don't have those data here, but if you will notice, over 44 percent of these men are currently married, despite having had same sex contacts.

The majority of these men are white, unlike the seropositive men, and the age range is approximately the same. It is interesting to note that among these men from the REDS study, over 60 percent of them had donated more than five times in the last 10 years, and they should have been ineligible every one of those times.

[Slide.]

What I am going to do now is walk you through the estimates of the number of men who might be eligible for blood donation if the exclusion criteria were to change. My goal in this exercise was to arrive at the number of MSMs who had same sex contact, but abstained from same sex contact in the last five years, or abstained from same sex contact in the last one year.

This group of abstainers might then be eligible to donate blood again if the policy were to change as you will be discussing today. I was, by the way, unable to estimate

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the number of men who have abstained in the last two years. Sex surveys have not asked questions typically in the last two years, so therefore I was not able to do that.

I started to develop these estimates. What I did was I first found the 1996 male population estimates for men 17 years and older who would be eligible to donate blood, and as you will note from these, approximately 96 million men in the United States fell within these age ranges in 1996.

[Slide.]

The next thing I had to do -- and I am sorry these figures are small, but I will read them to you -- I had to find estimates of the number of men who report engaging in sex with another man for three time periods - since the age of 18, in the last five years, and in the last year.

Since age 18 is on your far right, five years in the middle, and one year on your left.

The sources for these data were twofold. First of all, the General Social Survey, which is a population-based cross-sectional household survey of the U.S. population that is conducted almost always on a yearly basis. They have skipped a few years.

The second source of these data is the National Health and Social Life Survey, which is a population-based

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sex survey that was conducted by Ed Laumann and his colleagues from the University of Chicago in 1992.

Together, these surveys provide nationally representative estimates of same sex contact. By the way, I feel pretty confident about these data. These are from two large surveys. If you look at some of the other large surveys that have occurred in the United States over the recent times, as well as surveys from England and surveys from France, you will find that these estimates are quite strikingly similar across surveys.

Now, the data shown in this slide, the data shown in the top slide, which is for men 18 to 49, comes from aggregates of six waves of general social service survey data from the following years: 1988 through 1991, 1993, and 1994, and one wave of data from what we call the NHSLs or the National Health and Social Life Survey, which was conducted in 1992. The N on this is about 5,000, the total population, not the number of MSMs.

The estimates for the number of men ages 50 to 59, which is the bottom grouping, were taken from a single survey, which is the National Health and Social Life Survey. Very few surveys actually ask information about the sex lives of individuals, of older individuals, which is an interesting story in and of itself.

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Walking you through these estimates, looking at the top, the estimates of the number of men ages 18 to 49, who report same sex contact, decreases with age, ranging from just over 5 percent reporting same sex contact since 18, to about 2.6 percent having contact in the last year.

Now, I think it is important to note that the estimates are nearly three times higher for men who are questioned in the central cities of the 12 largest SMSAs in the United States.

Rates for men 50 to 59, which is the lower group of figures, are generally lower than they are for the younger men, and they range from approximately 4 percent since 18 to just over 1 percent in the last year.

[Slide.]

What I had to do now is after I got the estimates of the number of men who engage in same sex contact is to flip it around and say how many of the men abstained. This isn't as easy to do as it sounds, and I hope I don't confuse you, but Andy wanted me to walk you through how I did this.

To estimate the number of men abstaining in the last five years and one year, what I did was use the figure of the number of men having sex with men since age 18, which is the figure on the left, roughly 4,700,000 men as a rough estimate of the number of men ages 17 and over who are now

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excluded from blood donation.

Note that we do not have estimates on the number of men who are actually 17 years old who have same gender contact, so I used the same figure as I would for men of 18. Similarly, I do not have figures specifically on the number of men over 59 who have same sex contact, and I used the figures for the men 50 to 59.

What I did was calculate separate rates for the number of men abstaining for men 17 to 49, and 50 and over, because of the reasons I noted on the previous slide, which is the rates are very different for younger men and older men.

So, what this amounts to -- and I am not going to walk you through exactly how I did this, unless you want me to describe it during the questions, I can do that -- the figures that I arrived at are as follows: the number of men abstaining from having had any same sex contact in the last five years was 1,385,934. Those are men who reported same gender contact since 18, but not in the last five years.

The number of men abstaining in the last year is about 2,600,000. Again, the figures are somewhat different for the different age groups.

[Slide.]

Now, the last thing I had to do -- this took quite

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a while, by the way -- was to estimate how many of these folks actually might donate blood, might show up at the blood donation center.

What I did was I estimated that 5 percent would donate in a year. This is the estimate of the percentage of the general population who currently donate on a yearly basis, and it is probably somewhat high for this population, but it is what we used.

Thus, we arrived at the following figures. Among the men who have abstained in the last five years, which if you recall was a figure of 1,300,000--some, 5 percent of that would mean that around 69,000 men might come to the blood center to donate, and similarly, for men who have abstained in one year, which is a figure of around 2.6 million, 5 percent of that is about 131,000 men, roughly speaking.

Now, it is important to note that these two numbers, 69,000 and 131,000 include men who are currently donating blood. Andy earlier showed you some figures that he calculated that estimate estimates of only the new donor pool, that is, men who have not been donating blood all along, but who would show up and would be the newly donating men, MSMs, and those figures, which I have not written down here, but I think you recall what Andy said they were.

For men who abstained from five years, that would

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roughly be about 58,000 men that we feel may show up at the centers to donate. For men who have abstained in one year, we figured about 112,000 newly donating men may show up to donate.

[Slide.]

I am going to end by giving you just some general data on the trends in the MSM epidemic in the United States. I am going to show you data from three -- very recent data, by the way -- from three CDC studies on some possible trends.

This first map shows HIV seroprevalence rates among MSM attending STD clinic in 12 cities in the United States in 1996. Data are from cities reporting at least 50 eligible specimens from MSMs.

The seroprevalence figures range from anywhere from a low of 4 percent in Minneapolis to a high of about 31 percent in Houston. Note that 50 percent of the cities in which these data were collected reported seroprevalence rates of 20 percent or higher.

[Slide.]

This figure describes seroincidence rates among MSMs, which are the red bars, women, and heterosexual men, women being the green bars, and I think it is purple being the heterosexual men, who again are STD clinic attendees in

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seven cities.

These were folks who came to the STD clinics who were tested voluntarily for HIV two or more times from 1991 through 1996. HIV seroincidence rates among the MSMs ranged from about 0.81 to 7 new infections per 100 person years, and were roughly three to six times higher than were those for women and heterosexual men from the same clinics.

[Slide.]

This next slide shows some disturbing trends from 1993 to 1996 in the incidence of gonorrhea in eight cities among MSMs. As you are all aware, the incidence of gonorrhea declined substantially among MSMs in the 1980s as a result of changes in risk behaviors among these men, and these data from STD clinics show a possible reversal in these trends.

The proportion of men with GC, or gonorrhea, increased across the eight clinics reported in this slide, from 12 percent in 1993 to about 24 percent in 1996. This is an increase of about 50 percent, and these eight clinics were chosen because at least 5 percent of the GC cases in these clinics were among MSMs.

It is disturbing to note interestingly that in Seattle and Portland, nearly one-fourth of the MSMs with GC and nearly one-fourth of all MSMs in San Francisco tested

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HIV seropositive.

I also want to let you know that after this study from which these eight cities were taken, actually, it is a study of 26 cities, and if you look at the changing rates over 1993 to 1996 in the larger study of 26 sites, the increase was actually 75 percent among MSMs across all of the sites, although the rates were much lower and the increase was from about 5 percent of men having gonorrhea to about 8.7 percent.

[Slide.]

Actually, the last large study I am going to show you is a study which is called the Young Men's Survey being done by CDC in collaboration with a number of health departments around the country.

The study assesses both seroprevalence rates and risk behaviors. It is a venue-based probability survey of young men 15 to 22 years old. Given the age of these participants, it is quite likely that they are relatively recent seroconverters.

Young men are sampled at public venues that are frequented by this population including such things as various street locations, dance clubs, bars, et cetera, so these are not STD clinics.

With consent, these men are interviewed. They are

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counseled and are given an HIV test. Now, from 1994 through January 1997, they collected samples on roughly 2,350 young MSMs in six counties, and they were, as you can see there, from the cities of Miami, Dallas, Alameda, Los Angeles, San Francisco, and Santa Clara, California.

[Slide.]

Seroprevalence range from about 4 percent for the 15- to 19-year-olds to roughly 8 percent among the 20- to 22-year-olds. It is interesting to note that the African-American men had the highest rates, of around 13 percent, and I do want to report that these rates were remarkably similar across all the sites in the study.

[Slide.]

Not surprisingly, these are just to give you a little bit of information on the risk behaviors among these men in the past six months, again, for the six counties, and not surprisingly, the incidence of risky sexual behaviors was quite high, 39 percent reporting any unprotected anal sex in the last six months, and 29 percent reporting unprotected receptive anal sex.

[Slide.]

One, just very kind of an anecdotal thing I wanted to talk just briefly about in terms of trends, I think we are all aware that there has been incredible behavior change

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in the population of MSMs in the United States, but I think somewhat disturbing anecdotal information is beginning to trickle out and to worry us quite a bit at this point.

The data here are from a very small sample of infected gay men in San Francisco published in the New England Journal of Medicine. The study was completed after the initial reports about the effectiveness of the new HIV treatments.

The data have to be taken as very tentative, but what they reflect again, as I said, are at this point considerable anecdotal information that we are receiving at CDC, and that is the increase in risk behaviors among MSMs.

What we show here is, and what the men answered was, because of new HIV treatments, 26 percent of the men responded that because of these new treatments, they were less concerned about becoming HIV infected and this was about a year or so ago, say, maybe 14 months ago, I believe, 13 to 15 percent of the men stated they would be willing to take a chance at becoming infected or had already done so because of the availability of new treatments.

Okay. I am done and I have given you a lot of information, but I think it is important that I tell you a little bit about what I consider some of the data limitations.

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[Slide.]

Clearly, the estimates from the population-based data and the clinic data, I think we have to say they may not be representative of MSM blood donors. The population of MSM blood donors is a population about which we know very little.

Secondly, we have used cross-sectional data to describe the estimates of the number of MSMS who have or who are abstaining from same sex contact. Cross-sectional data are not the best data to do those kinds of estimates, but there were no longitudinal data available to me.

Thirdly, I want to emphasize again these estimates are based on the validity of self-reports, and we always have to question that.

[Slide.]

With regard to conclusions, it is clear that the overall seroprevalence rates, as well as number of infected donors have decreased substantially over time. It is also I think was obvious that same gender contact remains the most frequent risk among infected male donors, and that the majority of these MSM-infected donors are non-gay identified men of color.

Looking towards the future, the pool of additional new MSM donors may be relatively small even with a change in

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the exclusion criteria.

[Slide.]

Looking at trends in the epidemic among MSMs, I think the higher rates of HIV seroprevalence, the STD rates, and the rates of risk behaviors among subgroups of this population have continued to concern us. The rates of all of these are higher among MSMs who are young and among MSMs of color.

Again, the anecdotal information I showed you suggests that risk behaviors may be increasing with the availability of new treatments. I think the bottom line here is the HIV epidemic among MSMs is not going away.

[Slide.]

Finally, I guess I just really want to reiterate that the cultural and relationship issues, as well as the various reasons that MSMs have for donating blood make risk disclosure less likely in a blood center setting.

More particularly, nongay-identified men who have sex with men, men who have sex with men from communities of color, and men who are seeking testing, HIV testing, may be unlikely to disclose in the blood donation setting.

Thank you.

DR. HOLLINGER: Thank you very much.

Questions? Yes.

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DR. BOYLE: This is an observation as much as a question, but because I do surveys for a living, I want to mention the self-reported issue. Generally, a lot of us feel that the recency data is a lot more suspect than the likely prevalence data.

Would you agree with that or do you have any observations on that related to the past year same sex versus lifetime same sex?

DR. DOLL: I think it really depends on what kind of a question you are asking. If you are asking have you ever had sex with a man even once, I think in that case, I would say the recent data would be more valid than the older data.

DR. BOYLE: I just make the observation, if you look at the drug use literature and several of the other literatures, the willingness to admit to something within a very near time frame, last six months or last year, when you do longitudinal data and you are able to look back, it looks like people are more willing to admit ever or two or five or seven years ago than they are willing to admit current.

I raise that issue related to this because it impacts both on the estimates of how many people would come in, but it also relates to the issue of your willingness to say lifetime versus last year or last two years in the

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screening process.

DR. DOLL: I think you are asking two different questions. Cognitively, is it more likely that you are going to give reliable answers for recent behavior versus older behavior, past behaviors, or I think what you were really saying is are you willing to admit more recent behavior.

DR. BOYLE: Exactly.

DR. DOLL: I would agree with you with the willingness.

DR. SMALLWOOD: Excuse me. The member that asked the question is Dr. John Boyle, who came in after I made the introductions. Thank you.

DR. HOLLINGER: Thank you, Dr. Boyle.

Other questions? Okay. Just one question on the 12 largest cities that you talked about, what percentage of the blood comes from the 12 largest cities that are drawn in this country, do you have any information on that?

DR. DOLL: I don't. In fact, I asked Andy that question because I had the same question.

DR. HOLLINGER: Anybody? I guess we don't know that. That would be important I think to know.

Yes, Dr. Mitchell?

DR. MITCHELL: I think that the reason that you

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brought up the data about the clinics is to show that the risk of STDs is not declining substantially in clinic populations, but do we have a sense as to what happens to MSMs who go to clinics?

It just seems to me that there is such a disconnect between MSMs who are in clinics and those who might donate blood that it is hard to say anything, to draw any conclusions about the potential blood donors.

DR. DOLL: Yes, and that is one of the reasons I mentioned it in the data limitations, knowing how much one can generalize from the clinic-based data is important. I wish I could give you that answer.

I did want to point out to you the fact that again the majority of HIV-infected MSMs tend to be men of color who have higher rates of STDs overall, but I don't know. I wish I could tell you that, I just simply don't know.

One thing, if these men themselves are not coming to clinics, though, and this is an important point, their partners may well be.

DR. DAYTON: Let me point out that a possible decision or recommendation by this committee may be the numbers we are seeing, as I put in my model, are problematic, and therefore, we may just decide that that is the decision and that we are not ready to change the policy.

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As pointed out, there is a certain amount of looseness to all of these numbers, and there is a lot of stuff that we haven't been able to take into consideration, so keep that in mind as something very important.

We put in our best numbers, we get the numbers I described in the model. Those numbers are worrisome. The other considerations could make it better or worse, but do you want to take a chance based on that. Bad numbers are an important thing to take into consideration. They can lead you to a decision, as well a good numbers.

DR. HOLLINGER: Thank you.

The next discussion is on sensitivity and other considerations of the interview process. Dr. Williams from the American Red Cross.

**Sensitivity and Other Considerations of
the Interview Process**

DR. WILLIAMS: Good morning. I would actually like to start out with a reassurance, and that is, approximately one year ago, the General Accounting Office issued a report to the effect that the U.S. blood supply is as safe as it ever has been, and I think it is primarily through the emergence of recent research, both in the blood donor situation and in some of the risk communities, that we are allowed to focus on some of this information and study

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it in a little more depth than we have been able to previously.

What I was asked to do was focus on the donor screening process itself and the questions that are asked, and provide some considerations of that, as well as some of the recent research that has emerged from the National Heart, Lung, and Blood Institute-sponsored REDS study and some of the surveys that we have been conducting in blood donors.

[Slide.]

I would like to start off with a couple of assumptions about the screening process itself. Some of you may take issue with some of these, but I am stating them as assumptions as a basis of the discussion I am going to present.

The first is that the accurate deferral of potential blood donors based on medical and/or behavioral history is a critical component of current and future blood safety, and I broke this down into three reasons.

One is the one discussed previously, the possibility of false negative laboratory tests due to window period or errors, the second being the protection from threats in the future that might occur that are infectious disease related, for which we might not have a test

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available, be it a genome-based test or a serological test. We may once again be dependent on the question process.

The third area is one that often doesn't get consideration. That is the attempt to minimize staff risk from collection and processing of infectious units that are drawn in the blood center.

[Slide.]

The second assumption I would like to make is a little more subtle, and that in this consideration, we consider two separate ways in which the screening process can be assessed or validated.

The first gets to the scientific validity of the screening criteria used that are designed to reduce transfusion-transmitted infections. That is the consideration before the committee today, what is the scientific basis of the current screening question and is it optimal.

The second consideration is the validity of the screening process itself and how well it identifies and defers donors once the specific criteria are selected, and this gets to things, such as the mode of question administration, the way the questions are worded, issues such as that.

I think it is probably fruitful to consider these

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separately, but I want to point out that they are not completely independent. There are two areas that I think where there could be overlap. One is the one mentioned by Dr. Nelson earlier, which is recency of a question that might affect both the willingness of the donor to admit to a risk and/or the ability to recall the risk, which would work in opposite directions.

The second one is another one in which we don't really have data, and that is if the potential donating public has the impression that the screens currently being used are not scientifically valid, and forms their own opinion as to whether or not they should be eligible. This might impact their willingness to self-defer based on the current criteria. This is an area on which we don't have data, but I think one that there are some anecdotes, and they need to be considered.

[Slide.]

There are really four stages, three listed on this slide, in which a donor can self-defer from the process. The first is self-deferral prior to the blood drive based on education. This far and away is probably the largest group of deferrals that takes place, and I think some of these numbers can be extrapolated from some of the general population data that have already been presented here.

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The second opportunity is on-site self-deferral pre-interview. That would be someone who comes in, sees the educational materials, and leaves again without any staff contact.

The third, a little tough to read, I am sorry, is deferral by the medical history interview itself. There are not, to my knowledge, extensive published information on this, but through the cooperation of Dr. Bianco at New York Blood Center and Bart Peoples and Ms. Plonowski at Red Cross, we are able to get data from 10 different centers, and these were all really pretty compatible, showing that the on-site deferral of donors was in a range of .01 to .03 percent of interviewed donors specific to the MSM since 1977 deferral.

In comparison with some of the other data that I will show you, you will recognize that these are really quite low on-site deferrals, and probably most takes place before the donor ever appears.

[Slide.]

The one I added here is the consideration of missed deferrals, what donors, in fact, do not admit to a history for one reason or another at the time of screening, and this is the area that REDS has been conducting some survey research, and I am going to show you some data

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relevant to that particularly with respect to the MSM deferral factor.

[Slide.]

The REDS study, for those of you who aren't aware, is sponsored by the National Heart, Lung, and Blood Institute. There are five blood centers that have been participating in the study since late 1988, early 1989. They are the three Red Cross sites in Baltimore, Washington, Detroit, Michigan, and Los Angeles.

As well, there is Irwin Memorial Blood Center in San Francisco and Oklahoma Blood Institute. The whole study is coordinated by Westat, Inc., located here in Rockville.

[Slide.]

Now, REDS has many components to it, but the one I am going to speak about is the survey research component, and one of the data elements that we built into the study way back in the beginning was that on all donors coming into REDS sites, about 1.1 million donations per year, we collect additional demographic information.

What we collect is race, ethnicity according to the current census categories, a lifetime transfusion history, country of birth, and level of education. We have this information in the database for all donors, and we use this to then define a sampling frame for the survey, so that

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we can be sure that it is representative and it gives us the option to oversample certain subgroups if we choose to do so.

The survey methods that we use are based on some pilot testing. We arrived at the best process being an anonymous mail survey that was sent out in monthly waves to active blood donors, and this generally goes out within a month or approximately a month after the donation event.

We use a stratified random sample with oversampling for younger donors and non-white donors who have lower representation in donor population, and tend to respond at a lower rate to the surveys.

[Slide.]

The process itself utilizes an advance letter to introduce the survey, followed by mailing of the survey form itself, followed by a follow-up questionnaire and cover letter, because it is anonymous and we have methods to distinguish the two mailings of the survey.

As I said, we did pilot surveys and determined the feasibility, and most of the data I am going to show you today is from our first main survey conducted during 1993 in which the sampling frame was 50,162, and we had a 69.7 percent response rate or 34,726.

[Slide.]

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The question categories are really pretty comprehensive. We recollect all the demographics on the responding donors because we can't go back to the donation record given that it's anonymous. We collect donation history from the donor, their donation experience, how they reacted to the process, how they felt about the screening process and privacy issues, and so forth.

We have extensive questions about past and current behaviors with time frames, and these time frames were designed to match the current screening criteria used in the blood centers. We have some comments about AIDS knowledge, and we had an open section for the donor to suggest written comments, and we got quite a few of those.

[Slide.]

We published the first large data set from this study. It is in the March 26th issue of JAMA. I have a few reprints if anyone would like to get one from me. We determined levels measured by the survey for a factor that we call deferrable risk, and deferrable risk is defined as a behavior collected by survey after the donation which should have resulted in the deferral of that donor. These follow the pattern of the questions that are used in the screening of blood donors.

I am not going to go through all these figures,

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but all of the risks are represented. You can see them in the publication itself. The one I am going to focus on is the donation of males who report sex with other males since 1977. Again, it is a little hard to read, but the figure up there is 0.6 percent, which is rounded up from 0.57 percent, which I will use a couple of times later in the talk.

All in all, 1.9 percent of donors reported one or more, what we call deferrable risk, and given a total donating population allogeneic donors per year of about 13 million, that equates to about 240,000 donors per year who have one or more of these deferrable risks.

[Slide.]

Now, what I am going to go to now is a multivariate analysis using the MSM factor. I have got to dig out my notes here because I can't read that slide myself.

What we did was model the deferrable risk of MSM since 1977 as a dependent variable against all these other independent variables, and these were age, race, country of birth, marital status, education, and the ones that are shaded here are the ones that we particularly wanted to look at because they had potential for future interventions, and we wanted to help try to define potential research in the future.

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The other ones listed here which we felt had intervention potential were education, donation influence, first-time repeat donor status, same gender sex, new partner in the past year, other STD in the past year, donation for purposes of an HIV test, privacy concerns, and use of CUE.

[Slide.]

These are the results of the logistic regression based on the MSM since 1977, deferrable risk of the sample group of 16,548 males who responded, 105 reported this as deferrable risk, again 0.6 percent.

In doing the multivariate analysis, the factors that emerged or remained significant in the model were use of CUE, concerns about privacy at the time of donation, and donation for the purpose of receiving an HIV test.

CUE actually was used by 2.9 percent of the males with that risk. It is a low percentage, and, in fact, in terms of the survey, it is a low number of individuals, but it is a large survey and it did remain significant in the model.

This was compared to 0.3 percent in all males for use of CUE and an adjusted odds ratio, which is significant at 9.7.

Privacy concerns, looking at it the same way, 16.2 percent of respondents with the risk reported a concern with

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privacy at the time of screening versus 5.6 of males who did not report the risk, odds ratio of 3.2.

HIV test seeking, the question being worded, "Have you donated blood ever primarily for the purposes of receiving an HIV test," was reported by 5.9 percent of all males versus 16.2 percent in the risk group, for an odds ratio of 2.9.

Again, the deferrable risk was reported by 0.57 percent of male donors. We did collect some other time frames of risk, 14.7 percent of these donors reported having MSM contact in the past year.

Now, you may recall a figure used by Lynda Doll attributed to the REDS study of 31 percent, I believe it was. That was for all males who reported any MSM risk ever, and this 14.7 percent refers to the since 1977 figure, so we need to distinguish those.

[Slide.]

Now, just to extend those numbers a little further, if you multiply the 0.57 percent times the 14.7, and estimate that 52 percent of donations are by males, and that figure is 6.7 million nationwide, that comes out to about 5,664 donations by males with MSM contact in the past year, and as Dr. Dayton stated, this probably will remain fairly constant independent of policy change, but this is

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the number derived from this.

If you use some of the prevalence and incidence figures that have been put forward earlier, this potentially, considering 4 per 10,000 potential window period, cases in this population, could represent one or two window period cases, and based on a 2 to 8 percent HIV prevalence, could represent from 100 to as many as 5- or 600 prevalence cases. These are, in fact, compatible with the data from the CDC study and information on actual transmissions that do occur.

[Slide.]

In conclusion, an unknown but probably large proportion of males with MSM contact since 1977 appropriately self-deferred before the blood drive takes place. 0.01 percent to 0.03 percent of interviewed donors were deferred on site for MSM since 1977, and this figure can be compared to 0.6 percent of accepted donors who reported MSM since 1977 by response to a subsequent survey. This is a 20 to 60-fold difference, and it is of some interest I think to look at the magnitude of these numbers in future research.

[Slide.]

Confidential unit exclusion, concerns about privacy and HIV test seeking were all significantly higher

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in males who reported MSM risk since 1977.

[Slide.]

Among the 1.9 percent of current donors who denied this risk at the time of screening, an estimated 0.08 percent or 5,600 per year are males with MSM contact in the past year.

[Slide.]

There are plans underway to conduct another large survey. This is currently under consideration by the OMB, and we hope to have the survey in the field by late winter or early spring.

One thing that we are going to do, I think most importantly, is get at a little more detail about the motivations of the donors who do report deferrable risk, and we have broken down some of the many questions which are being considered today.

We are also looking at test-seeking behavior and privacy issues in more depth, as well as donation incentives, and various other aspects of the survey I think will put us in a good position that, as changes are made in the screening process, we will be able to evaluate them in pre/post-surveys surrounding interventions that take place in the future, and hopefully, get some good reproducible data on just the processes that are taking place.

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[Slide.]

As survey researchers always state at the end of the talk, risk estimates derived from the survey procedure are based upon self-report. Validity has not been assessed by other independent measures.

However, in the various conduct of the surveys that we have had, two pilots surveys and two larger surveys, the numbers have been very reproducible over time, and I think some of the back calculations that these allow us to do have been compatible with finding some other studies, so we are hopeful that we are getting reproducible information even if the accuracy level, compared to truth, is currently unknown.

Thank you.

DR. HOLLINGER: Thank you.

Yes, Dr. Piliavin.

DR. PILIAVIN: I think it is obviously a great set of studies, and I am always interested in what you are finding out in these. My question has to do with the population that is being studied and your extrapolations from that population.

At least four of the five sites are very high incidence cities. Yes?

DR. WILLIAMS: I would have to disagree with that.

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It is relative, but I think we do have some major urban areas. One of the sites, particularly Los Angeles, had fairly substantial prevalence levels early in the HIV epidemic, and now is actually low to mid-level, so I would not characterize them as high incidence compared to other cities in the U.S., no.

DR. PILIAVIN: But I am not talking about cities. An awful lot of the blood that is collected doesn't come from cities, and we know from data that Lynda presented that the relative rates of MSM are three to four times as high in major urban areas as in non-urban areas, and you are taking this 0.57 percent and extrapolating it to all the blood that is collected in the United States.

That strikes me as quite probably inappropriate given the rates of this behavior in different locations. If you just said that a certain proportion of people are going to present who misrepresent themselves in terms of this behavior, it would seem to me you would want to adjust it for the rates of the behavior in the locations where the blood is being collected.

I therefore think your estimates are too high is what I am saying in terms of the extrapolation.

DR. WILLIAMS: That point is well taken. I have two answers to that. Number one, each of the blood centers

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that are part of the study are very large centers, and although they typically are viewed as being based in a city, in fact, they cover very large areas which are both urban and rural.

In terms of the representativeness of the sites within REDS related to the entire U.S., they are five sites. Anytime you have to pick five, you can find a city that it won't represent. On the other hand, I think it is, in terms of prevalence and incidence, it is a reasonable reflection of low-, mid-, high-level areas, and, in fact, in the new survey, the survey size is being doubled and we are bringing in four to five new sites including some clearly rural and some clearly more urban areas to address that concern that we have discussed, as well. So, thank you for that.

DR. HOLLINGER: Just to follow up, I think it would be useful. Maybe you could tell us the prevalence of HIV in the American Red Cross, all the American Red Cross, and how each of these centers, HIV prevalence comes out. That data ought to be available to you.

DR. WILLIAMS: I really don't have those data available. I am sure they could be brought to the committee on a formal request, but I don't have the numbers in my head. Throughout the system, the number typically year to year is about 6 per 100,000 prevalence.

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DR. HOLLINGER: Dr. Nelson.

DR. NELSON: You mentioned in passing the risk of donating to seek results of an HIV test, and you showed rates of 16.2 percent for the MSM, and 5.9 for the control group, but then you said that that was ever seeking.

Was most of that for this test? In other words, was it of those who were positive, did they donate blood this time to find the results of tests, because you said ever, and obviously, anonymous and other test clinics are now more available than they were, and I just wondered if that is an estimate of the current effect of this behavior on the seroprevalence.

DR. WILLIAMS: I think the best way I can address that is the other time period that we collected. We used the "ever" category for this analysis. The other figure we have is have you donated primarily to receive an HIV test in the past year, which I think is more relevant to your question, and that figure is 3.2 percent.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: In the pilot phase, did you test other modes of interview in terms of their impact upon the reporting of MSM or other deferrable risks?

DR. WILLIAMS: We did not use modes other than male survey techniques. As you recognize with that kind of

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sample size, they get very cost prohibitive. Our primary differences have been in the mechanism of followup, and we found a way to do it better and with less expense.

DR. HOLLINGER: Dr. Williams, in the survey, did you ask a question of why they gave inaccurate answers?

DR. WILLIAMS: That is in the survey that is upcoming. We actually didn't expect some of the data that we found, and we didn't have that question in, but it is in the new survey.

DR. HOLLINGER: I think we are going to take only a 15-minute break now. It is 11 o'clock. We are going to start again promptly at 11:15.

[Recess.]

DR. SMALLWOOD: May I ask the committee members to please return to the table. Speaker Dr. Mark Weinstein would like to make a correction to a question that was asked previously.

DR. WEINSTEIN: The question that was put before me was how many withdrawals and recalls were there last year. I just want to give you a correct number. My guesstimate was incorrect here. There were 28 withdrawals due to CJD in 1997, and there were 16 recalls of fractionated products in 1997.

DR. HOLLINGER: What again?

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DR. WEINSTEIN: There were 16 recalls of fractionated products in 1997, 28 withdrawals due to CJD.

DR. HOLLINGER: Thank you.

Thank you for all getting back here so soon. We are going to continue on. We are going to have a switch in the next two speakers. Susan Stramer is going to talk on detection of silent infections by PCR. Susan is with the American Red Cross.

Detection of Silent Infections by PCR

DR. STRAMER: Thank you. Although it doesn't look like everyone is back yet, I will begin.

[Slide.]

The topic that I was asked to speak about is the detection of immunosilent or silent infections by PCR. First of all, we need to define what immunosilence is, and the working definition that I am using for this talk is the failure to detect an infectious individual due to serologic test negativity, and I am limiting this talk to only those markers that we test for including HIV, HBV, and HCV.

In the context of this discussion, the agent must be transmitted by male to male sex even once, and remain undetectable by current serologic tests for the periods of time under discussion today, one year, five years, 10 years, or perhaps forever, depending on where the discussions lead

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us.

[Slide.]

What are the causes of immunosilence? Why would seroconversion not occur or not be detected during the periods of time under discussion? These have already been referenced to several times this morning.

One reason could be preseroconversion, that is, this is an infectious unit that is undetectable by current tests, and it represents again window period donations.

Another cause may be it is infection by a genetic variant, such as HIV, Type O, and lastly, which has also been referred to this morning, but I will not go into, is test error, that is, the given test error rate times the detection rate for that marker.

[Slide.]

There have been a number of papers published in the late eighties describing long-term infected individuals who did not seroconvert in a short period of time or an expected period of time, that it has delayed seroconversion for six months or more.

I just want to review some of these early findings. Imagawa published in 1989, that was later retracted in 1991, that 31 of 133 male homosexuals in the MACS study, which is the multi-center AIDS cohort study,

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practicing high-risk behavior were positive by culture. So, the endpoint in this study was cell culture. 27 of 31, or 87 percent of these individuals remained seronegative for up to 36 months.

However, upon a relook at these samples, the virus could not be reisolated from any of the above, and the conclusion upon the retraction was that this represented potentially incomplete or abortive infection.

Certainly, other possibilities, such as contamination, should not be ruled out.

[Slide.]

In the same year, also using the MACS population, Wolinsky and coworkers published the HIV proviral sequences, this time using DNA PCR, were detectable for 6 to 42 months before seroconversion in 20 of 24 homosexual men again in the MACS study. However, sequential samples from any single person were not consistently PCR positive, so they had positive alternating with the negative findings.

In fact, 7 of 24 of these were PCR negative immediately preceding seroconversion. So, again, one possible outcome for this study is contamination.

[Slide.]

In another study, looking at the San Francisco Men's Health Study this looked at 806 homosexual men and of

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those, 41 seroconverted prior to 1991. If you look at these 41, 37 of these 41 of seroconverters had a window between virus detection and seroconversion that was less than six months.

So, 90 percent of these did seroconvert in a time period of less than six months, and the remaining 4 cases, 3 out of 4 of those did seroconvert within six months, but one of those had a PCR-positive sample at 12 months prior to seroconversion.

However, on intensive studies beyond this, it was shown that one sample from a positive individual did contaminate this sample at the 12-month preseroconversion sample, so this study clearly documented the fact that contamination did occur.

The conclusion from this study was long-term immunosilent HIV infections are rare even among high-risk individuals.

[Slide.]

Based on another study that I will talk about in detail, and actually, this is Lyle Petersen and coworkers in 1993, the conclusions based on larger, more recent cohorts, and these were blood donors again that I will describe later in detail, few, if any, persons remain infectious but seronegative for long periods of time, and even in worst

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case analysis support that newly infected individuals always seroconvert in six months or less.

Donors who have not engaged in high-risk behaviors within the six months previous to their donation are at low risk for being in the window period.

[Slide.]

Looking at hepatitis C as far as what the early data demonstrate, there is one cohort that is being followed by Miriam Alter, a community-acquired hepatitis study, in which 13 patients with acute hepatitis C defined as RNA positive, ALT elevated at greater than 2.5 x the upper limit of norm, in fact, most of these were elevated at greater than 15 x upper limit of norm, they were negative by serologic testing for hepatitis C in acute phase sample which was collected after six weeks of onset of illness, and in follow-up samples collected at six months, then an additional follow-up at three and six months, and all 13 of these remained 2.0 seronegative in this time.

However, when tested by the Ortho version 3.0 ELISA, 7 of these 13, that is 54 percent, were reactive in earlier bleeds. However, one must focus the fact that none of these individuals would represent donations because all donors had elevated ALTs.

From personal communication with CDC, 95 percent

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of individuals with reports of community-acquired hepatitis do seroconvert within six months.

[Slide.]

Looking at data on post-transfusion hepatitis from the CDC, if you look at the total cases over the years from 1983 forward, in blue, and post-transfusion cases of hepatitis, in yellow, you can see over the past four years, there have only been two reports of hepatitis C, and in the last two years, 1995 and 1996, there have been no reported cases of hepatitis C post-transfusion.

[Slide.]

The remaining period of time of my talk is defining immunosilence as the window period, and to do that, I really must define what the window periods are, because really, there are two. There is one window period from exposure to infectivity, which in classic virology terms is referred to as the "eclipse" period. That is the time of viral replication in the primary site in the absence of detectable viremia or the absence of infectivity.

Then, we have an infectious period prior to serologic detection, which is the second window period. This is when an individual is viremic. However, the questions are often asked are viremic donations infectious, and we don't really know that all viremic donations are

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infectious, and also, within this time period, depending on the sensitivity of the tools used, nonviremic donations infectious, so just because something is viremic doesn't mean it's infectious, and then again, the reciprocal is also true.

[Slide.]

If you look at the entire window period as a total, what we know about time here is from needle-stick exposures that was referenced earlier in Andrew Dayton's talk. Well, needle-stick exposures -- and this represents a cohort of 51 health care workers studied by the CDC -- 95 percent of those individuals seroconverted within six months.

[Slide.]

If you look at the distribution of those 51 individuals, 90 percent of them seroconverted within 46 days, and only 2 of them extended beyond six months, 1 at 213 days to seroconversion. So, the vast majority did seroconvert within a reasonably short time, that is, 46 days.

[Slide.]

Here is another study from Larry Corey at University of Washington showing the time from discrete sexual event that cause infection to acute viral syndrome,

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and the time period here in days from discrete sexual exposure to when acute viral syndrome occurred, so this is really the first window period that I talked about, and in this case, for the individuals it occurred within a month.

[Slide.]

Looking at what we know for Window Period 2, that is, the infectious window period prior to serologic detection, this was really best studied in the study I referred to earlier by Petersen and coworkers, in which seroconverting blood donors were studied.

Repeat reactive confirmed blood donation was traced to the previous donation, and that previous donation, the recipients were investigated to see which recipients actually seroconverted from receiving the preseroconversion negative unit, and of 701 seroconverting donors, there were 182 in which recipients could be followed, however, 3 of those 182 were HIV-positive prior to study. So, the final number under investigation is 179.

[Slide.]

If you look at the time interval between the positive unit to back to the preseroconversion unit, there was an indirect relationship between time of the negative donation to the positive donation, and the time it took for the recipients and the likelihood for those recipients to

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seroconvert.

That is, if the interdonation interval were short between the seropositive unit and the prior seronegative unit, there was a high likelihood or 76 percent chance that those units would be infectious and transmit to the recipients.

As you see, for the last category, greater than 720 days, only 3 percent or 1 recipient was infected of the interdonation interval between the negative unit and the positive unit was very long.

[Slide.]

Looking at these graphically, the observed data are in the turquoise line, and the green line is the predicted data. If you take the mean or 45 days from the study, the interdonation interval was the shortest.

There was a very high likelihood or high probability that the unit would be infectious. So, this is the derivation of the 45-day window period, and then as you can see, the probability decreases as the interdonation interval extends.

[Slide.]

Hopefully, you can see all the little time points here. So, from this study, using a mean of 45 days, which really is a range of two different ELISA tests, 56 days for

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the very first, earliest HIV antibody tests, reducing it to 42 days for the next test, but that had a mean of 45 days, we can really crank down, if you will, the window period here by implementing tools or tests that have greater sensitivity.

So, with antibody tests that detect both IgM and IgG, we can cut 23 days off the window, leaving 22 days. With the implementation of p24 antigen, we can cut another 6 to 10 days or actually, for the analysis I used in this study, another 11 days off the window, which leaves 11 days remaining, and of that, looking at RNA testing, another 6 days could be reduced, leaving a period of time in 5 days, which by calculation, we can detect no RNA-positive samples in this period of time.

Really one question being asked is in these RNA-negative individuals, would they be infectious, and there really are very limited data to date although from animal studies presented by Harvey Alter at the AABB, material put into chimpanzees in this very early time thus far has not transmitted infection to recipients or to other chimpanzees.

[Slide.]

Looking at plasma seroconverters, if you plot 51 seroconversion donors and look at the ramp-up period of time

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here, and have these project down to one copy per mL, really, the 22 days remaining in the seroconversion window period from the most sensitive antibody tests is reproduced, and over that 22 days, this represents the very early time period, that 5 days where there is no detectable RNA, or during the ramp-up period of viremia in the individual, then, this represents the RNA-positive period up to peak viremia, and then really the development of antibody later in infection.

So, these data do reproduce the model I just showed you.

[Slide.]

In other studies, they have also been reproduced other than plasma seroconversion data from the San Francisco Men's Health Study, Toronto Sexual Contact Study, the ALIVE study, and other studies looking at various routes of exposure. This had a total of 395 seroconverting donors seen every 3 to 6 months.

If you stratify the results of those studies into gay men versus I.V. drug users, you can see during the different window periods that we are trying to close that these numbers really reproduce those numbers I showed you on that horizontal time line. That is, IgM to IgG seroconversion that is the 23 days I said the more sensitive

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antibody tests decrease. You can see the period here is 21 to 27 days.

There is no significant difference even though the I.V. drug users was a little bit longer in time, and that holds true for all the different markers that we are looking at, p24 antigen to first antibody, from 8 to 17 days, DNA detection, very comparable to p24 antigen, and lastly, the longest window closure can be achieved by doing RNA testing. Here, for the I.V. drug users, there was a significant difference in time period from detectable RNA to seroconversion, a little bit longer, but still only 27 days.

[Slide.]

Using these data for window periods, combining them with incidence rates, you actually can look at yield, and this is really the yield to residual risk of what remains or what would be detected that we define as immunosilent based on the preseroconversion window period, and at per-million donations, we have numbers of 1.48 for HIV, 9.7 for HCV, and using HBsAg only for HBV, a number of 6.65, and this is the Schreiber paper that is referenced at least once in everyone's presentation.

[Slide.]

Looking at PCR studies to try to actually close the window and decrease the seroconversion window, one

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method has been discussed. It has been actually implemented in Germany as pooled PCR testing, and I will go through these numbers because they may be difficult to read, at least I am having some trouble reading them.

713,000 donations were combined into 1,702 pools and tested for HIV, HCV, and HBV, and these were about 592-fold dilutions of the original sample. There was no yield of HBV, but there were 69 positive pools for HCV and 7 HBV-positive pools, and there are really 3 outcomes from each of these findings. Either the results were not reproducible, the individual donors upon followup didn't seroconvert, or that the donors did seroconvert.

In this study, what was done is all of these results were combined to estimate their yield, so for HBV, we had wanted 102,000, and for HCV, we had about 1 in 10,000.

[Slide.]

However, these findings were not reproducible in other laboratories, and that may be due to the other laboratories using different primer pairs or stability of the analytes, but then again it may have been due to contamination of the samples in the study that was performed.

In fact, at the ISBT meeting, there was a partial

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data retraction from the investigators of the study, so if you adjust the yield for their study using seroconversion as your endpoint, it would yield for hepatitis B at 1 in 240,000, and a yield for hepatitis C at 1 in 360,000 tested.

In fact, in two other locations in Germany and the Red Cross doing pooled PCR testing, they have obtained no yield for either HIV, HBV, or HCV that has not been in a serologically positive individual. So, they have found no preseroconversions by implementing this pooled PCR technique.

In fact, lookback data from the first study that I referenced, in 19 recipients of red cell units from these implicated HCV RNA-positive serologically negative units, there has been no recipient who has been found to have seroconverted or have been positive for HCV RNA.

[Slide.]

Looking at another study performed at the American Red Cross, this being an unlinked study, pooled PCR testing was also investigated and pools of 500, that is, a dilution of 500, looking at 20,000 donations, and these were the markers tested for in that study.

The take-home message is here, and I won't discuss the false positive results or the parvovirus B19 results although I think I just did, we did have 1 yield of

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hepatitis C RNA-only sample that is 1 in 20,000.

[Slide.]

That individual donation was seronegative by multiple tests, two FDA-licensed EIA tests, and a version 3 experimental strip immunoassay. Those were all stone-cold negative. The isolated yield was genotype 3a.

We had done some spiking as positional controls in this study, and the spiked sample was genotype 1a. So, the isolation of this one finding was not the result of contamination, but we believe it was a true yield.

In the individual donation, there was relatively low copy number probably because no special precautions were done for sample handling, and we know RNA is particularly unstable.

[Slide.]

So, what does this finding mean? One explanation most likely was that it was a window-case incident donor. However, the donor was infected by a genotype that is more unusual in the United States, and perhaps it may not have been detected by the current screening tests for HCV, although it was tested by all tests and was found to be nonreactive.

The last explanation is it could be an immunosilent infection, however, we have no follow-up sample

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available since it was an unlinked study, so we don't know how long this individual would have remained RNA-positive in the absence of antibody, but I will show what we expect that time period to be.

[Slide.]

If you look at the reproducibility of seroconversion in HIV, HCV, and HBV, these have been studied in plasma seroconversion donors, and what we have done actually to validate pooled PCR testing and look at what our yield would be by this technique, how much window period closure we could get.

We have looked at seroconversion panels from 28 HIV, 19 HCV, and 17 HBV, and I just want to go through those data very quickly.

[Slide.]

Here, you have the development of antibody, the development of p24 antigen, and here you can see the RNA yield, and using pools we would only get about a 2-day window period reduction, but here you can see the rapid ramp-up of RNA and it does parallel exactly p24 antigen, that is, p24 antigen detection as a subset of the entire RNA detection.

[Slide.]

This phenomenon is very reproducible as it has

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been reported in the past, however, there was one atypical seroconversion panel from Boston Biomedica, and here you can see, in yellow, consistently high titers of RNA, but here you can see fluctuating levels of antibody.

Antibody is first detected here, a high spike of probably IgM, and then it declines, and I don't know if you can see the cut-off line here for serology, but one sample actually goes below the cut-off, but what you have here in the orange line is p24 antigen, and between the two, one sample is always positive by one of the two current serologic tests.

But the take-home message is here, these were all strongly RNA-positive.

[Slide.]

If you put all the data together for HIV, here again you see a consistent ramp-up period. This is the period of time prior to p24 antigen, which was just the median of this population. It is just that the cut-off of the sensitivity, if one were to do pooled PCR testing, and then later you have the development of p24 antigen in these samples, and then a decrease in RNA levels due to antibody production.

[Slide.]

Looking at the same thing for HCV, two more

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important findings for HCV is that the viral titers pre-seroconversion are much higher in hepatitis C, and the window periods are much longer. We don't do an HCV antigen test of any earlier antibody detection for hepatitis C.

Here you can see the RNA period, antibody development by version 3 ELISA, and there is a 26-day window period here.

[Slide.]

This is reproducible and here you can see many negative, seronegative and RNA-negative donations. One disadvantage about using these plasma panels is you don't know when exposure actually occurred. So, Window Period 1 that is exposure to infectivity cannot be determined from the use of these panels, but what you can see again is that these events are relatively reproducible following the ramp-up of virus.

So, virus is produced and then here again there is a long window period prior to the development of antibody for hepatitis C.

[Slide.]

So if again you combine all the data that we have looked at, we have very high viral titers here greater than 3.3 per million, and then once antibody is produced, the titers still remain high and then decrease over time when

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you get a full band pattern on a supplemental test.

[Slide.]

Looking at hepatitis B the same way here, about 40 days after the detection of HBsAg antigen here -- which is in orange -- we get an anti-core response, and in all seroconversions panels investigated, either anti-core was positive or HBsAg was positive, but the other finding on these panels is the HBV DNA, not dissimilarly to HIV RNA and HIV p24 antigen, HBsAg and HBV DNA parallel each other identically, and in this case, virtually identically, such that there would almost be questionable yield from DNA testing, and there would be no yield from pooled DNA testing, which is what our data eventually will show.

[Slide.]

This is a chronic infected individual, but again in 40 days, even though there is no detection of anti-HBs, there is detection of anti-core, HBsAg, and HBV DNA. So, this period of time is covered by both HBsAg and DNA if one were testing.

[Slide.]

So, again, looking at these in a box and whisker plot, if one were to do pooled PCR testing, which is a cut-off of here, you would have no yield virtually by doing HBV DNA pooled testing.

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[Slide.]

Even though this data is unclear, I just want to contrast this to here you have for hepatitis B, yield by HBV DNA testing, shown in yellow here the numbers that would be detected if we were doing pooled testing relative to the numbers detected in conventional ELISA, but simply one could look at improving HBsAg sensitivity as in these experimental tests, for example, and one could close the window quite significantly for those hepatitis B seroconverters that really represents any yield that we would have by implementing pooled PCR testing.

[Slide.]

To summarize all the window case data I have shown you, these are the median copy numbers detected for preseroconversion samples. For HIV, it is 3,250 copies, HBV, 600 copies, and HCV, 3.2 million copies over a window period here of HIV of 6 days, 10 days for HBV, and 41 days for HCV.

Virtually 97 percent of this window period could be closed by implementing pooled PCR testing for HCV, whereas, there would be no window period reduction for HBV and only about a 1.6 to 2.8 day window period closure for HIV.

[Slide.]

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In conclusion, just to go through this agent by agent, for HIV there have been reports of immunosilence greater than 6 months, however, those studies are not reproducible and in large part attributed to tube contamination.

The residual preseroconversion window period, which I referred to as immunosilence for HIV, can be closed and has been closed about 25 to 50 percent by p24 antigen testing and probably for the very small remaining window of HIV, can be closed by another 25 to 50 percent by pooled PCR testing.

[Slide.]

For hepatitis C, which is rarely, if at all, transmitted by male to male sex, there are long window periods and high viral loads preseroconversion. As I have said, about 97 percent of the remaining window could be closed if we implemented some type of pooled PCR testing.

RNA-positive antibody-negative yield from the pooled PCR tests performed in Germany and the absence of seroconversion on followup are not reproducible, and their adjusted incidence then was 1 in 360,000 for HCV.

[Slide.]

For hepatitis B, we have a good test for HBsAg, such that there would be no yield by pooled PCR testing, and

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following the decline of HBsAg, all infected individuals are detected due to anti-core, and the yield in fact, as I said, for HBV, can be improved even as simply by doing tests for improved HBsAg detection relative or as compared to pooled PCR testing.

So, that's it.

DR. HOLLINGER: Thank you.

Questions? Dr. Nelson.

DR. NELSON: You mentioned the interesting case of the type 3a hepatitis C that was immunosilent.

DR. STRAMER: Right, was not detected.

DR. NELSON: It was not detected.

DR. STRAMER: Immunologically.

DR. NELSON: I guess my understanding is most of the types in the U.S. are 1a and 1b with scattering of other types, but in Europe and other places, there is a wider range. Is there any data about the likelihood of genotype variation in hepatitis C escaping detection with the current methods or is that not a problem, or can you quantitate that issue?

DR. STRAMER: I brought up the 3a case. It is an interesting finding, and it certainly could have had a delayed seroconversion response if we had follow-up samples. We know in the U.S., greater than 70 percent of hepatitis C

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isolated is genotype 1a and 1b.

In order to study what you asked, we would have to make genotype-specific serologic tests and investigate this, and to my knowledge, there has been no work along those lines.

In larger studies that we are about to undertake, which will be linked, we should be able to, if we genotype any recovered isolates, be able to answer that question hopefully.

DR. NELSON: I guess the country in the world that probably has the most hepatitis C is Egypt.

DR. STRAMER: Right.

DR. NELSON: And they have a quite different genotype as I understand, type 4, I think, and I know there is a lot of research going on there, but I don't know about what kind of assays they are using and the sensitivity. It might be important to find that out.

DR. HOLLINGER: The final presentation today is by Mike Busch, and he is going to be talking about false negative responses.

Seroepidemiology

DR. BUSCH: Thanks. It has been a pleasure to work with Andrew Dayton on this project, and I think there has been a lot of good work to try to focus the issues.

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What I was asked to do is to address several areas, particularly the issue of trying to bring the window period data and incidence rate data in gay men versus blood donors to bear on the specific issue of what the impact of reduction of the deferral period would be on risk of window period donation, so that is mostly what I will do, and then also I wanted to share considerations to the committee about a new agent, such as KSHV or the new HHV-8 agent on the discussion because I think, to my mind, a major issue in this debate is that of a newly identified agent that might still be endemic in the male sex male community, and that as you consider a potential change in policy, that you think forward what might have happened had we changed the policy before HHV-8 was discovered and the data that I will share was brought forward, and whether that policy wouldn't be perhaps inappropriately, but perhaps rapidly reversed as a safety measure.

[Slide.]

Susan can't present in any setting without sharing all of her last pooled PCR stuff, and I can't present anymore without talking about a test that we have been building and have applied here. It is called the de-tuned antibody test. This is an outline of what I will be presenting.

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I want to first present the principle and some data on this new method for measuring incidence and then specifically show the incidence rate of HIV in the blood donor population overall, the mix and first time versus repeat donors.

Then, I want to show incidence data in HIV, very new incidence data in San Francisco specifically, but again and very similar data has been generated recently in a number of regions in collaboration with CDC from other regions of the country, other cities, again using this de-tuned EIA approach to measure HIV incidence, and then given the differing incidence rates in the donor pool versus the male sex male community, I want to apply those data to understand what the impact of the deferral change would be on residual risk.

Then, to indicate for hepatitis B and hepatitis C, we actually don't have contemporary incidence rate data, so here I will present data on the prevalence of these agents in the gay community and the donor pool, and then based on relative prevalence rates, extrapolate estimated incidence in gay men and then similarly use that estimate to project out the impact of deferral change, and then finally, present this HHV-8 discussion.

[Slide.]

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Going quickly into this de-tuned, basically, the problem with measuring incidence, obviously, we use it a lot in our discussions now to estimate the risk of window period donations and to project the yield of new tests.

It is also very valuable, as discussed, to understand the dynamics of the spread of HIV in the population, and as we are considering issues, such as changing deferral criteria to understand incidence in our different subgroup of donors, first time, repeat, demographically characterized or potentially historical risk factor characterized.

[Slide.]

The problem we have, though, is that measuring incidence is very difficult by classic methods. You need to enroll populations, follow them over time, and watch them seroconvert, and that is, one, very expensive; two, it is actually very often biased because you can only measure incidence by classic methods in populations which are being actively followed, so if you have people that are dropping out of the study, you can't measure their incidence because they are not being followed, and oftentimes in other populations, if you enroll people and want to measure their incidence, you have to counsel them to prevent further spread, and so you are actually potentially impacting the

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incidence downward as a consequence of enrollment, so you really can't measure a natural true incidence rate.

So this led particularly Rob Jennsen, Glen Satton at CDC, and Sue Stramer and myself, to develop an assay we called the de-tuned HIV test which allows one to quickly measure incidence from any large sample set that is tested.

[Slide.]

The principal slide that Rob sort of developed is instead of all the work to close the HIV antibody window by building better tests, we actually took a test that was a run-of-the-mill test and made it bad. We purposely de-tuned it, so that it delayed detection of seroconversion.

This is a conceptual sort of titer slide with infection. You seroconvert to detection by sensitive methods, but, in fact, the titer of HIV antibody increases over a period of, in fact, many months, and by building a test that in essence delays detection until one reaches a fairly high titer of antibody, one can detect among positives the subset of positives who were recently infected.

By measuring and understanding the rate at which people are picked up in what we call the de-tuned window, we can project the incidence rates. I am not going to go into the data, extensive data developing this, just a few slides

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about it and then apply it.

[Slide.]

The principle of the tests that we use are actually an Abbott viral lysate EIA which has a broad dilutional dynamic range, and these are the standard conditions, and just suffice to say that we modify these conditions running the samples at very high dilution, reducing the incubation times and setting the cut-off way up in order to delay detection.

[Slide.]

This just shows some representative seroconverters. There were about 105 seroconverters that were studied, many of them having very frequent serial bleeds extending over either months or literally years, and what you can see is the standard test comes up quickly and plateaus, whereas, the de-tuned modification of the test comes up very slowly.

[Slide.]

This just shows on a large number of seroconverters a plot of time from seroconversion by the standard method to various levels of seroreactivity on the de-tuned assay.

What you see here then is a best fit curve the Glen Satton developed, that basically shows, in essence,

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that about 129 days after seroconversion is detected by the standard assay, about 4 months, people cross the 75 percent cut-off level that I will be mostly focusing on, and again not going into a lot of detail.

[Slide.]

Just shows a sort of curve, survival to seroconversion on the de-tuned assay. Again we are working with the 0.75 cut-off, and the median is 129 days delay in seroconversion, and what you can see here is that there is really the vast majority of people who are less than that, more recently infected, will score positive and beyond 150 days, virtually 100 percent of people will be called long-term infected, so that the method is quite sensitive and specific for identifying recently infected people among positive samples.

[Slide.]

So the very simple way we use this test now is to take samples from any population that is screened, the whole donor pool, a population of sampled people at anonymous clinics, wherever you are testing, and you simply use the standard methods to identify among the screened people the people who are positive by standard criteria.

All you do is reflex the positive samples through the de-tuned assay and identify the subset of positives who

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were recently infected. Then, by identifying that group of people who were detected as infected by the standard methods, but negative by the de-tuned version, you have identified the people who are in the 129-day window of time between detectability by standard methods and the de-tuned assay.

So, to derive an annual incidence rate, all we have to do is to adjust up the 129 days to annualize it by multiplying by 365 over 129, so that estimates the number of people who each year would have seroconverted, and divide by the total number of susceptibles or the total number of negatives coming out of the population.

[Slide.]

Just shows work that is actually in a publication that is under review, comparisons of the observed incidence in various populations that have measured incidence formally, San Francisco Men's Health Study, alternative test sites in San Francisco, and large blood donor first repeat blood donor population from REDS.

The observed incidence in these populations through classic follow-up methods versus the estimate derived by simply running the de-tuned test on the positives and very quickly estimating by the formula in the last slide, the incidence.

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You can just basically see that the dramatically different incidence rates ranging from highs of 1 to 3 percent, to lows of 2 per 100,000. These incidence point estimates are quite similar.

[Slide.]

Now, to get to the real data relevant to the blood donor pool, the incidence in repeat donors is something that we have classically been able to measure, and this is the REDS estimate for the three Red Cross regions from '93 through '95.

This is sort of a subset analysis of the Schreiber paper, and in that period, we had 20 seroconverters with a person time estimate -- I forget the exact number -- but 1.2 million repeat donors, so it yielded an estimate for incidence of 2.6 per 100,000 with the confidence interval shown here.

By the de-tuned test, we identified 10 recently infected people who were non-reactive by the de-tuned assay, and simply running the formula, that yielded a point estimate of 2.95 per 100,000 person years with the confidence interval shown.

[Slide.]

We have never been able to measure incidence in one-time donors before, and that has often been a criticism

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in our estimates of risk, et cetera, is that maybe the one-time donors, who account for about 20 percent of the donor pool, maybe they have a much higher incidence and risk.

So, for the first time here, we were able to measure incidence and just focus on the bottom line here. Out of 2.7 million, one-time donors, during the study period, 547 were found to be HIV-positive, and when those were subjected to the de-tuned assay, 69 were determined to be recently infected, and from that rate of picking up people in that 129-day window, we estimated the incidence in the one-time donors at 7 per 100,000 person years, and it was quite stable over a 4-year period.

[Slide.]

So, now for the first time, we can derive a true weighted incidence or estimate of the incidence of HIV in the mix of donors that we have. In REDS, 22 percent of donations are given by these first-time donors who have about a two-plus, two- to three-fold higher incidence rate than repeat donors.

So, if we simply multiply that times 22 percent, we get a contribution of first-time donors to incidence, and similarly, a contribution of repeat donors, and by adding that together, we can say that the overall incidence in our

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donor pool is therefore about 3.9 per 100,000 person years.

[Slide.]

Unfortunately, these slides are small, one of them, this one. This is now the comparison data that we now need to understand the incidence in gay men to compare with that among these blood donors.

Really, here again, we are just going to look at the first couple lines, and I will say the numbers. This is a very recent study. This is all the individuals in San Francisco who sought testing in the anonymous testing clinics in San Francisco in 1996.

In that period, there were about 7,700 people went in for testing, 172 people were found to be infected, for a prevalence of 2.2 percent. When these samples were subjected to the de-tuned assay, 36 were found to be recently infected, which yielded an overall incidence estimate of 1.3 percent.

Now, what was important and one of the main reasons I show this is these individuals, when they are given the testing, they are asked, they have to fill out an interview, which indicates risk factors, et cetera, and that is linked to the test results, although not to the individual.

The important finding here is that actually all of

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the incident cases were in individuals who had had male/male sex. So, the basic premise here is that although there was some low level prevalence in individuals from other risk categories, in people seeking testing in San Francisco, all of the newly infected individuals were individuals who acquired HIV from male/male sex, and the incidence in that group was about 2.5 percent.

[Slide.]

This is another survey in San Francisco where we have incidence data from the de-tuned assay. This is the Young Men's Survey, a subcomponent of one of the studies that Lynda Doll presented prevalence data on, and here, using the de-tuned assay, we can get the incidence rate within this population.

In about 1,000 individuals, these are young men sampled in street, sort of catchment methods, 1,000 individuals tested in two waves of this study; 11 people were found to have recent HIV infection by the de-tuned assay, which yielded an incidence of 3 percent in young gay men in San Francisco with a slightly lower rate in the more recent year cycle compared to the prior year cycle.

You can see that these rates are fairly constant, higher in hispanic, black, et cetera.

[Slide.]

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One last slide on incidence in San Francisco.

This is a different study of young gay men in San Francisco. This is actually a random neighborhood survey method, and this is classic incidence rates, but you see similar rates of 2.6 percent with some evidence of decline in incidence over the last few years.

[Slide.]

So, these are incidence data and perhaps should be couched as really worst case. Obviously, this is San Francisco and some of the catchments here are people coming in seeking testing or surveys on the street in the vicinity of gay bars, for example, so in a sense, this is worst case incidence, but as we will come to, and as Andrew said at the beginning, even given worst case incidence, incidence will drop out as a major consideration due to the window period issues.

Here, what we have got is in our current donor pool, we have got an incidence of about 3.8 per 100,000 person years, which translates, if we run the 16-day infectious window period times this incidence to a risk in the current donor pool of about 1.7 per million, and this is incorporating p24 antigen screening into the residual window period.

Now, in male sex with male, we have talked about

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incidence rates in these high-risk populations in the range of 2 percent. Some of the numbers that Andrew has been running estimate an incidence in male sex male more generally of 1 percent.

Now, the ratio therefore of the incidence in gay men versus blood donors is extraordinarily high, 250 to 500-fold higher rate of HIV infection among male sex male, active male sex male individuals compared to the background donor population, and if we were to accept blood essentially exclusively from individuals that had this kind of incidence rate, the risk of getting a unit, the risk of a donor, a person with recent male/male sex being in the infectious window period is extraordinarily high, where the curve is 1 per million, we would be talking about risks in the range of 1 in 1,000 from window period donations.

[Slide.]

However, when we then ask what the effect of deferral would be on reducing that risk, it is profound, and the reason is the window period is transient, and from the data that Glen Satton analyzed from health care workers, which is by far the best data, and I think is fully supported by all the other data that is out there, although there are these rare anecdotes of AIDS cases, they are almost always rapidly fatal in these individuals who have

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delayed seroconversion, but anyway, so using the 95 percent, 6-month seroconversion confidence interval, and applying that to, in essence, factor down the incidence and the risk estimate in the absence of deferral, so if we just took blood from male/male sex donors, the risk would be 924 per million.

But if we make them wait a year for male/male sex, the likelihood that they will be in that window is actually this number times 0.025 percent, which is extremely small, so it drops it down to 2.3 per million, and that assumes that all the blood was coming from individuals who had deferred for a year from male/male sex.

So the relative risk, even if all the blood was collected from male/male sex donors who had deferred for a year, is only 1.35 times that of the current donor base, and if you were to defer for five years, it would be infinitesimally different, and you basically are back to background donor base risk estimates.

So that your deferral really, to my mind, does build in enough time that the residual risk attributable to a small contribution of remote male/male sex donors to risk becomes insignificant, particularly in light of things like we just saw, the first time versus non-first time donor relative risk is about 3-fold, and here we are talking about

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a 1.3-fold relative risk.

[Slide.]

So, doing the same thing for hepatitis B, first, to present a little bit of hepatitis B prevalence data, which there is not a lot out there in gay men. This is data from San Francisco Men's Health Study, Dennis Osmond, and basically, I think perhaps just the two top lines here, this is hepatitis C and hepatitis B.

Basically, for hepatitis C, if you look at the rate of HCV infection, it actually overall the rate was about 5 or 6 percent, but if you stratify by acknowledged intravenous drug use, you see that virtually all of the hepatitis C in gay men is in gay men who also use drugs, so the prevalence there was 18 percent.

The prevalence in the nearly 600 gay men who denied injection drug use was only 1.5 percent, as we will see, that rate is not dramatically different from the background rate of HCV in first time blood donors.

Now, in stark contrast, for hepatitis B, the rates are exceedingly high, irrespective of IVDU. These were gay men who enrolled back in the mid-eighties, and so these estimates of 80 percent prevalence of anti-core, exposure to hepatitis B, are really very high.

So, rather than using these numbers themselves,

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the next slide shows one other source of hepatitis B exposure data in gay men.

[Slide.]

This is coming from a recent analysis, unpublished at this point, in the Young Men's Health Survey again, and in I believe this was 1995, the young gay men in this study were tested for hepatitis B exposure, and about 23 percent had evidence of exposure to hepatitis B indicated by anti-core. Actually, a little less than half of these individuals had already been vaccinated.

Then, for hepatitis B surface antigen, only 6 of these anticore positives, or 5 percent of the exposed, were carriers at the time of testing. So, this will be approximately the rate we use.

[Slide.]

Plugs these data into that same formula, which I think you saw earlier, and just to go slowly through this, basically, the idea is, is that from those two sources of data I just showed, we have estimates for hepatitis B exposure rates among male sex male non-injection drug users, and hepatitis C exposure rates, about 25 percent and 1.5 percent respectively.

We know the rates in first time donors, anti-core rates run 2.9 percent in first time blood donors from REDS,

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and hepatitis C runs about half a percent confirmed HCV-positive rate.

So, that allows us to derive a prevalence ratio between prevalence among male sex male non-injection drug users and first-time blood donors, and for hepatitis B, that is 8.6-fold. So, in other words, people who engage in male sex male have an 8.6-fold higher rate of HBV exposure, historical exposure, than do current first-time blood donors. Hepatitis C, it is about a 3-fold higher rate.

Then, we sort of did something that epidemiologically is kind of a leap, but we do have data to support the validity of this, and that is we use this relative prevalence ratio to factor up the estimate for incidence and the estimate for risk that has been measured in first-time blood donors.

These are the current donor incidence rates from REDS for HBV and HCV from the Schreiber paper, and these are the current risk estimates for HBV and HCV from the Schreiber paper, and basically all we did was to multiply these estimates times the prevalence ratio to derive an estimated or projected male sex male incidence rate for each virus and male sex male projected risk for each virus.

So, basically, the assumption is that the incidence parallels the prevalence and that the 8-fold

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higher prevalence of HBV would translate into an 8-fold higher both incidence and associated risk of window period donations.

[Slide.]

Then, does the same thing which we did for HIV, which is to recognize the fact that individuals are going to just go through this transient phase of delayed viremia seroconversion, and again the numbers for relative risk of these window period donations that I showed in the last slide and that are shown here reflect the assumed risk if all blood donations were being collected from individuals who were still engaged in male/male sex.

That is these assumed numbers, but the proposal is not to make these individuals eligible, let alone draw all blood from them, but rather to defer them for at least a year, and by deferring them, they will have moved through the window period and only a very small fraction will remain potentially in the delayed infectious window phase a year out and infinitesimal level five years out, and, in fact, even at a year out, the incremental or the additional risk associated with prior male sex is trivial compared to the background incidence of risk in the donor pool.

So, from these analyses, working with Andrew, my conclusion is that window period is probably not a big

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factor here.

[Slide.]

So, the other thing I wanted to address was the concern or the consideration about what if some new virus is discovered, and then people begin to get concerned about blood supply issues and then data begins to be generated as to the prevalence of this agent in various risk categories.

I apologize. These slides, I did fax them to FDA yesterday, but they didn't get copied. I will give a full set to Lynda, and she can distribute it as soon as possible.

[Slide.]

This slide shows data compiled from work that we were involved with, with Don Ganem's group in San Francisco using a latent nuclear antigen for HHV-8. Just for a little bit of background, this virus I think everyone agrees now is unequivocally the causative agent of Kaposi's sarcoma. There is also pretty strong data that it is the causative agent of certain body cavity lymphomas, and recent, very intriguing data that it may be a major cause of multiple myeloma.

Clearly, the KS and body cavity lymphomas are predominantly in immunosuppressed patients, but in any event, as people have built assays to measure serologically for these Kaposi sarcoma virus infection, which is also

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termed human herpesvirus-8, we found surprising prevalence rates.

What you can see, and this is all sort of apple to apple data, there is a lot of different tests out there and a lot of variance. This is all data generated in Don Ganem's lab using a single type of immunofluorescence assay.

What you can see is that about 80 percent of gay men with Kaposi's sarcoma test positive on this antibody test, but important for our discussion, what you can see is that by homosexual males at STD clinics and by homosexual male HIV-positive blood donors, about 30 percent test positive for evidence of exposure and probable persistent infection by the Kaposi sarcoma virus.

In contrast, in infective hemophiliacs and transfusion recipients, the prevalence is very low. In mostly HIV-infected STD females, the prevalence is very low, and among HIV-negative donors, the prevalence is running about 1.5 percent.

So, clearly, a much higher prevalence of this newly-identified, clearly pathogenic agent in the male sex male population.

[Slide.]

This shows new data in press from the New England Journal from Don Ganem and Dennis Osmond study. This is

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again back to the San Francisco Men's Health Study. Looking in this large population base sample at the prevalence of KSHV seroreactivity by risk category.

You can see that in exclusively gay, 35 percent; mostly gay, 31 percent; primarily gay, 12 percent; equally or primarily heterosexual, 3.5 percent; and exclusively heterosexual in this population, zero percent.

So, you see there is very dramatic association with male/male sex.

[Slide.]

It raises the specter of blood transfusion transmission of this agent. This is a paper from Jay Levy's group. Actually, this was an Irwin blood donor during a period of a year or so, unbeknownst to us, Jay Levy was getting buffy coats and using them in HHV-8 related culture work.

He called us one day and says we have got a positive control culture from one of your donors.

[Slide.]

This slide was actually out of place. That was the slide that just shows, from the HHV-8 prevalence in the Men's Health Study, the relationship between number of male/male partners in the prior two years and seroprevalence, and this is actually the number of female partners in

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seroprevalence, so a clear high association with number of male/male partners.

[Slide.]

Back to Jay's data. What he showed was out of studies involving about 72 of our blood donors, he identified this one donor who was PCR-positive on fresh PBMCs. This donor, in extensive in vitro work, they were able to passage the virus from this donor's cell in vitro to other donor's cells, which led to the speculation that this might be a transfusion transmissible virus.

This just shows in Jay's lab, there is a different serologic test, and if he is finding actually a 20 percent seroprevalence in the background donor pool.

[Slide.]

Skip this. This is just detail from his Lancet paper where he alleged that transfusion transmission may be a problem.

[Slide.]

This is actually from Dennis Osmond's New England Journal work, which in KSHV, lo and behold, in this population-based sample, history of blood transfusion is a marginally significant correlate of HHV-8 seropositivity, so in addition to Jay's one case report of an in vitro transmission of HHV-8 from a donor in an epidemiologic

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population study, there is an association between transfusion and HHV-8 seropositivity.

[Slide.]

Let's skip this. This is just a multivariate.

[Slide.]

The last few points. Basically, we have been studying this question more directly of the transfusion transmissibility. This has actually led to extensive focus within the PHS Blood Safety Committee on is this a problem, and a new study has been developed, but also Jim Mosley and Eva Operskalski looked back at the transfusion safety study cases, and importantly, in that study, the prevalence of HHV-8 again by Don Ganem's test was about 30 percent in the positive donors, but the prevalence among recipients who got HIV-positive blood, is really low, whether or not the recipients became infected or not, but there were 2 recipients who did test HHV-8 seropositive.

These recipients both got blood from donors who tested HHV-8 seronegative.

[Slide.]

This shows the direct data then. There were 14 cases where recipients actually were transfused with HIV-positive and KSHV-positive blood, and importantly, for herpesviruses, most transmissions are from cellular

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components. 13 of these recipients did get cellular blood components.

[Slide.]

This just shows that fortunately, none of these recipients became HHV-8 or KSHV-positive. Ten of them did seroconvert to HIV, but none of those 10 developed KSHV, and there were 4 recipients who seroconverted to neither virus despite getting blood from donors who were positive for both.

So, this is reassuring, but this is an N of 14, and we are left now with the remaining question of potential transfusion transmissibility, and a large study is now in the planning stages involving the REDS group and the FAC study group to try to demonstrate further whether this is a transfusion transmissible phenomenon.

I will stop there. Thank you.

DR. HOLLINGER: Thank you, Mike.

Questions? Dr. Tabor.

DR. TABOR: I would like to just caution about referring to an association of HHV-8 transfusion at the present time. Even though I don't want to be in the position of saying it could not be transmitted by transfusion, the data that you showed had a p of 0.057. Even if that were below the conventional cut-off of p .05,

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it really would only mean that there was a 1 in 20 chance that it could occur by chance alone.

It is not a very high association at best and certainly very preliminary I think, to say the least.

I would also like to ask a question. In some of the early data, the earlier slides that you showed about hepatitis B, the hepatitis B numbers that you showed were based on anti-core testing alone, and I wanted to ask whether the slide that showed an increased risk among MSM populations of -- I think it was something like 8.6 for hepatitis B and 3.0 for hepatitis C -- whether the hepatitis B in that slide was based on anti-core testing only.

DR. BUSCH: No. The factor was based on the rate of anti-core in the male sex male versus the rate of anti-core in first-time blood donors. That is how I derived the factor of 8.5.

That was then applied to the current risk estimate in the current blood donor pool, which is based on the presurface antigen window phase incidence approach.

DR. TABOR: So, it all comes back to surface antigen testing and really does reflect infectivity?

DR. BUSCH: Right, but there clearly is a presurface antigen transient infectious phase, and the concern is, is if there is a higher incidence in gay men,

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there will be a higher rate at which gay men who donate would be in that presurface antigen infectious phase, but that phase is transient and occurs relatively quickly following exposure, and as long as we build in a deferral, it become trivial.

DR. TABOR: I see. Thank you very much.

DR. HOLLINGER: Yes. Dr. Martone.

DR. MARTONE: In looking at the KSHV data, I think the totality of the data would suggest that the risk is very small. The first slide you showed, where you looked at the prevalence among the various groups, the prevalence among patients receiving HIV-positive blood and hemophiliacs didn't seem to be much greater than the general population.

Then, some of the other data that you presented, even with that study which showed that p value of 0.057, would suggest to me that the risk is very small.

DR. HOLLINGER: I guess you could argue if it is cell associated, then, the hemophiliacs wouldn't really see it. That is one issue. The other issue is on the KSHV study was done by PCR by antibody.

DR. BUSCH: These were serologic studies.

DR. HOLLINGER: Serologic. So, I guess the other question would be maybe you just haven't waited long enough. They are low at 1.5 percent. Perhaps there is a latency and

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it occurs later on.

DR. BUSCH: I don't think so. I mean most of these people are well out from exposures. I believe that KSHV is not an issue here. I don't think it's a transfusion transmissible agent. I just bring it forward as kind of a paradigm.

Had this debate taken place three years ago, I mean now we have generated a moderate amount of data on KSHV that is reassuring. But were we looking at this two or three years ago, when the virus was first discovered, when these prevalence rate data were just coming forward, transfusion questions just being raised, in light of the decision process that has taken place with CJD and many other things, I just think it is important that you consider how we would have reacted to that agent and how we might have to react as new agents that are transmitted and have been transmitted by male/male sex historically become identified and these kinds of data generated.

DR. HOLLINGER: Dr. Martone.

DR. MARTONE: Did you mean to suggest in one of those studies that the prevalence of KSHV was 20 percent using the specific test in the general population?

DR. BUSCH: Right. That is a very controversial assay that Jay Levy has reported on that no other labs have

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reproduced. Most labs in the donor pool identify HHV-8 seroprevalence rates of 1 to 2 percent, but this particular study from Jay Levy's lab has reported 20 percent, and one of the studies that CDC and FDA and the REDS group are going to begin very soon is actually a study that will take a representative population of 1,000 donors and run all of the existing developmental assays on them and have PAC supplemental data, et cetera, to try to figure out what is the truth.

DR. HOLLINGER: Dr. Nelson.

DR. NELSON: In that regard, Charles Rabkin from the National Cancer Institute has looked in low risk and high risk populations using a number of tests, the latent antigen, core, six or seven different described tests and has found, as you might expect, in the low risk population like might be representative of blood donors, where a history of male to male sex is low or excluded, that there are people in whom one of the six tests is positive, or two, so I think the issue is really kind of related to the fact that these are developmental and that there isn't really a good standard at the moment to know what is positive, you know, which test really represents true infection and what represents noise.

I suspect that until this is solved, we still may

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find some discrepant results, some investigators reporting very high rates, and others quite low, but Charles Rabkin has looked at this. It was kind of impressive.

It seems like we have got a ways to go to really define who is infected in a low risk population.

DR. HOLLINGER: Dr. Khabbaz.

DR. KHABBAZ: Mike, as you talk about new and emerging, do you know anything about the hepatitis B virus mutant strains? I know these are rare strains that are seen. Do we know if they are detected, the current, the surface antigen?

DR. BUSCH: Blaine may know more about that. To my knowledge, they have not been seen in the States, but I think the selection that has gone on in Asia has been to a great extent vaccine induced. So, with the expanded vaccination in the U.S., perhaps there may begin to be some.

DR. STRONCEK: I am not sure if you are the right person to ask the question, but there were slides in our package on false negative testing errors in viral testing. Could you comment on what impact that would have on the transmission of HIV if we changed these parameters?

DR. BUSCH: The study you have there is one that the REDS group did, and we are updating and planning to publish it, basically involved looking at the large donor

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pool and determining the rate at which donations were given subsequent to a prior positive donation.

For this analysis, we allow autologous donors who are allowed to give repeatedly to be included. The bottom line of the study was we identified one clear false negative test result on a follow-up donation from an HCV seropositive donor, that was just clean positive before, and just frankly missed on the subsequent donation.

The denominator, at the time that the abstract that you are looking at was developed, was about 1,500 subsequent donations from confirmed positive donors. We have since increased that denominator to about 2,500 with no additional errors detected. So, that is an error rate of 1 in 2,500, whatever. That error, of course, then has to occur on a positive unit.

So, to estimate the contribution of test error to risk of a unit getting through, you multiply the error rate times prevalence. Now for most purposes, hepatitis C is the problem here, because the prevalence of C in our donor pool is quite high compared to all the other viruses, and it is virtually 100 percent transmissible for C seropositives if they were to get through.

The issue that Andrew has brought forward is if we had a doubling or more of prevalence of HIV as a consequence

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of this changed deferral policy, there could be a unit that would get through. We get about 1,000 units a year now.

If we got an extra thousand, which many of us think is never going to happen as a consequence of this deferral change, theoretically, one could every two years, based on these numbers, have an error occur on that positive unit and a positive unit get through as a result of that.

It is contingent on the increased prevalence occurring as a result of the deferral policy change, which many times in the past we have expected or that policy changes reducing deferrals to a year, et cetera, we have always said, well, gosh, that might raise the prevalence rates, and we have never seen it happen, so even though historically, we have relaxed policies, that has never been translated into increased prevalence rates.

DR. HOLLINGER: I think we are going to adjourn for lunch, and we will reconvene here at 1:30.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 12:30 p.m.]

AFTERNOON PROCEEDINGS

[1:40 p.m.]

DR. SMALLWOOD: We will start with the open public hearing. I will turn the meeting over to the Committee Chair, Dr. Hollinger, and we will be prepared for our first speaker.

I just may add, if there are any individuals that did not contact me prior to this meeting that would like to speak, I would like for you to please let me know that now. If not, then, we will proceed with those individuals that have contacted me, and we will try to keep on track with the agenda. Thank you.

Open Public Hearing

DR. HOLLINGER: Thank you, Dr. Smallwood.

In the open public hearings, the first group that has asked to speak is Sue Preston representing Alpha Therapeutics.

MS. PRESTON: Good afternoon, ladies and gentlemen. As you just heard, my name is Sue Preston, and I am with Alpha Therapeutic Corporation.

Although Alpha Therapeutic Corporation has no intention of changing our donor deferral criteria at this time, Dr. Susan Stramer with the American Red Cross asked that we present some data that may be helpful in your

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discussion today on HCV and HIV window period duration.

[Slide.]

Alpha Therapeutic Corporation, among others, is a principal investigator for an investigational new drug application held by the National Genetics Institute to explore the applicability of testing pooled samples of donations for HIV and HCV genome sequences by polymerase chain reaction, PCR.

I will not present the technical details of the test, but for those of you who are interested, I believe Dr. Andrew Conrad will be at this Blood Products Advisory Committee maybe tomorrow, and you could ask questions of him.

[Slide.]

I will briefly outline our formation of the sample pools, the eligibility criteria for subjects to be enrolled, and follow-up testing, and then show our preliminary analysis of our data.

Sample from each donation collected from approximately one-half of our licensed sites, approximately 32 sites, were sent to our Central Testing Laboratory located in Memphis, Tennessee, for routine serological viral marker testing.

Aliquots from the same samples were combined into

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a 512 cubic matrix for PCR testing. We employ this matrix to allow rapid confirmation of suspect positive individuals, and you can see this is a depiction of our cubic matrix, and because we have each donation in there three times, by triangulating we can identify the positive donation in very little time.

The pooled samples in not more than a 512 matrix are sent to the National Genetics Institute where polymerase chain reaction testing is performed for HIV and HCV genome sequences in separate reactions. The results are returned to the Memphis laboratory for correlation with other test results and disposition of the individual units of plasma.

The IND sets forth a minimum of 300,000 donations from at least 10,000 donors to be tested. Part of the investigation plan was to follow eligible subjects to seroconversion.

[Slide.]

For HCV, the selection of subjects to be enrolled, they had to be positive by PCR and nonreactive by the HCV antibody test, which we currently use Ortho's 3.0 ELISA. ALT testing is routinely performed for all donations with the Genetics Systems test, and all donations are tested for the presence for HBSAG with Genetics Systems 2.0 EIA.

[Slide.]

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For HIV, the selection for subjects to be enrolled to follow-up were that they had to be positive by PCR and/or reactive for p24 antigen with positive neutralization and nonreactive for the HIV-1,2 antibody.

During the course of this clinical trial, we were employing the Coulter HIV p24 antigen ELISA, also the Coulter neutralization test kit, and the antibody was tested with Genetics Systems HIV-1, HIV-2 EIA second generation.

When appropriate, the Cambridge western blot was utilized to confirm repeatedly reactive antibody samples.

[Slide.]

The testing schedule for subject followup was as they were enrolled as a clinical subject, for HIV, each donor was tested weekly for three months or until seroconversion, and HCV, it was weekly for six months or until seroconversion.

[Slide.]

The types of testing for each subject for both of these followups were antibody testing and PCR testing.

[Slide.]

The clinical trial ended in mid-September and to date, there are a total of 344,843 donations covered by the IND. Of these, 3,853 donations still have samples that are pending resolution. Of the 340,990 donations with finalized

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results, 77 donations -- and let me stress this is not donors -- 77 donations are positive for HCV, and 15 donations are positive for HIV.

Some of the positive samples have been quantified at National Genetics Institute with copies per mL values up to 30 million for HIV and up to 300 million for HCV in antibody-negative samples.

All donations have been found nonreactive for HBsAG. As of today, we have not found a confirmed anti-HIV-1,2 or p24 antigen positive sample that, if tested by PCR, is not found positive by PCR, and the same is true for the HCV antibody testing.

To date, we have 4 donors that represented the positive donations. Two of those have been enrolled and 2 were eligible, but were not enrolled. We have lost them. HCV, we have had 11 donors who were enrolled, 8 that were eligible but were not enrolled, and we have 3 pending enrollment right now.

So, that brings us a total of 26, 22 HCV and 4 HIV donors that we have detected during the course of this IND.

[Slide.]

In terms of just the subject followup, the return rates for HIV was 50 percent, for HCV it was 58 percent in terms of being able to get the subjects enrolled.

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[Slide.]

This is a chart that represents on each of the bars, each of the subjects, each of the donors that had PCR-positive samples during the clinical trial. The two top bars represent the donors that are enrolled, and the two bottom bars represent the donors that were not enrolled. The red is where there are PCR-positive only. The blue represents where there are PCR-positive and p24-positive, but antibody-negative. The yellow represents when they seroconverted to antibody and they are also p24-positive and PCR-positive on these particular donors.

I won't say very much. There is only very limited data on HIV. If I could have the next slide and we will talk a little bit more about HCV.

[Slide.]

Each of these bars represent the subjects. There were 19 donors in total that were the donated PCR-positive donations during the course of this clinical trial. Eight of them are not enrolled, and the ones that are not enrolled are basically the bottom 7, and the one here that hasn't seroconverted. That one was lost, and we weren't able to enroll that donor.

I tried to mark on here -- I don't know that is very clear, especially in the back -- when the last negative

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donation was or the last negative test point was, because as with any of these, there might be long lags, and here is one that had a long lag, but 8 out of the 13 that seroconverted, the last PCR-negative time point was in 8 days of their seroconversion sample. Some of them were as close as 2 days.

The number of samples that are represented in here vary from 2 to 17, and I think another thing that we found interesting among these data, we also looked at ALT, and when we might see ALT elevations that would cause us to defer the unit or defer the donor, and really, most of these remained negative for ALT. Only a few had shown ALT before they seroconverted.

If you can go to the next slide, I will just show a table.

[Slide.]

I wanted just to illustrate one of the subjects. Where it says SPECT, it means very highly suspect, we are doing the confirmation testing right now. We expect that is going to be positive, where these were positive, and then here on August 10th, this is when this particular donor became reactive for HCV. The first donation here is on June 30th.

On this particular one, the ALT would have caused

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this donation to be rejected on August 1st. So, there was a whole month of potential donations where we would not have caught that donor.

[Slide.]

This subject, who was also HCV-positive -- any one that is blank means we are still pending those results, and the ones that are SPECT are the ones that we are in the final process of confirming -- but here is an illustration where the ALT really didn't kick off until at the same time that that donor became reactive in the antibody test.

In conclusion, our preliminary analyses suggests that PCR, as performed by the National Genetics Institute, with aliquots of full donation samples, is effective in detecting viremic donations when there are no other currently licensed test kits that could identify the positive individual.

Although the risk factors for the individuals that were found to be positive for HIV or HCV viral genomes were not determined, our limited amount of data support the American Red Cross data that individuals infected with HCV do seroconvert in the range of 20 to 99 days from the time of the first sample detected positive for viral RNA with a mean and median of 48 days.

ALT testing was not as effective as PCR testing

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for early detection of viremic donors.

Thank you.

DR. HOLLINGER: Thank you.

Any questions? This was all with the EIA-2, is that correct?

MS. PRESTON: That is correct.

DR. HOLLINGER: Have they been looked at with the 3?

MS. PRESTON: Some of these donors, yes, we are looking at with the 3. We have now gone to the new peptide test for all of our donors, and we will be looking at all of these, as many samples as we can collect.

DR. HOLLINGER: Can you explain again where the bloods came from again, how this got started?

MS. PRESTON: Alpha has 63 licensed source plasma collection sites. Approximately 32 of those sites were selected for participation at this clinical trial. As with all of our donors, we take samples of the plasma and send it to our Central Laboratory where tests are performed for HBSAG and anti-HCV, anti-HIV, RPR, all of the tests.

So, we took aliquots of those same samples and aliquotted those into a cubic matrix with robotic pipettors, and then those samples, the combined, the matrix samples were then sent to National Genetics Institute.

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DR. HOLLINGER: And then when you found them positive, then, you followed them up, is that right?

MS. PRESTON: Yes, we did.

DR. HOLLINGER: Dr. Nelson.

DR. NELSON: You mentioned there were roughly 344,000 samples or collections.

MS. PRESTON: That is correct.

DR. NELSON: Do you know how many donors that represents?

MS. PRESTON: That is the question everybody would like to know. We don't have those data yet. Obviously, we will be collecting that. At the present time, our systems are manual for some of that data collection, so it is rather onerous to get that information.

DR. HOLLINGER: Thank you.

The second presentation is by Marj Plumb, Director of Public Policy, Gay and Lesbian Association.

MS. PLUMB: Thank you very much. I am the Director of Public Policy for the Gay and Lesbian Medical Association.

On behalf of the Gay and Lesbian Medical Association, I appreciate the opportunity to present our concerns about the FDA's blood donor deferral policy regarding men who have had sex with men since 1977.

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The Gay and Lesbian Medical Association is an organization of nearly 2,000 lesbian, gay, bisexual, and transgendered physicians, medical students, and their supporters in all 50 states and 12 countries.

Founded in 1981, GLMA, as our organization is known, works to promote quality health care for lesbian, gay, bisexual, and transgendered patients and to combat homophobia within the medical profession and in society at large.

As physicians, our members have a responsibility to their patients, to society, and to the public health. As an organization, GLMA had an additional responsibility to ensure that when health care policies are enacted, they are based on sound scientific principles and evidence, and not on bias or prejudice against lesbian, gay, bisexual, or transgendered individuals.

Many of our member physicians provide physical and mental health services to a diverse population of lesbian, gay, bisexual, and transgendered patients. Additionally, a significant portion of our membership provides care to large numbers of HIV-infected individuals.

Our members' concerns regarding the deferral of men who have had sex with men is borne out of this day-to-day experience of caring for a patient population

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that is frequently shunned, stigmatized, and often overtly discriminated against by society, health care institutions, and homophobic medical providers.

In 1983, AIDS was a new disease of unknown cause that was devastating the gay community, and that was presumed to be caused by a blood-borne pathogen transmissible by the exchange of semen and blood.

Despite the lack of information available, GLMA was one of the first organizations to encourage gay and bisexual men who deemed themselves to be at risk or who had symptoms of AIDS to remove themselves from the blood donor pool.

Simultaneously, as a means of helping to ensure an adequate blood supply, GLMA encouraged gay and bisexual men to find friends or family members who did not engage in behavior that put them at risk and who did not have symptoms of AIDS, to donate blood.

GLMA's courageous stance early into the epidemic was possible because GLMA members were on the front lines in addressing this new disease and because GLMA members were some of the first physicians in the country to care for people who had AIDS.

GLMA's position was also consistent with the belief that all citizens of the U.S. have a civic

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responsibility to donate blood, a responsibility our country has historically encouraged.

When the FDA first developed blood donation guidelines in response to HIV-AIDS, little was known about the disease. Since that time, however a number of new developments, most importantly the development of an HIV antibody test, have played a critical role in HIV-AIDS prevention, education, and treatment.

Despite these developments, however, guidelines remain in place that continue to preclude certain people, such as gay men, from donating blood. These guidelines are commonly defended with the statement that giving blood is a privilege, not a right, a statement that flies in the face of the fact that giving blood has always been promoted as a responsibility of all citizens of the U.S.

It is a statement that also ignores the scientific advancements that have allowed the FDA to develop a safe blood supply. As you know, the current FDA recommendation states that any male who has sex with another male, even once, since 1977 must not donate blood. Yet, the advisory defers a women who has had sex with that same man for only 12 months.

Unless the FDA is willing to recommend that screening of potential donors include asking what sex acts

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individuals are participating in, and then rank deferrals by the associated risk of oral, vaginal, and anal sex, whether safer sex was used, and then factor in the number of sexual partners and concurrent drug use, such disparate deferral time periods between women and men and homosexual sex and heterosexual sex will continue to reflect bias and prejudice and be discriminatory.

The deferral criteria was developed to protect the nation's blood supply and the workers who process blood donations. It was established during a time when anxiety about the nation's blood supply was high and scientific advancements and the detection of the HIV virus were slow in coming.

In 1997, surely, we do not intend to say that a man who had sex with another man in 1978, 19 years ago, and has been celibate since, cannot exercise his civic responsibility to give blood.

Surely, we do not intend to have a policy that does not permit a man who had oral sex with a man three years ago, and has tested negative for the HIV virus twice since then, to give blood, yet, welcomes a blood donation from a woman who had anal sex with that same man 13 months ago.

Surely, we do not intend to have a policy that

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does not permit two men who have been in a monogamous relationship throughout the AIDS epidemic from donating blood.

It is the responsibility of all people to assure an adequate and safe blood supply in the United States. Everyone must understand that they need to answer the screening questions honestly and self-defer if they may be at risk for being exposed to any disease that could be transferred through transfusion.

Any person having sex with multiple partners or unprotected sex with individuals whose serostatus or risk factors are unknown presents a possible risk to the blood supply, whether that person is male or female, and whether their partners are of the same sex or the opposite sex.

This activity should result in a finite deferral as with gonorrhea and syphilis exposure. Similarly, an extended public health campaign should be undertaken to help the public understand who should give blood, who should self-defer from giving blood and why.

We need to remove the stigmatization from blood donor deferrals and emphasize that standards and protections apply to all people equally.

GLMA recommends that the FDA use the knowledge that has been gleaned from the ever expanding field of AIDS

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research to create sound, logical, and fair blood donation guidelines that reflect today's significantly improved laboratory tests for HIV and a much better understanding of the window period of undetectable infections.

If the FDA does not change its policy to better reflect the science of the epidemic, it will confirm our worst fears. Almost two decades into this epidemic, public health policy is politics as usual.

GLMA believes that it is still the responsibility of every individual to ensure that there is enough blood in our nation's blood supply and that it is still the duty of the Federal Government to ensure that all individuals in our society have an equal opportunity to meet that responsibility.

To do less when not scientifically or medically justified is to make certain individuals in our society second-class citizens.

The continued permanent deferral of HIV-negative gays and bisexual men from donating blood is not scientifically justified, infringes on the rights of these individuals to meet their civic responsibilities, jeopardizes the availability of an adequate supply of blood products throughout the nation, and is blatantly inconsistent with other deferrals.

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GLMA believes that the Food and Drug Administration should immediately update the current donor deferral recommendations based on the best scientific information available in order to reflect equivalent standards of evaluating homosexual and heterosexual sex risks.

This can be done to allow HIV-negative persons with low risk behavior regardless of sexual orientation the opportunity to fully exercise the civic responsibility of donating blood. This change in policy would protect the nation's blood supply and uphold the basic tenet of citizenship, participation in society.

The Gay and Lesbian Medical Association is eager to work with you as you make your recommendations. Our members have a wealth of clinical and public health expertise that they would be happy to share with the FDA. Together, we can assure that appropriate standards that will protect the nation's blood supply are implemented. These standards should not be based on a donor's sexual orientation or the gender of their sexual partner.

Thank you for the opportunity to address you today. The nearly 2,000 members of GLMA are ready to provide any help you may need.

Thank you.

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DR. HOLLINGER: Thank you.

Any comments? Okay. Thank you.

The next presentation is by Dr. Steven Kleinman from the American Association of Blood Banks.

DR. KLEINMAN: Good afternoon.

The American Association of Blood Banks is a professional association for approximately 2,200 institutions engaged in the collection and transfusion of blood and blood products including all American Red Cross blood services, regions, independent community blood centers, hospital-based blood banks and transfusion services, and more than 8,500 individuals engaged in all aspects of blood collection, processing, and transfusion.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. The AABB's highest priority is to maintain and enhance the safety of the nation's blood supply.

The Uniform Donor History Questionnaire developed by the AABB serves as an FDA-approved model for blood donor screening in the United States. The Transfusion-Transmitted Disease Committee of the AABB, which includes representatives from America's Blood Centers -- that organization is called ABC -- and American Red Cross

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representatives, or ARC, was charged last year with the responsibility to review the current questionnaire.

The committee was asked to make recommendations for improvements, specifically to determine what we need to know about and from donors in order to ensure a safe and adequate blood supply, and to make recommendations to effect the appropriate changes.

Several recommendations have been made by that committee to improve the clarity, sensitivity, and specificity in the donor screening process. Specific to today's discussion, the following changes are recommended by the AABB for the Uniform Donor History Questionnaire and for BPAC to consider.

Question 25 of that document, which is administered to male donors, is currently worded: "Have you had sex with another male, even once, since 1977?"

We believe this should be modified to: "Have you had sex with another male, even once, in the last 12 months?"

Question 26, which is now administered to female donors, is currently worded: "In the past 12 months, have you had sex with a male who has had sex, even once, since 1997, with another male?"

This should be modified to -- and again for female

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donors -- "In the past 12 months, have any of your male sex partners had sex, even once, with another male?"

Modifying the deferral time for male to male sexual contact to match that of other potentially high risk sexual exposures will improve the clarity and consistency of the 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.

However, the 1977 time frame for questions concerning male to male sex was implemented at a time when the data regarding HIV transmission were limited and when HIV serological tests were less sensitive than the current assays.

It is now possible to use the large body of scientific data concerning the natural history of HIV infection to reexamine the appropriate time interval for such a deferral. Studies by Dr. Michael Busch, CDC scientists, and other colleagues indicate that:

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1. Routinely conducted blood donor HIV laboratory screening has reduced the HIV seronegative infectious window period to an average of 16 days, as we have heard presented this morning.

2. In clinically asymptomatic individuals, HIV infection will result in the development of HIV antibody or HIV-1 p24 antigen in less than one year in all cases.

3. Which we have heard this morning, in health care 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 the cases. However, in two cases, the intervals were 213 days and between 8 and 9 1/2 months, but we are unaware of any confirmed data that show a longer period for seroconversion.

Accordingly, the AABB respectfully encourages the committee to recommend the 12-month deferral in lieu of the dating questions that go back to 1977. This modification should have no detrimental effect on the risk of transmitting HIV through transfusion or the safety of the blood supply.

Thank you.

DR. HOLLINGER: Thank you, Steve.

Questions? Dr. Nelson.

DR. NELSON: With regard to your presentation and

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the previous presentation, and the changes that are recommended, and the issue of having a different standard for homosexual men or lesbian or et cetera, and heterosexuals, my understanding is the recommendation would still exclude a man who had a male partner even if they were monogamous in the past 12 months. Is that correct?

DR. KLEINMAN: Yes, that is correct.

DR. HOLLINGER: The next person who asked to speak, Michael Busch representing America's Blood Center, ABC.

DR. BUSCH: Lou Katz from ABC was unable to attend and asked me to present. This is the position of America's Blood Centers.

America's Blood Center represents more than 70 independent community blood centers who supply almost half of this country's volunteer blood supply. We concur with the statement you have received from the American Association of Blood Banks regarding changes in donor questions designed to minimize the risk of transmission of HIV and other blood-borne viruses to blood component recipients.

Focusing our questions on recent behaviors rather than remote should improve the accuracy of donor recall while not penalizing potential donors for remote, but

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unsubstantiated risks.

ABC members would encourage this reevaluation of donor questions to include the lifetime deferral of donors with remote injection drug use, as well, since the issues of risk of infection and clarity are the same, and the data cited in the AABB statement is applicable.

DR. HOLLINGER: Thank you, Dr. Busch.

There is a statement that Corey Dubin wanted to make who is not here today, one of our committee members not here today, and I believe that is going to be made by Terry Rice from the Committee of Ten Thousand.

MR. RICE: I am here to make a statement on behalf of the Committee of Ten Thousand and our Science and Medicine Working Group for Corey Dubin, who was unable to attend today.

The members of COTT Science and Medical Working Group are strongly opposed at this time to any modification of the FDA donor deferral policy regarding men who have had sex with men. It is our contention that any change of this magnitude must be subjected to a lengthy and in-depth analysis before any change is undertaken.

The usage of high risk plasma donors by the blood products industry during the 1970's and 1980's played a critical part in the devastation of the hemophilia community

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by both HIV-AIDS and hepatitis C.

The practice of targeting high risk populations for their HBV antibody rich plasma during the 1970's and 1980's is now well documented and known to have been an important factor in the hemophilia/AIDS epidemic. Given this history, any modifications in the current policy poses potentially exploding implications for the hemophilia community.

While we now enjoy the benefits of very successful viral inactivation techniques, such as heat treatment and solvent detergent, there remains both known and unknown risks associated with the usage of plasma from so-called high risk donors.

In the context of known viral pathogens, such as HIV and HCV, any change in policy presupposes that these viral inactivation technologies are being applied and monitored in the most effective and safety conscious fashion possible.

We have serious concerns in the area of enforcement regarding Good Manufacturing Practices and Standard Operating Procedures. What we have witnessed over the last year in this area leads us to conclude that there remains a great deal of progress to be made before we can relax our current degree of vigilance.

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In the context of emerging or unknown viral pathogens, it is our position that the continued deferral of those individuals involved in practices known to be at risk for the transmission of virus makes both good scientific sense as well as sane public policy with regard to the protection of our nation's blood supply.

Obviously, HIV is not the last blood-borne virus that will catch us by surprise. It is almost a given that we will face other unknown pathogens that place the users of blood and blood products at risk. Given this, it remains important to go the extra distance to gain the greatest degree of protection possible.

From our perspective, the devastation of an entire community from what we now know was a preventable epidemic should have taught us all the need for a healthy dose of caution when considering the usage of high risk donors for the production of blood products. We must continue to err on the side of safety if we are to adequately protect the users of blood and blood products.

We clearly understand the dilemma of an adequate blood supply and supply of plasma for the production of plasma derivative products, such as immune globulins and anti-hemophilic factor. However, we have yet to see a major public effort including the Clinton Administration, the

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Congress, and the American Red Cross to place regular blood donations on the national agenda.

Rather than undertaking this more difficult and time-consuming effort, we consistently reach for the easier and less difficult fixes, believing that our technology will ensure safety. We as a community know that this perspective can at various historical moments be flawed and sometimes devastatingly dangerous to those whose lives depend on blood products.

It is time that we as a nation place blood donations in the current context of good citizenship and undertake a national program that will underscore the need for all Americans to regularly donate blood to ensure an adequate and safe national supply. We must not always look to the quick fix to solve the problem of an adequate blood supply, especially in a situation such as this where we find significant risks associated with the proposed modification.

We urge the FDA and the BPAC to take a lengthy look at this proposed modification before any action is taken. As always, it is our preference to work with both the FDA and the blood and blood products industry to assess what is best for our nation in terms of regulatory standards. However, we are committed to strong and vocal opposition to a change in this policy that is undertaken

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without the necessary analytical and public policy review that we find imperative to any change in the donor deferral policy.

Yours in the Public Interest, Corey S. Dubin and the Science and Medicine Working Group of The Committee of Ten Thousand.

The one thing that Corey did not have a chance to put into his statement was the fact that I think that we have to be conscientious to understand that the typical tort systems in this country do not provide us the sense of safety in the event that there is an adverse consequence of a particular cost-benefit savings analysis and policy.

The fact is that the courts are defective in bringing redress to those who are harmed, and in light of any subsequent steps forward by industry in general to provide some means of compensation in the event that an adverse occurrence does occur, whether it be through a no-fault system or through a relaxation of their protections under blood share laws, I do not believe that we can depend solely on the good nature of industry to protect the blood supply and to do the best job possible under Good Manufacturing Practice.

Until we are willing to take some of the risk off the persons who use blood products and place some of that

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risk back onto the shoulders of those that are deciding what is a cost-benefit analysis, safety measure, we are constantly going to have adverse consequences being borne solely and totally by persons who use these blood products, and unfortunately, the public sector who has to pick up the tab after an adverse consequence occurs.

Thank you very much.

DR. HOLLINGER: There are three other documents that I think the committee has, and we are not going to read them in their entirety. The people who presented them are not here, I do not believe, to present them.

One is from Beverly Stein and Gary Oxman from Multnomah County in Oregon discussing the issues that we have just been going over.

The second is from Dr. Edward Ehrlinger, who is from the University of Minnesota, some comments also.

The third one is from the AIDS Legal Referral Panel in San Francisco, and that was Eileen Hanson.

The committee all has these documents.

Before we close the open public hearing, is there anyone else that wishes to make a statement?

[No response.]

DR. HOLLINGER: If not, then, we will close the open public hearing and we will begin the deliberations for

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the committee at this time.

We going to have a presentation of the questions which we did not look at initially, and Dr. Dayton is going to provide those to us, if you would, please.

Open Committee Discussion

Presentation of Questions

[Slide.]

DR. DAYTON: The first question is: Do the committee members agree that scientific data support the concept that history of male/male sex is a risk factor for transfusion-transmitted diseases?

[Slide.]

Question No. 2: Do the committee members believe that FDA should modify its current recommendation that men who have had sex with men even one time since 1977 should not donate blood or blood components to be used for transfusion or further manufacturing?

[Slide.]

Question 3 has several parts to it. If FDA's current recommendation should be modified, do the committee members agree with the following policy options?

- a. Permanently defer men who have ever had sex with another man.
- b. Defer men who have had sex with another man in

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the last 5 years.

c. Defer men who have had sex with another man in the last two years.

d. Defer men who have had sex with another man in the last 12 months.

[Slide.]

Are there other policy options that FDA should consider regarding male/male sex as a behavioral risk factor for donor deferral?

What additional studies are needed to clarify the underlying scientific issues?

Thank you.

DR. HOLLINGER: Thank you.

Panel Discussion of Questions

DR. HOLLINGER: I think I am going to just go through the first question because I have a feeling that that is not going to be an issue, but maybe it is. Are there any issues about the first question?

The question is: Do the committee members agree that scientific data support the concept that history of male/male sex is a risk factor for transfusion-transmitted diseases.

Dr. Mitchell.

DR. MITCHELL: I believe that some of the points

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that were raised by some of the public members regarding specific sexual acts do need to be looked at. The question is whether anal intercourse, both for males or for females, pose some kind of a risk and should we be looking at that.

It seems that the data that was presented here, although there wasn't much on female anal intercourse, that there doesn't seem to be much transmission of HIV from women who are infected sexually, but at some time there is going to be, and I think that we need to be looking at that trend to figure out how much of a risk that is.

DR. HOLLINGER: I would like to call a vote at least on the first question and then we can move forward.

The question is: Do the committee members agree that scientific data support the concept that history of male/male sex is a risk factor for transfusion-transmitted diseases?

All those that agree with that statement, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those that oppose or that do not agree with that statement?

[No response.]

DR. HOLLINGER: Our consumer representative, Ms. Knowles?

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MS. KNOWLES: I understand that I am a non-voting member.

DR. HOLLINGER: But we always ask your opinion anyway.

MS. KNOWLES: I agree.

DR. HOLLINGER: Thank you.

DR. SMALLWOOD: The results of voting: 13 yes votes. There were no no votes, no abstentions, and the non-voting consumer representative agrees with the yes votes.

DR. HOLLINGER: I would like to maybe get a little bit more discussion. The second question is: Do the committee members believe that FDA should modify its current recommendation that men who have had sex with men even one time since 1977 should not donate blood or blood components to be used for transfusion or further manufacturing?

I would like to open this up now to the group.
Dr. Boyle.

DR. BOYLE: I am interested in responding to this in part because my son is a lifetime user of blood products, so I am obviously very concerned about issues of safety, availability and costs, and in looking at the information here, I think we should look at each of those three things.

In terms of the information that I heard presented

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here and read through, that if we were changing the policy, and the policy seems to be related to deferral periods, since we seem to have attempted the first point, in terms of safety, the information that I heard seems to indicate that a change in the deferral period would result in some non-zero increased risk. It might be small, but it would appear to be non-zero.

In terms of availability, increased availability, I heard a number of things about that. If I understood the numbers correctly, that if you went to a one-year deferral it would increase the number of available donors by 100,000 out of 14 million per year, which is something on the order of a 1 percent increase in terms of supply, and I may have gotten those numbers wrong, but that is what it appeared to be, which I would say is not a significant increase in availability.

Lastly, in terms of costs, on the one level the costs are perhaps none, but somebody was suggesting a two-tiered system if you change deferral period, and that obviously would have an impact on cost.

The last issue that I would raise is that we have acted as if all we are doing is changing deferral period, of which there is a measurable consequence. We can measure how many people would be eligible, we would know how many people

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would approximately be at risk, but we are not changing deferral period, we are changing a question, a question that is used on a questionnaire, that is used in screening materials, it impacts upon what people believe in terms of coming in and going out, in terms of how much at risk you are when you actually come in to donate, and I would suggest to you we have no idea what the consequences of changing that question is.

Before I would want to change a policy that we have heard seems to work well and seems to assure a reasonably safe supply of blood, I would really want to know what changing those questions related to deferral, how it would actually impact upon donors and upon supply, and I don't think that is something we know.

Thank you.

DR. HOLLINGER: Correct me if I am wrong, some of the committee members, I think they said about the 1 percent, I think they said that it represents about 1 percent of the donor population. I don't think it said it would increase it, but I think the total amount that it is currently, which represents probably less than 1 percent of the blood that is collected in this country. Is that correct, Dr. Dayton?

DR. DAYTON: It is basically donors, but we really

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feel it is going to represent less than 1 percent increase in the blood supply.

DR. HOLLINGER: Thank you.

Dr. Nelson.

DR. NELSON: I may not have clearly understood the calculations. They were fairly complicated. But in terms of how many additional donors it would allow, it would depend upon what the changes in the recommendations are, and an estimate that used a population based estimate of the numbers of men who report having sex with a man, I wonder did that exclude sex with a man in the last year?

Does that mean that if you took the numbers of men who had sex with a man, and then you took the proportion of those who did not report sex with a man in the last year, and then you multiply that by the estimate that might donate blood from that population, do you then come up with -- what was it, 170,000 or something?

DR. DAYTON: I am not sure if I totally follow the question, but let me give you what I think is the answer you are looking for.

DR. NELSON: Well, if it's just a proportion of who have sex with men, but you exclude men who report having sex with men in the last year or the last five years of whatever, then, it is a smaller number.

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DR. DAYTON: Right. We gave you two numbers, and they are both the number of newly appearing MSMS at the donation door, and with a five-year exclusion category, a five-year deferral period, that would be about 58,000.

With a one-year exclusion policy, it would be about 112,000, and those numbers have already had subtracted from them the donors who are already giving, but are appearing with inaccurate responses.

Does that answer your question?

DR. NELSON: I think so.

DR. STRONCEK: I agree with many of the speakers that pointed out that the current restriction on blood donors can be arbitrary and offensive to certain people that would make good blood donors. On the other hand, the policy has been very effective and it has kept the blood very safe, and I wouldn't want to do anything that would make the blood less safe.

So, even though I am not comfortable with the current policy, I don't think I am really comfortable with any other question on this page either. I would feel better if we are going to try and modify this policy, if we don't look at it in a little broader scope, maybe come up with deferral mechanisms based on behavior rather than broad classes of individuals, and we heard from Dr. Dayton this

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morning a suggestion that possibly other strategies be used, testing people that could be at a high risk group, and if they are proven to be negative, then, they can go on and donate blood.

DR. HOLLINGER: Along those lines -- and maybe one of you can answer this -- there has not been a case of transfusion-associated HIV since '87, is that correct, or '85, is it '85? Or '87, am I correct in that?

DR. BUSCH: There is AIDS cases that were attributed to transfusion that have been investigated by CDC, and I think that number is something like 30 or something, but then in addition, all of the data from the Lyle Petersen study, which was a lookback from seroconverting donors, all of those recipients were recipients of screened blood who, in fact, got infected and developed HIV as a consequence. I guess probably 50 or 70 transmissions documented although there have been fewer in the last few years.

DR. NELSON: Some are between 25 and 50 per year.

DR. HOLLINGER: That is what I wanted to find out.
Thank you.

DR. NELSON: Isn't that right, Jay?

DR. EPSTEIN: You are right.

DR. HOLLINGER: Thank you.

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DR. TABOR: Dr. Hollinger, I think what you are thinking of is the figure regarding cases transmitted by plasma derivatives.

DR. HOLLINGER: Yes.

DR. TABOR: And the figures you quoted were essentially correct for plasma derivatives, none since '87 except for HCV, which there was one outbreak in '94.

DR. HOLLINGER: Thanks for correcting that. I appreciate it.

Yes, Dr. Ellison.

DR. ELLISON: I would like to take the opposite tack. I happen to think the numbers we have had presented here are -- they are not pie-in-the-sky -- but no one really knows what is going to happen.

On the other hand, I think that the presentation by the AABB and ABC is the way we should be looking at this in terms of what is going to happen if we change the policy.

Secondly, I think the policy as currently articulated does have a discriminatory impression on a certain population, and I would like to see it changed. As to the duration I am not sure, but I think that it should be changed.

DR. HOLLINGER: Thank you. Dr. Verter.

DR. VERTER: I would like to preface, if I might,

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a couple remarks with the statement about it is more general, something that happens in the committee quite often, and that is the amount and the quality of the data presentations, and also the timing.

I am probably the least knowledgeable about blood on this committee, but in speaking to my other colleagues, both past and present, I think there is a general similar opinion. Occasionally, we are given data before although even that data is sometimes hard to interpret because it is very brief with no explanatory text accompanying it.

Oftentimes we are presented with a volume of data at the meetings which, to say the least, they are overwhelming and almost impossible to correctly interpret in my opinion. So, what I am about to say is in that context, but it also is stated that it has occurred previously and maybe at some time, Dr. Hollinger, the committee can discuss with the FDA to better that in the future.

Some of this is a little redundant, so I won't take too much time, but essentially, I agree with some of the statements that have been made. There has been a large amount of data presented, which we already agreed presents certain cohorts in a risk setting that is higher than other cohorts.

A lot of this data was based on many assumptions,

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some of which I certainly haven't had a chance to assess, haven't read some of the literature that was quoted, nor had an ability to ask people about the design of their studies, but a lot of it is based on things like self-reporting, generalizations from the REDS cohort to the U.S. cohort.

There was a study presented this morning from I believe Germany, where there were some statements made about HCV, but if you look at it, just a little more than 50 percent of those HCVs actually went on to followup, so that to me leaves a large chance of variability in what the response truly is.

However, even with all that, all those limitations, I am probably willing to concede that it is probably within one year or probably almost certainly within five years of last MSM contact, a man will demonstrate seroconversion if he is going to seroconvert.

However, that relies on a lot of the assumptions, and so, as has been stated just recently, if we were to change the policy, I am not sure what the timing would be, that is one issue, but more importantly to me, it is what I think our mission is on the BPAC in this sense.

I think our primary mission is to protect the blood supply and to protect the recipients. In addition to that, I think we have some responsibility to the health care

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workers who might be put at an additional increased risk from having to process blood that they normally wouldn't have to process.

So, we have not heard that side, either side of that. We have not heard what the potential risk is to the health care workers, how many new cases of HIV, HBV, HCV, or AIDS might occur from a change in this policy, nor have we heard what the increase in the number of recipient cases, those who rely on the blood products, might be. It was alluded to by Corey's statement, but no numbers, no analysis has been done.

So, I am inclined today at least to not change the policy, however, I would like to open the door a little bit in the sense that maybe some subcommittee can be appointed to more thoroughly review all the studies, ask the relevant questions to the principal investigators of those studies, and come back to this committee with a more succinct presentation, with more text that would help us.

DR. HOLLINGER: Thank you, Joel.

Yes, Dr. Linden.

DR. LINDEN: When I came in here this morning, I was all ready to support changing it to one year based on what I knew before I came here today, because I think it does give the appearance of being discriminatory and it is

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inconsistent with other risks that are one year, and I think that, I mean we ought to have confidence in our tests or we don't.

But looking at the data today, I was really struck by the estimates on the number of infected units that we would be putting into the pipeline, and we believe that virtually all of those would be caught by the testing, but I don't think we heard proof that it will be 100 percent.

There is some very, very small chance of error or other reason for units, and not just for HIV, which may be of less concern, but with other analytes, as well, and I am also concerned about other pathogens since we clearly saw data that this is an activity that puts people at increased risk for a variety of different transfusion transmissible diseases, blood-borne pathogens.

So, I would agree with some of the colleagues on the committee. I think this is something that needs to be looked at and it probably should be changed. I think that the idea of maybe having people come in and have initial testing and then a second test, you know, there may be a variety of different strategies that can be looked at, and I agree that this issue needs to be looked at in more depth. I am not sure I am prepared to vote that we are ready to change it right now.

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DR. HOLLINGER: Dr. Holmberg.

DR. HOLMBERG: I agree with Dr. Linden and also Dr. Verter, that we came here today with the questions before us, and yet there has been a lot of things presented to the committee. I, too, even last night, was looking in one direction, and the more I hear, I am very concerned.

I think that we have heard from the FDA, about the zero tolerance that has been expressed by the Committee of Ten Thousand. I think that we need to very carefully look at do we want to change that position.

I think that today is a good day to start talking about changes in the questions, however, I do not think that we can make a decision today, and I don't feel like I am prepared to make a decision today on it.

I also would like to say that I do support what the America's Blood Centers stated in the sense that I also think that the question concerning I.V. drug use also needs to be looked at.

So, we are not just talking about the male-to-male sexual act. We are looking at some of the other questions and also going back two decades with that date. Again, I would just caution the committee, and my position is going to be that I really have to have time to think about these things a little bit more, and I really don't think that we

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can make a decision today.

DR. HOLLINGER: Dr. Piliavin.

DR. PILIAVIN: I think I am leaning towards agreeing with the last two speakers, as well. I am concerned about the discriminatory aspect of it, and I am also, as a social scientist, very concerned with basing decisions on a person's having done one thing once.

If we all look at ourselves, we have undoubtedly all done one kind of ill-advised thing once, and perhaps we may have all done something that might get us not to be able to give blood if it were interpreted along certain lines if the rules were changed.

The thing about the data that were presented today that concerns me the most, however, is the hepatitis B data, the very high incidence in a lot of the samples of men who have sex with men, of hepatitis B.

I mean those numbers were really up there in the 70 and 80 percent, and if you were to think about having that proportion of any group of people coming in to present as blood donors, you are going to be doing an awful lot of collecting of blood that is not going to be used with the hepatitis B tests now.

I am not just thinking in terms of the danger aspects, but thinking in terms of efficiency, how much

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processing you have to do.

Again, I agree with the previous speakers, that we should certainly consider this. I would definitely like to have a question that does not rely on the possibility of somebody having done something once when he was a teenager or once when he was having a drunken party with some of his friends that is not a lifestyle issue and therefore is unlikely to have a relationship to the issues that we are concerned about.

But I do think it is going to take quite a while to figure out how to do that, how to come up with the right question. I definitely like Dr. Boyle's concern about the question.

So, yes, right now, I don't think I am prepared to vote to change this wording even though I am really unhappy with it and want us to consider a change in it once we have thought more about it.

DR. HOLLINGER: I guess the other thing, too, is the inconsistency, I think is the other thing which I think Ms. Plumb brought out, that bothers I think a lot of us also and how to deal with that issue, too.

DR. PILIAVIN: In general, I am for consistency. In this case, when the statistics on transmissibility, on diseases that we know are transmissible, are so different

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between groups of people who in the past have engaged in certain behaviors, I am not sure we want to be completely consistent if we are dealing with that different levels of possible risk.

DR. HOLLINGER: Exactly. Dr. Nelson.

DR. NELSON: I, too, am concerned about the discriminatory, and I think it is a real issue, but in fact, blood banks do try to discriminate without detailed personal individual data. I mean I have not been able to donate blood for the last 20 years because every year I have gone to Thailand, and Thailand is an endemic area for malaria.

Even though I have visited primarily cities where malaria is endemic, and so I am discriminated against, too, I am happy, I mean I live with the discrimination, but, you know, the idea is to try to use rather a crude tool, and not a personal tool, you know, to try to make the blood supply as safe in the workable, day-to-day workings of a very busy blood bank, blood donation system.

If we were to change the rule from '77, ever having had sex with a man to five years ago or to one year ago, it would still be discriminatory, because we would still be discriminating against bisexual orientation even though a substantial proportion of the men who have sex with me are monogamous and not at higher risk than many

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heterosexual couples.

So, changing the rule would not really eliminate the discrimination. I am concerned, though, about the issue that if we made it one or five years, that that would automatically exclude all of the same sex couples, homosexual men, et cetera, but what we are trying to pick up is the person who just had a casual contact and having him try to date that, was it 12 months ago or 13 months ago, was it five years ago, or five and a half years ago.

I think that the reporting on that might be less accurate than the current system is where we try to exclude, we try to be as discriminatory as possible, and unfortunately, you know, this is the way the system works, but I am trying to figure out is there a way to improve the system, making it less discriminatory without compromising the safety, and I would be willing to think about that.

I don't think the issue is the length of the window period. I think the issue is identifying behavior that an individual might have to report in a given time period.

DR. HOLLINGER: Dr. Mitchell.

DR. MITCHELL: I am also very concerned about what is classified as discrimination. I mean I believe that we have to be selective, but when you say discrimination, when

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you are saying, well, I am discriminated against because I choose to go to Thailand every year, instead of saying, well, I can't give blood because I went to Thailand once when I was a child, I think that those are two very different things.

We need to be selective, but we need to be selective based on risk, and I think that it is wrong to say that if you are a male who had sex with a male several years ago, that you are at equal risk to someone who is regularly engaging in risky behaviors.

I also think that some of the data, I was very disturbed by the usage and the comparison of some of the data for the highest risk people in STD clinics, and so on, and saying that there is no difference between them and, let's say, a monogamous male couple, or someone who has been abstinent for five years.

I have problems with that. I think that we need to base our decisions on the actual risk. I do believe that currently, the system does not do that adequately, and I think that we need to look at that.

I am sensitive to the concerns of the Committee of Ten Thousand, people with hemophilia, because they are dependent on the blood supply on a regular basis. However, the protections are much greater for that group of people,

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and again, as you heard previously, there hasn't been the infection from HIV or HCV for a number of years because of the other technology that is put in place.

I understand what they say about being reliant, that there is human error, there are technology errors, but I believe that the evidence, the prevailing concern I guess about classifying people who are at what I consider to be relatively low risk, that is, someone who may have been abstinent for one year, five years, seven years, 10 years, and excluding them from the blood supply because they are in a specific category that we currently exclude even though they are not at high risk.

DR. HOLLINGER: Dr. Martone.

DR. MARTONE: As I heard the discussions, I think there were three basic issues. One was the window period issue, which I think most of us are reasonably assured with now that that really is not an issue, that if you lower this thing to one year, that that window period doesn't significantly increase any degree of risk.

The second one is more problematical, and that is the test error issue, which was discussed at length. I agree that just answering this question that we are going to change this thing to MSM in the past if there was one experience in the past year without anything else might be a

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problem.

But on the other hand, I think with the current technology that we have, with the current laboratory technology, and with proper administrative controls, that we could probably do this and still give the same degree of protection to the blood supply that we have now.

How you do it, I don't know. It is probably a discussion for a workshop or another committee, but some of the suggestions have been made, such as a screening question asking if someone has had a negative test in the past year, or having them actually get tested at the site.

The third issue was that of emerging infections. I agree that is a major concern for not only recipients of blood, but any international traveler or health care professional.

When you start talking about theoretical aspects of emerging infectious diseases, however, I don't think you want to restrict it to MSM. I think this is also a problem of heterosexuals, of children who don't have sex, and a large segment of the population.

So, with that, I don't agree with just changing the time element on this thing without something else, but I think that something else does exist with current technology and administrative controls.

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DR. HOLLINGER: Ms. Knowles.

MS. KNOWLES: My experience in dealing with calls from the public leads me to believe that actually more education is needed. There are certainly people who are heterosexual, who have had many partners or who have been placed in situations, and they know they are at risk, but they are perhaps in denial because of their sexual orientation.

Others know they have had partners that might have put them at risk, but they really have difficulty in seeking appropriate testing options and sites, and so therefore, I feel that education is really needed, and that perhaps we might be well served by reworking some of these questions, so that they are more up to date with where we are at today.

DR. HOLLINGER: I guess also in some respects, I don't have a lot of problems with the 12 months although I am hearing some other sides of this that I think I have altered my thought processes a little bit since I came.

What bothers me is the number of donors that don't answer the question appropriately. I have said this before on these donor questions. If you have sat and given blood and sat there in a room, either at a facility, a church, or somewhere else, and you are asked questions, such as -- and I will read some of them -- do you have AIDS, AIDS-related

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complex, or a positive test for AIDS virus, are you a male who -- we have already known the questions about male having sex with another male -- ever used a needle to take drugs including steroids even once, are you a female who has had sex in the past 12 months even once with a male who has had sex with another male since 1977, have you received money or drugs in exchange for sex even once since 1977, or had sex within the past 12 months with someone who has even once had sex -- have you ever had sex even once in the past 12 months with anyone who has taken drugs by needle, are you donating to be tested for AIDS, all these are very powerful questions.

As a physician who sees these patients who often have given blood, and have not answered the questions properly, and then will tell me, oh, yes, I used drugs between -- I mean it is a common thing -- since 1972 to '74, or a variety of things like this.

It at least makes me wonder about the way the questions are -- because you have to answer these specifically for each question, and I have often said I think all of those questions ought to be answered as a block without making you answer those questions and making a decision at the end, and then they could say, look, I am going to ask you a bunch of questions, you don't to answer

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specifically for any of them, but when I am finished, if there is something that would suggest that you should not donate blood, then please answer it.

That would not then put all of this pressure on you to answer whether it is because of drugs or sex or with another male or any of these things that might change it. That is the one thing I felt is needed in at least these questions.

Yes, Jane.

DR. PILIAVIN: What you have just described is a technique that is used by a lot of really good survey research people as a way of trying to get around the social desirability bias in regular ordinary surveys on things like sexual behavior, for example.

I think it is an excellent suggestion of how we might change it. Another thing that I think is problematic in the way people go through that procedure, and as you know, I gave a lot of blood in my past, so I have heard those questions a lot, not the most recent ones which are getting more and more intrusive.

But I think people turn off and tune out the way you do with the stewardess who is giving the instructions on the plane. If you have given blood enough, you know the questions and you don't even really listen to them very

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carefully, and I think when you change the questions, it is really important to tell people the questions have been changed, but I think there is an awful lot of people who aren't listening very carefully anymore, and how to get around that I don't know.

There is also, of course, the issue of people deluding themselves, and they don't intentionally try to mislead you because they don't ever get to that point, they have convinced themselves that even though they may have engaged in these behaviors, it is okay because, and they don't really mean me, because, of course, the person I had sex with couldn't possibly have had a disease, and so on, and so forth, those kinds of things, so there is inherent problems in the questions.

The last thing I want to say on this point is if we do get to some point at which we are going to be changing this time frame, and changing the at least only once since 1977 thing, I think it would be important to have a good healthy cushion on the time period that we think is the real time period, and if we think the real time period is a year, we should have the question say at least two years, because there is something called telescoping that people aren't really good at telling you how long ago something happened.

If we want it to be really one year, we should

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make it two or five, so just to make sure that if they have had an incident that they remember vaguely in the past, that we are sure it is long enough ago, so that we will be comfortable with it.

DR. HOLLINGER: Thank you.

Dr. Khabbaz.

DR. KHABBAZ: As I think about this, I am thinking back of a comment that somebody made this morning, that really we are considering this question in light of a blood supply that is very, very safe, and it is very, very safe as a result of all the policies that we have instituted, which include donor deferrals and testing, et cetera.

I thought the presentations this morning were very well and raised important issues. I have to admit that I had a hard time going through the calculations. There is a lot, of course, of estimates and a lot of -- estimates, I guess, that were made -- assumptions, thank you, exactly -- assumptions that were made, and I think what is at issue is not improving blood safety since it is very, very safe, but addressing other issues and other difficult issues, discrimination, the question of how to get a better response, and whether the questions that have worked for safety are the right questions for the day and whether they can be improved on in terms of being more specific for risk

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groups and risk behavior.

I, too, feel like I am not ready to address the question because I would like to see some more discussion and some more questions, what specific questions, and also assessment of how different questions might impact on safety.

I think I would endorse a suggestion made that perhaps there be some other discussions, a subgroup, a workshop, or something to address possible changes to improve on this.

DR. HOLLINGER: Any other discussion? Yes, Jay.

DR. EPSTEIN: Blaine, I just wanted to give a historical note. Direct questioning was introduced in 1990 to specifically delineate behavioral risk factors. Prior to that time, the construct in place was precisely as you described, which is that a donor was presented with various risk information, often as a background brochure, and then simply asked if any of this applies to you, do you agree that you will not donate.

The feeling in 1990, at which time we were also dealing with an issue that had been addressed or framed in terms of discrimination, namely, the deferral in place for persons who had immigrated from Haiti, was that we needed to shift the focus and talk about behavior and not group

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membership.

Almost the quid pro quo in the logic of the time was that if you are going to talk about behavior, you had better be specific. Of course, there were surveys done to find out whether such specific questioning would compromise blood availability because of it being embarrassing and potentially offensive to prospective donors, and we discovered that, in fact, it was well tolerated by donors, that donors understood why this was happening, and there wasn't a chilling effect on supply, and indeed we then went forward.

Now, technically, the FDA recommendation is that donors be asked direct questions about behavior consistent with formats that were provided in '90 and updated in '92, but we don't actually require that the record document each and every answer, although that has become the predominant practice, and I suppose you could say that it has become the industry standard.

So, I am only saying here that there is some tendency for history to repeat itself and that the proposal that you make, which seems wise at the moment, was seen wise between 1983 and 1990, but was seen as unwise from 1990 to 1997.

I don't which is correct, but I just think it's

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useful historical note.

DR. HOLLINGER: I understand what you are saying and except for the fact while it did not compromise the blood supply, we have already heard that, yes, you get people coming in to donate, but they are just not telling you. They are listening to those direct questions, they are just not answering them correctly, and I think that is even worse.

DR. EPSTEIN: I guess my reaction to that, of course, that is true, and I think that the REDS study, which found 1.9 percent risk histories in people who are accepted for donation is alarming. On the other hand, if you flip it around, if you compare marker rates in persons in the general population to those accepted for donation, you find approximately a 50-fold to 100-fold reduction in those rates, suggesting that the education and the deferral process are effective to the tune of 1 to 2 logs.

So, what is the right response? Do we bemoan the fact that that is not a perfect strategy or do we applaud the fact that it is, in fact, highly effective?

I think that a 1- to 2-log risk reduction obtained by education and history is a significant safety measure, and we would readily acknowledge that it is imperfect.

DR. HOLLINGER: Dr. Piliavin.

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DR. PILIAVIN: Jay, I don't think that Blaine was suggesting going back to talking about risk groups.

DR. EPSTEIN: No, no

DR. PILIAVIN: I think what he was proposing is giving people this list and letting them tell you whether any of those applied, so that they don't have to commit themselves to which.

DR. EPSTEIN: No, I understand that quite precisely. I was only pointing out that those two changes were concurrent, moving away from risk group, moving toward behavior, and implementing direct questions happened at the same time in 1990, but still, the system in place before 1990 was a donor was asked if any of this risk information applies to you, do you agree that you won't donate.

DR. PILIAVIN: But that information that was presented to them, was presented in a very different context.

DR. EPSTEIN: That is correct. It wasn't delineated risk factor by risk factor.

DR. PILIAVIN: Behavior by behavior. I mean this is behavior by behavior, it is not risk group by risk group.

DR. EPSTEIN: No, no, no, much of it was behavior oriented, but there were no specific behavioral questions. What changed in 1990 was we implemented specific behavioral

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questions.

DR. PILIAVIN: Right. I think that all Blaine is suggesting is you ask all of those specific behavior-oriented questions, ask the person to keep a little private tally of the yes/no, yes/no, yes/no in front of them, and then at the end, you say do you have any yes's written down in front of you.

DR. HOLLINGER: Dr. McCurdy.

DR. McCURDY: If I remember correctly, the change to direct questioning was based on a study that was limited in scope, but fairly clearly demonstrated that there were more people who gave forth information about at-risk behavior than it did through the regular questionnaire of look at it, read it over, and say that we belong to one of those and we don't need to tell you which one.

I don't know that I really want to add a great deal or can add a great deal to debate. I believe that the 1977 date, et cetera, should be changed, but not now, and the reason I say not now is that we need, I think, some additional time to review the information that was provided today, at least as far as the committee is concerned.

I have seen a certain amount of it before, but more importantly, there are some things that are coming down the pike that would help blunt any problems that might arise

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as a result of this.

I am talking about genomic amplification testing. I am talking about reviewing the questionnaire, which I think is a good idea. I think there is a possibility that it will be reviewed with the help of some behavioral scientists who will help validate the questionnaire and any changes that might be done, hope that it will be field-tested.

I think both the REDS study and the CDC study brought up the issue of privacy, which I think is not only distinct privacy, but perceived privacy, and they are not necessarily the same thing, and it may be possible to improve the quality control of the quality assurance of the ways that the questionnaires are being done.

My direct experience in blood center work is now more than 10 years old, but the amount of time that was spent trying to determine for sure whether the questions were asked in a way that would be non-judgmental or you haven't done any of this, have you, or something of that nature was I think very limited, and I think all of these are things that could be put into place and would make changes which would permit the modification of the time frame, which I do believe and agree is something that we should do, but not now.

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DR. HOLLINGER: It is like that red light that goes off above your chair when you answer yes, you know, bah-bah, and you see it.

Yes, Jane.

DR. PILIAVIN: Just one final thing. I quite agree that if we can get better methodology, it would be great, and in the past, on this committee, I remember once we had a presentation, a computer presentation of questions, and there is all sort of evidence that people are more likely to tell the truth to a computer than they are to tell the truth to a person.

A lot of it has to do with the sort of thing that Dr. McCurdy is talking about, is the perceived judgment of the person you are giving the answers to, and the way they ask the questions can somehow suggest that. The computer asks the questions exactly the same every time with no inflection in its voice.

DR. DAYTON: I was wondering if I could make an interjection.

DR. HOLLINGER: Yes, Dr. Dayton.

DR. DAYTON: I think in terms of what may be coming down the pike, there is a lot of things that are happening that may, in the next couple of years, drastically change these numbers.

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In specific, the arrival and increasing popularity of home test kits and the resulting increase in home testing, and where this comes into play, if you remember, as you all realize actually, one of the most problematic numbers is the prevalence rate times the number of people who show up at the door, and that is where you get these extra thousand or so positive units entering the blood banking system, getting past the questionnaire.

But if you also remember we corrected that prevalence rate to an effective prevalence rate, and we did that by taking out the people who were positive and have been tested and knew they were positive.

As the home test kits and the ease of testing become more widespread, that number is going to go way, way down. The number I quoted you was 75 percent, but there is already some data coming out or very preliminary data from Joe Catania, that the most active MSMs may actually be tested at the 90 percent, may know their results at the 90 percent rate as opposed to the 75 percent rate.

So, if we have an increased amount of testing, which looks like it is going to be the case, a couple of years from now these numbers are going to look very, very different.

One last comment, and it is really for the public,

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I just wanted to describe where we came from when we started putting together these numbers, and I came into this analysis very naively and I just said, well, we are probably going to go with a one- or two-year deferral, and then I just started putting together numbers, and we created the model in time to get it to the committee, but we really only filled in the numbers just several days ago.

We were quite surprised by a number of the findings. We were surprised that the window period issues had as little effect as they did. We were surprised that the test-seeking behavior had as little effect as it did, and we were somewhat surprised that the prevalence turned out to be, for HIV, the key issue.

I just wanted to put those two comments into the record.

DR. HOLLINGER: Also, not taken into account in the formula is the recipient, that is, not all recipients live. Those who get perhaps the highest number of units of blood will die, and may receive that unit of blood which is positive. So, all of those things -- and that would be very difficult to get that information into an equation, but we do have to consider that also, I think, as well.

I think we will go ahead and respond to the question if there are no other burning issues here.

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Yes, Dr. Nelson.

DR. NELSON: Maybe I misunderstood the ABC recommendation or statement. They were talking about permanent deferral of people who had injected drugs, but I thought that was policy now. Is that not right, in terms of deferral? I mean that is not part of this question.

DR. BUSCH: The ABC, I think has just raised the issue that the current permanent deferral of anyone who has injected drugs could be reevaluated in the same context as this to reduce that to a year or two -- I don't remember the numbers -- but I think in Alan's survey that knowledge of remote drug use -- and, as we know, when we pick up HIV, HCV positives, the vast majority were actually exposed very young.

DR. HOLLINGER: I think we will go ahead and pose the question. Again, the answer to this question, as I understand it, about modifying the current recommendation, it doesn't necessarily mean that one has a recommendation for the next part, which is how long or anything like this. The question is should it be modified.

The third question deals with what kind of options there are, and it doesn't have to be any options. I mean it could be this or one year, two years, five years, et cetera, and that can be dealt with.

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DR. KHABBAZ: I have a hard time voting on a question that says modify without linking it to what would be modifying it to.

DR. ELLISON: It would seem to me if we vote no on 2, we don't bother to address 3.

DR. HOLLINGER: That is correct. My understanding is if you vote yes on 2, you don't necessarily have to agree with any of the conclusions in 3 at the present time. I know there have been some issues about that this has to be reviewed, and so on.

Yes, Dr. Mitchell.

DR. MITCHELL: I guess that is my question. It seems like some of the members think that it should be modified, but not today, so how do they vote on No. 2. I mean what is that?

DR. HOLLINGER: I think we should accept 2 for the way it is, and then deal with 3 if we have to get to 3.

DR. MITCHELL: So, if people think that it should be modified sometime in the future, they would vote yes for 2, is that what you are saying?

DR. DAYTON: Question 2 was never intended to be that we would never change it. Obviously, the intent was should we change it now.

DR. PILIAVIN: So, yes means change it now.

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DR. DAYTON: Right.

DR. HOLLINGER: You will have to tell us then from the FDA, because there is some question on the committee. I would view this as saying it should modify it, and as someone had said, I think you had brought up the question of when.

DR. DAYTON: Let me try to clarify that. If you say that you should not modify it, that doesn't mean we are not going to come back and reexamine it a year or two years from now. It just means that until we get more information, it will stay as is, in which case we don't need to address 3. But if you feel that now is the time to change it to something else, possibly one of the options in 3, then, you should vote to modify it.

DR. HOLLINGER: Bill.

DR. MARTONE: I, for one, I will speak for myself rather than the committee, I feel uncomfortable with that. I don't want this thing to go away for two or three years and not be worked on. This, I think needs immediate attention, not something that is going to be done in five or 10 years.

DR. DAYTON: That certainly would be a possibility under Question 4, are there other policy options.

DR. MARTONE: So, how do we vote, so that our

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intentions are brought out on this committee, and that is, yes, we think the criteria should be modified with the following provisions?

DR. HOLLINGER: Take a look at 4, Bill, and see if that resolves your concerns.

Yes, Dr. Linden.

DR. LINDEN: I was wondering if we could say something along the line of asking whether the FDA should reconsider their current recommendations, you know, and study it now.

DR. ELLISON: I guess I am the only person that spoke, or at least I spoke more positively than anybody else in answer to this question, so perhaps I should point out that that is my concern, that if we come back here next March or next December, I haven't heard what we are going to be looking for other than Dr. McCurdy's suggestion that there is something in the pipeline that might be more positive.

I don't want this to go away. I am going to vote yes on this question, and the reason I am going to vote yes is I am concerned that if we don't, that it is dead, and I don't think it should die.

DR. HOLLINGER: Dr. Verter.

DR. VERTER: I will ask Jay to respond to this,

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but my sense, Jay, is that in the past, when we have reached this impasse and tried to reword the question 30 or 40 times, you usually stand up and very bluntly say we have heard what you are saying.

DR. EPSTEIN: I am not sure I know the sense of the committee in the aggregate. I think that the message that you would perhaps like a subcommittee to examine the data more closely and perhaps generate other options came through loud and clear, but I am still not sure how the committee as a whole feels about whether we should be seeking to modify this criterion, which in my mind means you think there is something wrong with it versus we shouldn't, which would read to me you don't think there is anything wrong with it.

DR. PILIAVIN: Your interpretation of a yes vote is not his version of a yes vote.

DR. EPSTEIN: No. I think what we are saying is if you vote yes, your advising us to proactively engage and get this job done and change this deferral, that you think that is the right thing to do.

Now, unless you give us further guidance, it is not really clear what the sense of the committee is, which direction to go from there, but you have at least advised us that you think that the bulk of the scientific data support

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making a change in some near term, it's wrong, and you don't want it to stay this way. That is what you are saying if you vote yes.

DR. DAYTON: If you vote yes to this, presumably, then, you would be choosing one of the options in 3, or maybe coming up with something similar along those lines, because it is really the length of the deferral.

DR. HOLLINGER: That is not how I interpret it, and I think the committee doesn't have to interpret it that way.

DR. DAYTON: You win.

DR. HOLLINGER: Joel, do you have something burning here?

DR. VERTER: One final comment. I think the problem is, as we have seen before, some of the questions don't meet the expectations of the committee. I am not quite sure how to vote. What I would like to do is say as of today, I don't think it should be modified, but I think someone needs to go through, as I said earlier, the data and present it to us better. The chances are it will be modified.

DR. HOLLINGER: Dr. Kleinman.

DR. KLEINMAN: There are people who have looked at this outside of the FDA structure. We have had a committee

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within the AABB that has looked at the donor questionnaire for the last year to two years. There are social scientists that are engaged in research here.

But nobody is going to look at it if it is FDA policy to have it one way. I mean you are not going to invest a lot of time trying to improve things if you say, well, this is what I think it should be, but regulatory policy says it can't be that way.

So, I think that some indication from -- I mean if it's the intent of the committee to say this at least deserves some reexamination to see if somebody can come up with a better idea, then, in my mind, if you tell the FDA not to modify it, you tell everybody else in the blood community it is regulatory policy and don't spend your time trying to come with a better answer.

I think you need to word the question in a way that an intent comes through, if you are not totally satisfied with the current question, that there is room for further study and that people will do that further study in a timely fashion.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: There is one word in Question 2 that is modify. If you change that word to review, it addresses many of the issues here. If you leave it as modify, you

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would have to pick up review back under 4 or 5, but the real issue is review versus modify, and I think there are people here who would say it should be reviewed, who probably wouldn't say it should be modified today, and vice versa perhaps, but I think we either leave it as modify or change it to --

DR. HOLLINGER: Wait a minute. Jay.

DR. EPSTEIN: There is a risk here of getting lost in semantics. I think that you have the option in Question 5 to tell us we should pursue studies, and you can do that even if you vote no to whether we should modify the recommendation. I think that, you know, we are reading in too much. We are just asking, in a general way, what tack should we be on, trying to change this or leaving it alone.

Now, if the tack we should be on is seeking to change it, I can understand that the committee is not prepared to recommend any particular option, and may wish closer examination of the data, and they wish to generate more options, but you are communicating to us the sense that you do think that blood safety, the donor population, the public health are ill served by the current recommendation in some significant way, and therefore we should work to change it.

DR. PILIAVIN: But, Jay, speaking as the person

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who always has been trying to reword your questions, and I know that is what you think when I open my mouth, I really think it is going to make a difference to clearly at least two people, Dr. Boyle and me, how we vote.

If we could substitute either review or reconsider for the word modify, I can't explain why it is important to me, but they really seem to have a really different meaning to me. I will vote yes if it says reconsider, and I will abstain if it says modify.

DR. HOLLINGER: Dr. Verter.

DR. VERTER: I agree with you totally. I think it is a critical word. To me, should means you had better go do it. Review means we don't know, but we need some more information. I think that is the key.

DR. EPSTEIN: Put it this way. I think that if you wish to change -- first of all, it's your prerogative, the Chairman's prerogative whether to change the wording -- if the committee members are more comfortable voting that FDA should reconsider, I can accept that, and I think that would be a useful piece of advice to the FDA.

DR. HOLLINGER: As I said, I think the only thing that is lacking, I mean if you read the question as modify the way they have it, the only thing that is lacking in 3 is a fifth part, which is none of the above.

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Then, you have 4 to deal with to describe what you wish to have done. So, I think the question is pretty straightforward personally.

Paul.

DR. McCURDY: As I said earlier, I think it should be modified, but not now. The way Jay has framed the question, I think makes it so that I can vote yes to this, because I believe it should be modified, and I think it ultimately will be modified.

Dr. Dayton said "now." "Now," I can't vote yes to, but I guess the way Jay has framed it, like it should be -- I mean to me that says it needs to be reviewed and considered for modification. I think once that has happened, ultimately, it will be modified.

DR. HOLLINGER: Dr. Holmberg.

DR. HOLMBERG: What do we need to do as a committee to change that word? I think that I could live with that change.

DR. HOLLINGER: You can always vote on it.

DR. HOLMBERG: Pardon?

DR. HOLLINGER: We can vote on it.

DR. HOLMBERG: Please.

DR. HOLLINGER: How do you want to rephrase it?

DR. ELLISON: Could I move that we change the word

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"modify" to "reconsider."

DR. PILIAVIN: Second.

DR. HOLLINGER: Moved and seconded. We will vote on that, change the word from "modify" to "reconsider."

All those in favor, raise you right hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Anyone abstaining?

[One response.]

DR. SMALLWOOD: The vote to change the word "modify," there were 9 yes votes, 3 no votes, 1 abstention.

MS. KNOWLES: I agree to change the word.

DR. HOLLINGER: So, now we will vote on the question then. Do the committee members believe that FDA should reconsider its current recommendation that men who have had sex with men even one time since 1977 should not donate blood or blood components to be used for transfusion or further manufacturing?

All those in favor of that question as written, raise your hand.

[Show of hands.]

DR. HOLLINGER: Opposed?

[One response.]

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DR. HOLLINGER: Abstaining?

[No response.]

MS. KNOWLES: I agree.

DR. SMALLWOOD: The results of voting with the question reading as follows: Do the committee members believe that FDA should reconsider its current recommendation that men who have had sex with men even one time since 1977 should not donate blood or blood components to be used for transfusion or further manufacturing? The results of voting: 12 yes votes, 1 no vote, no abstentions, and the non-voting consumer rep agrees with the yes vote.

DR. HOLLINGER: Thank you.

Let's go on to the third question.

If FDA's current recommendation should be modified, do the committee members agree with the following policy options?

- a. Permanently defer men who have ever had sex with another man.
- b. Defer men who have had sex with another man in the last 5 years.
- c. Defer men who have had sex with another man in the last two years.
- d. Defer men who have had sex with another man in the last 12 months.

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And (e) would be none of the above if we added none of the above.

We could change the question, but we would have to put it before a motion.

Yes, Joel.

DR. VERTER: In light of our response to the second question, should this be deferred totally?

DR. HOLLINGER: Dr. Mitchell.

DR. MITCHELL: I am wondering whether we should give a sense to FDA as to which way we are leaning, so they can come back with clearer choices.

DR. HOLLINGER: Any other thoughts about this? Bill.

DR. MARTONE: In view of the discussion, I sort of think this question is almost irrelevant, but the issue on the table was a 12-month period, and maybe we should just skip this question and go on to No. 4 and 5.

I would make a motion to table this particular question.

DR. PILIAVIN: Second.

DR. HOLLINGER: I have no problem actually with this question, and if I were going to vote on this question, I would probably vote on it with the last two years as a modification.

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DR. PILIAVIN: A motion to table is not debatable.

DR. HOLLINGER: We had a motion to table this question. Was there a second to that? There was a second. So, we will need a vote on that.

All those in favor of tabling this question, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed to tabling it?

[Show of hands.]

DR. HOLLINGER: Abstaining?

[One response.]

MS. KNOWLES: I agree it should be tabled.

DR. HOLLINGER: The question is tabled.

DR. SMALLWOOD: The motion that was voted on was to table Question No. 3. The vote was as follows: 8 yes votes, 4 no votes, 1 abstention. The non-voting consumer rep agrees with the yes votes.

DR. HOLLINGER: I think it is our responsibility on looking at this to try, if we can, to give the FDA some guidance about what the thoughts are of this committee at this point in terms of reconsidering the current recommendation.

That will probably go under the next question: Are there other policy options that FDA should consider

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regarding male/male sex as a behavioral risk factor for donor deferral?

It could take under 5 also: What additional studies -- if we have a problem with that -- what additional studies are needed, so that you can make a decision?

I think the more important question is are there other studies that would change your mind one way or the other, are there any other studies that could possibly get to the answer to this question.

Yes.

DR. NELSON: One suggestion that was mentioned that I think would be important would be to have a testing of a donor followed by a certain deferral period, HIV testing, and then the donor, the blood would be obtained a period after that, and that would apply and no risk behavior in that interval, so it would be a two-stage, as I understand it.

DR. HOLLINGER: What kind of question would be asked, Kenrad?

DR. NELSON: A person could have reported sex with another male or something like this.

DR. HOLLINGER: Within what time period?

DR. NELSON: Prior to the first testing, and then come in and be tested, and then subsequently eligible for

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donation and retest it at that time, as well.

DR. HOLLINGER: So the question would be at any time?

DR. NELSON: No, there would be an interval, maybe a year or six months or, I don't know, whatever.

DR. HOLLINGER: The question is what question would be asked the donor in which it would trigger that kind of followup. Would it ask the question about male-to-male sex within 12 months, two years, five years? I mean at what interval?

DR. NELSON: That is debatable. That would be a strategy the months or years or whatever that would be in that interval, we would have to decide what to study or what to propose. Somebody had proposed that.

DR. HOLLINGER: I am not trying to badger with it, but I want it clarified, and then if they come back in six months and they have had sex again in that six months, then what? Then, it goes on for another six months? It is a difficult issue.

DR. MITCHELL: I think we need to review that. I mean I think that we need presentations. I think that part of the reason for not acting today is because we need to explore other options and how that would work and whether it's practical. So, that is what I would expect.

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DR. HOLLINGER: Other studies? Are you saying other studies or other information that you need to have?

DR. MITCHELL: Yes, whether it is practical, if this were a policy, how would it be implemented, so that it would be practical is the question that I would ask.

DR. HOLLINGER: Dr. Holmberg.

DR. HOLMBERG: I would like to see some more data presented covering the plasma industry. I think that a lot of the data presented today was primarily for the whole blood industry, and yet when Alpha presented with the PCR testing, it was very obvious that we are talking a lot of donations versus a donor.

I think that we need to clear that out and see where the risk factor is, not only for the whole blood industry, but also for the plasma industry.

DR. MARTONE: I would like to follow up on this suggestion over here in that I would be interested in learning of studies of, or opinions about, a screening question that would be linked to MSM sex within the past year, i.e., linked to -- if that is no -- have you had an HIV test in the past year, either as a question or bringing a test result in.

If the answer to that HIV test was yes, it has been done in the past year, there has been no sex in the

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past year, and the test is negative, the possibility of that person immediately entering the system to get his second test for that particular donation.

The other thing is I would also like to more carefully look into this other potential of a woman having sex with somebody with AIDS or HIV in the past year. That bothers me as a potential high risk individual entering the pool. While I recognize that this wasn't to discuss that issue, I would like to see some data on that.

DR. PILIAVIN: If we are going to be doing this kind of modification, it would seem to me, if want to be consistent, we should have, not only the MSM behavior, but the drug injection behavior, and women having sex with other dangerous people should all come into this same category.

We should have some sort of structure of asking have you ever, and then among the people who say yes, I have, have something that says have you in the last year, and then those are the people for a whole set of behaviors who would then perhaps fall into this do a test, have them come back category.

I mean this would solve a lot of problems in terms of the perception of discrimination, as well as actual safety issues.

DR. MARTONE: The reason why I was interested in

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bringing this link into a screening question about have you had an HIV test in the past year, is that we all know that many people in the group MSM have had HIV tests that are negative in the past year. That just might expedite the process, so I was basically interested in that as a potential screening question.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: I would just like to clarify two things that I think are going on here. One thing is my own personal prejudice, which is we are talking about two different issues here, two rights in conflict, one safety, and the other is perceived discrimination. My own personal feeling is that one weighs heavier than the other, but that is an issue.

But what everybody has suggested or a number of people have suggested is that even if you are concerned with the safety issue, the screening questions or the screening approach may be inappropriate and may be working against that objective.

A number of people have made suggestions about what might or might not improve that screening, and I think the one thing I come away from here is I would certainly like to see some testing done of different approaches to screening to see whether or not we can improve the accuracy

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and the validity of those responses.

DR. HOLLINGER: You look at safety and you have to look at the data, and the data is that most people, perhaps all patients, will seroconvert in that period of time that one is taking, and we can't ignore this fact unless somebody presents us some data, which no one has, that I have seen presented here today anyway, about seroconversions that have occurred, say, after a year or so.

Therefore, it would seem that that is a risk factor. I mean we can't manufacture any different data than that, so that if a male has sex with another male within the one year, that person is deferred, but it seems like if it has been more than a year, or two years, as I said, one could use something to give you a little bit extra safety in there about, well, was it really six months or 10 months or something like this, or was it more.

But whatever you use, the fact is that for me to handle that, I need some data that tells me that there are seroconversions that are occurring after that, and I haven't seen that data, and I would like some data to be presented that would make me think otherwise about this long length of time.

Dr. Nelson.

DR. NELSON: In thinking about it, currently, I

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think that there is a difference in the way that a man who has had sex with a man, and a heterosexual, questions or deferred, and it is based on the prevalence in the groups, and what have you, but clearly, it is discriminatory, but I think that there are men who have sex with men who are in a stable relationship, and there are heterosexuals who are in a stable relationship, and there are men who have sex with a man where one or both partners have multiple partners, and there are also heterosexual couples where one or the other has multiple partners.

In reality, even though they are not at the same prevalence now, at least in the United States, in the future, it is quite possible that the risk will change and that there will be -- and the heterosexual rate is going up, so that may well be even now in certain populations in the States, so I would wonder if focusing on behavior rather than a risk group or a population, that a deferral strategy could be studied wherein it is not ever having had sex with a man, but having had sex with a man testing negative and then in an interval, neither of the two have another partner, and the same applied to heterosexual couples.

Now, obviously, there is some question about whether one partner knows in detail, in all instances, the other partners, so that is a potential problem. But I would

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think that would allow some men who have sex with men to participate as blood donors without -- I would think there might be a way to do it without increasing the risk in a real way, and it would get away from the labeling of a risk group as opposed to a behavior during the interval during which an infection could be non-detected by our current screening methods.

DR. HOLLINGER: Dr. Kleinman.

DR. KLEINMAN: I just want to mention to the committee that blood collection activities are a regulated activity by FDA, and FDA has a policy right now on what questions you need to ask donors, and that policy is the policy you are reviewing.

So, when you take that into the background, it precludes the ability to do real-time studies because you have to ask if you are really in the blood donor collection setting, you cannot avoid asking these questions. You are required to ask these questions. You can't test out alternatives.

So, the study, I mean unless you were able to get FDA to agree that in those kinds of settings, for purposes of generating research data, you could do something different than the usual regulated questioning.

So, you are left with studies that have to try to

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obtain information after the fact like the survey research that Dr. Williams reported on, and maybe some other approaches that one can use, but those studies are always criticized because, in fact, they don't duplicate the actual screening environment, and the one study that was published some years ago on computerized screening was rather flawed because essentially, those people had to go through the usual procedure, as well as the computer procedure, and so you have already created a bias.

So, I just want to point out that while I think it is desirable to try to evaluate alternatives, I don't see how those actual alternatives can be piloted, data collected, and then make a decision about whether a policy as a whole should be changed, because we are constrained from trying those alternatives.

So, maybe the committee could address how that would have to be worked through.

DR. HOLLINGER: Dr. McCurdy.

DR. McCURDY: Unless I misread, in our packet there was a donor questionnaire that I believe came out of the Irwin Memorial Blood Center, and it is my understanding that for a number of years now, the questions have emphasized activities, at risk activity, and have not talked about risk groups. I think that went out, I don't know

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when, but it was in the -- I think it may have even gone out before I left front-line blood banking.

So, I think that right now we are emphasizing activities. The other issue, since the NIH is responsible for supporting a fair amount of research, I think one of the most important things about research in this area is that it would be very difficult to tolerate even a temporary reduction in safety in the guise of research, and that is a very difficult thing to do, but I suspect if we came up with some innovative ways to do that, working with the FDA, we might be able to get the studies done.

I think the issue is that the new approach -- and most everybody thinks computers -- I am not sure that that is necessarily the way to go, but the new approach can't tolerate even a temporary reduction in safety.

DR. HOLLINGER: Dr. Stroncek.

DR. STRONCEK: I guess from the data this morning, I think there were two issues. One is the window period, and the second one is the prevalence of HIV in donors donating blood. I think we have talked about the window period quite a bit, but the prevalence issue, to me it was based on if we have a lot of donors getting collected, that are HIV-positive, there may be a mistake and some might slip through.

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So, I guess we still need -- I don't disagree with that -- so, I think we still need to have screening criteria to prevent people who would be HIV-positive from actually having that needle stuck in their arm and the blood drawn.

Now, we pointed out that most of our screening criteria are behavior based, but there is still a couple, such as male having sex with male, that is really a group, and I think what I would like to see is are there behaviors within that group that can be used to separate out individuals that are very unlikely to be HIV-positive from those that are very likely to, and I suspect there are. I suspect the number of sex partners and there is other things that you can separate out that, so then you would have the questioning even more behavior driven rather than group driven.

I think you have to look at -- well, maybe with the heterosexual contact, those questions are activity driven already or behavior driven already.

DR. HOLLINGER: Again, I would like to bring up, since we are talking among committee members here, we know the window periods are not longer than a year, it seems like they are not longer than a year, at least I have not seen any, we know that there has not been any reported seroconversions that are longer than a year, so what is the

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issue? I mean what is the hesitation?

I am sure maybe if we look long enough we might find one, but what is the hesitation that the committee has with this? I can tell you from looking at a lot of samples, that that has just not occurred.

Yes, go ahead.

DR. BOYLE: One of the questions is the whole issue that was discussed earlier, is things like telescoping. You ask somebody did this happen in the past year, and we know that in certain types of questions, if it happened nine months ago, you say yes, and other times it is 12 or 14 months, so asking a question did this happen in the past 12 months is not the equivalent of measuring whether it happened in the past 12 months.

DR. HOLLINGER: Exactly.

DR. BOYLE: We don't know whether people are more willing to say it ever happened versus it happened in the past 12 months. That is why I think the research needs to be done on the screening, and a lot of the questions can be done in terms of issues of the way the data is processed, the cognitive testing, the issue of telescoping, the issue of willingness to disclose, and so on, it can be pilot-tested outside of the blood center setting, and, if necessary, even under regulated conditions that you have to

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ask this questionnaire before that they move forward.

You can alternate a different one before or after. There is a lot of things that could be done to test some of the tissues that are of concern here.

DR. HOLLINGER: Good point.

Yes, Bill.

DR. MARTONE: To offer another answer to your question, I think the issue of telescoping is an important one, but we weren't presented any data with that today. We were presented data on test errors, and I think that is my major hang-up with it at this point.

That is why some sort pre-serologic screening, either by history or by a test, I think might obviate that. As far as I see it, that was the biggest concern that was presented here today.

DR. HOLLINGER: So you are worried about somebody that doesn't respond to the question, but is positive, comes in, and because a positive sample is looked at as being falsely negative.

DR. MARTONE: Yes, an erroneous negative test.

DR. HOLLINGER: Unfortunately, some of the issues, which I think is an important issue, is going to be dealt with tomorrow. It would have been nice to maybe have some of those questions --

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DR. MARTONE: Well, it may be, but I mean there is always going to be sample mixups.

DR. HOLLINGER: That is right, transcriptional errors, and so on.

Yes, Jane.

DR. PILIAVIN: I want to get back to this prevalence issue. It is also not just the possible mixing up, but someone raised the issue of needle-sticks, and so on, with the health workers, and if it is indeed the case that something like 70 to 80 percent of men who have sex with men are positive for hepatitis B, that is an awful lot of possibilities there.

Again, I would like to see something like what Dr. Martone is --

DR. HOLLINGER: Jane, it is not that high. I mean if you look at high-risk age group, it has been 80 percent with hepatitis B markers, which is usually only somewhere between 5 and 15, or maybe 4 to 15 percent may be HBs antigen-positive. It depends on the population.

DR. PILIAVIN: All right.

DR. HOLLINGER: But when you are dealing with the people who might come in and donate, then, the markers fall down to maybe 40 to 60 percent, and again, of those that are probably infected, it is probably closer to 4 percent or

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somewhere in that range.

DR. PILIAVIN: Okay. I will stop worrying about that then. I want to echo what Dr. Boyle said about the methodologies of testing. I have been sitting here wanting to say the same thing, that, you know, there is no reason why you can't have a split design in which half of the people get the new set of questions, and you make a judgment in your mind at that point about if those were the questions, would this person be deferred or not, then, you go on and ask them the questions that FDA says you have to ask, and then you really defer them on the basis of everything you have learned, and then the other half go the other way.

So, I mean there is just no reason why decent studies couldn't be done that way either with the computer with new questions, or whatever.

Then, there is one more thing I want to say in response to Dr. Nelson. One of the things statistically about the sexual behavior of men who have sex with men, of men who have sex with women, and of women who have sex with men, is that the number of partners of people in those three groups is highly statistically significantly different.

So, if you think in terms of a person presenting who says I am in a monogamous relationship, and this person

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really does believe that they are in a monogamous relationship, that is, they know they haven't been having multiple sex partners, it is still statistically the case that if that person is having sex with a man, then, the likelihood is that it is of a much higher likelihood that if the person is having sex with a man, that the partner is indeed having multiple partners, and that is multiplied if it is a man having sex with a man, simply statistically on the basis of what we know.

So, the question of people who claim they are in monogamous relationships, who are men who have sex with men, is still more problematic just on the basis of what we know about these groups of people.

DR. HOLLINGER: Dr. Ellison.

DR. ELLISON: One comment about the health care workers. There is a recommendation that health care workers that are at risk should get immunized for hepatitis B. Speaking of my own specialty, anesthesia, if you plot years of practices versus markers of infection, it is a straight line up for the first 20 years of practice, or it was. I hope it is not anymore because most anesthesia residents are immunized as soon as they enter the program.

DR. HOLLINGER: Yes, Jay.

DR. EPSTEIN: I just want to comment on a

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technical point about the use of the computer-assisted interview. This issue was brought to a previous meeting of BPAC a couple of years ago, and FDA's position is that we are not requiring de novo validation of safety and effectiveness of a computerized interview.

We will review and approve applications or supplements based simply on operational validation, in other words, does the software do what it is supposed to do, are the correct questions delivered, are the answers properly recorded, et cetera.

So, we are sort of off that dime for several years already.

DR. HOLLINGER: Thank you, Jay.

Dr. Busch.

DR. BUSCH: Just a thought with respect to the concern over test error, which I think is excessive, on the other hand, I think it has not been measured adequately. When you talk about the increased prevalence associated with relaxing these criteria, in fact, first-time donors are really where the prevalence lies and what we are concerned about here is an influx of new first-time donors with some higher risk group.

One possible study that would get data in perhaps would be not an inappropriate policy, would actually be to

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double test first-test donations, in other words, two independent assays performed on all first-time donations. It is a relatively modest proportion of donations, about 20 percent and at a minimum, if it were done in the research mode, it would get us a lot of data very quickly on the rate of discrepant results, well over probably 1 percent of all first-time donations are positive with very specific confirmable results and probably 4 percent are reactive for the various assays.

The problem there will be one of the FDA issues that those of us who work in the business know well is called testing to compliance, and basically, how do you deal with two tests without FDA coming and sorting it out. It would obviously be something we should do in a research study with FDA, I think.

DR. HOLLINGER: Dr. Mitchell.

DR. MITCHELL: In addition to what has already been talked about, I think that there needs to be an overall policy. It appears the prevalence is what is important as far as risk of HIV, and it seems to me that there should be a way of saying when certain populations get to this prevalence, then, we need to look at behaviors within those populations, and I am curious as to what that prevalence rate would be.

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DR. HOLLINGER: I think clearly, I mean the data clearly has documented that males that have sex with males are in a group that has a high prevalence of disease, and I guess that is what is concerning the group here somewhat, and yet they only represent, as they said before, 1 percent or less than 1 percent of the donor population.

DR. MITCHELL: My concern is that the distribution of HIV is changing, and we are seeing an increase in all other populations except men who have sex with men, and at some point in the future, we are going to need to examine all of these other groups, and so I am just asking for something to say the yellow light is on, we need to look and see if we need to change our policies at some time in the future.

DR. HOLLINGER: Thank you.

Jay, I am not sure where to go with this, or, Dr. Dayton. I think obviously, the committee feels that the third questions need to be tabled, that they didn't feel it sounds to me like there was enough information to generate a specific request about modification or reconsideration.

I think you have heard some suggestions mostly in terms of trying to get more information from the people who are responding in the first year, and so on, to get more information about test result errors, transcriptional

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errors, and things like this that occur.

Anything else, any other thoughts?

DR. MITCHELL: One last thing is about time frame for this. I think that this needs to keep on the front burner and be reexamined in the very near future.

DR. HOLLINGER: Dr. Holmberg.

DR. HOLMBERG: Again, I would just like to reiterate that I would like to see what the potential increase in the plasma donors as far as, you know, reducing this down to a one-year deferral, what would be the prevalence of those additional donors in the plasma.

Also, I guess what I would like to maybe recommend, that we encourage the presenters to sort of consolidate some of their slides and be a little bit more concise, maybe limit them to a number of slides, and a time limitation.

DR. HOLLINGER: Thank you. I think that is a good suggestion. So, it sounds like the committee wishes to at least for the present time, retain the question as it is listed, but wishes to look for other ways in which it might be modified.

Are there any other additional studies that might be needed to clarify these scientific issues that could be obtained, that would allow you to make any different

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decisions than what are made right now in terms of changing the time period?

Yes, Bill.

DR. MARTONE: I think one study, which is already in progress, that I would be very interested in, is this seroprevalence survey for herpesvirus.

When do we have the results on that, does anyone know?

DR. HOLLINGER: Dr. Busch, do you have an answer?

DR. BUSCH: With respect to HHV-8, and actually we are probably going to do 6 and 7, as well, I would guess by mid-1998. Part of the problem is just getting all the tests set up in particularly CDC's Central Serology Laboratory, because again the study was going to apply basically all the existing HHV-8 assays, as well as several HHV-6 and 7 assays, to 1,000 representative donors, mostly tests, and get some prevalence data.

DR. NELSON: That is only to define what is in the donor population, it is not to define the rate of transmission, right?

DR. BUSCH: Right, and then Ken has got a study of transmission that would be a follow-up study based on the best test, because of the limited volume of sample that he has would further study the transmission question.

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DR. MARTONE: Is it possible to get some of that data presented here in a closed session?

DR. HOLLINGER: If there are no further items for the committee, then, we are going to adjourn for the day and we will reconvene tomorrow morning at 8 o'clock.

[Whereupon, at 4:06 p.m., the meeting was recessed, to resume at 8:00 a.m., Friday, December 12, 1997.]