TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

67th MEETING

Pages 1 thru 316

Gaithersburg, Maryland
September 14, 2000

MILLER REPORTING COMPANY, INC.
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at

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

67th MEETING

Thursday, September 14, 2000

8:00 a.m.

Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
735 8th Street, S.E.
Washington, D.C. 20003-2802
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Linda A. Smallwood, Ph.D., Executive Secretary

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John M. Boyle, Ph.D.

Mary E. Chamberland, M.D.

Richard J. Kagan, M.D.

Jeanne V. Linden, M.D.

Gail B. Macik, M.D.

Daniel L. McGee, Ph.D.

Mark A. Mitchell, M.D.

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Sherri O. Stuver, Sc. D.

NON-VOTING CONSUMER REPRESENTATIVE

Katherine E. Knowles

NON-VOTING INDUSTRY REPRESENTATIVE

Toby L. Simon, M.D.

TEMPORARY VOTING MEMBERS

Paul R. McCurdy, M.D.
Kenrad E. Nelson, M.D.
Carmelita U. Tuazon, M.D.

C O N T E N T S

C O N T E N T S (Continued)

II. Deferral, As Blood or Plasma Donors, of Males Who Have Had Sex with Males

P R O C E E D I N G S

Statement of Conflict of Interest

DR. SMALLWOOD: Good morning and welcome to the 67th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. At this time, I will read the conflict of interest statement. I would just like to say that this statement is dedicated to Mary Gustafson who recently left us but never had the opportunity to hear it.

The following announcement is made part of the public record to preclude the appearance of a conflict of interest at this meeting. Pursuant to the authority granted under the committee charter, the Director of FDA's Center for Biologics Evaluation and Research has appointed Dr. Kenrad Nelson as a temporary voting member, and the Senior Associate Commissioner of the Food and Drug Administration has appointed Dr. Carmelita Tuazon as a temporary voting member.

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

In accordance with Title 18, United States Code, 208, Dr. Kenrad Nelson has been granted a general matters

waiver which permits him to participate fully in the committee discussions.

The following participants have associations with firms that could be affected by the committee discussions; Drs. Boyle, Chamberland, Hollinger, Knowles, Linden, Macik, McGee, Schmidt, Simon and McCurdy. However, in accordance with Title 18, United States Code, Section 208 and 2635.502 of the Standards of Conduct, it has been determined that a waiver or an appearance determination is not warranted for these deliberations.

With regards to FDA's invited guests, the agency has determined that the services of these guests are essential. There are reported interests which are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants.

They are as follows: Dr. Michael Busch is employed by the Blood Centers of the Pacific. He has received fees and travel expenses from Chiron, Roche, Abbott and the American Red Cross to speak at scientific meetings. In addition, he has a contract with Chiron, GenProbe for laboratory work supporting the clinical trial of nucleic acid testing and a past grant to the Blood Center of the Pacific from Roche Molecular Systems. Dr. Busch collaborates on research with scientists from Alpha, the

American Red Cross, Ortho, Abbott, Chiron, GenProbe and Roche.

Dr. Dodd is employed by the American Red Cross, Holland Laboratory. Dr. Sharyn Orton is employed by the American Red Cross. Dr. Alan Williams is employed by the American Red Cross, Holland Laboratory.

In the event that the discussions involve other products or firms not already on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

With respect to all meeting participants, we ask, in the interest of fairness, that you state your name, affiliation and address and any current or previous financial involvement with any firm whose products you wish to comment on.

If there have been any omissions or oversights concerning any of the committee members, would you declare so at this time.

Hearing none, at this time, I would like to introduce to you the members of the Blood Products Advisory Committee.

Welcome and Opening Remarks

DR. SMALLWOOD: As I call your names, would you

please raise your hand. Dr. Blaine Hollinger, Chairperson. Dr. Mary Chamberland. Dr. Paul Schmidt. Dr. Daniel McGee, who is a new member with the Blood Products Advisory Committee serving as our biostatistician. Dr. Gail Macik. Dr. Jeanne Linden. Dr. John Boyle. Dr. Sherri Stuver, who is also a new member of the Blood Products Advisory Committee serving us in the capacity of infectious diseases. Dr. Paul McCurdy. Dr. Carmelita Tuazon is serving as a temporary voting member. Ms. Kathy Knowles, our consumer representative. Dr. Toby Simon, our industry representative.

For this meeting, there are some members that are absent or that will be late. Dr. Norig Ellison, Dr. Marion Koerper and Mr. Terry Rice will be absent for this meeting. Dr. David Stroncek will be absent today only. He will be here tomorrow. Dr. Richard Kagan will be late this morning, but he will be here for both of our sessions.

I would like, at this time, to recognize and introduce to the committee as well as the audience the Director of the Center for Biologics Evaluation and Research, Dr. Katherine Zoon. Dr. Zoon will come forward to recognize Dr. Blaine Hollinger who will be leaving us as Chairman of the Blood Products Advisory Committee.

Dr. Zoon?

DR. ZOON: Thank you, Dr. Smallwood. It is a

pleasure to be here this morning. I always am reminded, when I come to the BPAC--I see many faces that are very familiar that I have known for many years. It makes me reflect on the enormous contribution of this advisory committee. Having CBER involved in a variety of product areas in our center, I have to say the BPAC is the most active committee we have.

Your agenda is always packed full. The issues are always important or controversial and I think the deliberations of this committee have been extremely valuable in providing guidance and recommendation to the center on many important policy issues. So, as a whole, collectively, I would like to thank all of you very much for the enormous public-health contributions you have, are and will continue to make.

In saying that, there is some special recognition today for Dr. Blaine Hollinger. I would want to say, personally, his leadership on this committee has been outstanding. He has navigated through some very important issues. His endurance is admirable and his intellectual, scientific contributions aiding the agency and the center in making good blood policy has been enormously helpful.

With that recognition, I would like to provide you with a couple of plaques of appreciation. So if I could ask you to come up.

First, I would like to read a letter from Dr. Jane Henney, who is the Commissioner of the FDA, to you. It says, "I would like to express my deepest appreciation for your efforts and guidance during your term as a member of the Blood Products Advisory Committee. The success of this committee's work reinforces our conviction that responsible regulation of consumer products depends greatly on the participation and advice of the non-governmental health community. In recognition of your distinguished service to the FDA, I am pleased to present you with the enclosed certificate. Thank you very much."

In addition, we have a plaque from the center saying, "For Outstanding Service and Leadership as the Chairman of the FDA's Blood Products Advisory Committee for the Years 1996 to 2000." I am eternally grateful. Thank you very much.

[Applause.]

DR. HOLLINGER: Thank you very much, Kathy. Really, this has been a great committee for me. I have thoroughly enjoyed it and, particularly, the members. Somebody once said, "Why would you ever do something like this? It is really something bad."

My wife reminded me with a story she told me the other day. It was about a wife who was spending all this time with her husband who was in the hospital going in and

out of coma. She was by his side every day.

One day, he woke up, after several months and looked at his wife and motioned her to come over closer to him. She got by his side. With tears in his eyes, he said, "You know what?" He said, "You have been by me through all the bad times." He said, "You were there when I got fired. You were there to support me." He said, "When my business failed, you were there at the time. When I got shot, you were there. When we lost our house, you were there. And now, when my health has failed, you are still there."

He said, "You know what?" And she came closer to him and sat down and said, "What, dear?" warmth sort of increasing in her heart. And he said, "You know what?" He said, "I think you are bad luck."

Actually, this has not been bad luck for me. I have got to tell you that. I have certainly enjoyed this committee. We have a lot of work today. This session today is really--I think I have received more calls from the news media about this meeting today than any other meeting I have been associated with.

So, Kathy, thanks very much, from the agency's standpoint, and we will get on with the meeting, then. Thank you.

DR. SMALLWOOD: Thank you. I just would like to make an administrative announcement that any presenters that

are using powerpoint for their presentations, if you would make sure that you see the AV technician that is over to my right with the white shirt on, sitting at the table there, so that he can be prepared for your presentation.

I would also like to ask that everyone that will be speaking, anyone from the floor, please speak directly into the mike and announce your name and affiliation.

We have a very full agenda today. As you can see, we are a little late starting, getting into the official business, but we would like to proceed accordingly and we ask that you would govern yourselves as such.

At this time, I will turn the meeting over to our Chairperson, Dr. Blaine Hollinger.

Dr. Hollinger?

COMMITTEE UPDATES

DR. HOLLINGER: We are going to start the meeting today with some committee updates. The first one is a summary of the PHS Advisory Committee on Blood Safety and Availability Meeting from August 24. Dr. Nightingale will give us an update.

Summary of the PHS Advisory Committee on Blood Safety and Availability Meeting, August 24, 2000

DR. NIGHTINGALE: Good morning.

[Slide.]

Thank you for giving me the opportunity to present

the summary of the advisory committee meeting to you.

[Slide.]

The meeting of August 24 of the advisory committee arose because of a resolution of the advisory committee that was made on April 26. The advisory committee said, "Recognizing the significant economic issues currently affecting the blood system, the advisory committee seeks to review the role of various considerations and decision making related to new and existing blood safety measures."

I hope, Dr. Hollinger, if your committee ever gets control of its own agenda the way that mine has, that you will show more respect for the English language.

[Slide.]

We paraphrased the resolution to what was the serious business of the committee which is the question of what are the principles on which a policy to assure a safe, available and affordable blood supply should be based?

[Slide.]

The intellectual background or, perhaps, the political background as well, of the committee's agenda is this; there are, currently, two major ways in which policy decisions have been framed before our advisory committee. One of the frames is, under a given policy, how much would it cost to save a life and the alternative framing which many of us see as functionally equivalent is, under a given

policy, how many lives would be lost. The jar between those two frames of the same question has been a recurrent concern of the advisory committee and of the blood community as a whole.

One of the answers to both of those questions that has been proposed by many parties has been the concept of no-fault insurance or compensation for unavoidable blood injury, which was proposed by the Institute of Medicine, the Krever Report and elsewhere, and it was adopted by the advisory committee on April 26 when they said, "There is a small but non-zero risk associated with the use of blood products or plasma derivatives that cannot be eliminated with current technologies. The advisory committee, therefore, supports the prior recommendation of the Institute of Medicine and of others that a prospective national system to compensate recipients for injuries or death caused by blood products or plasma derivatives and not associated with a reckless or intentionally harmful act should be enacted and funded by Congress.

While this is one alternative to proceeding under the status quo, I think everybody in this room is aware of the complexities of no-fault insurance in other arenas, the complexities in implementing a fair and just no-fault--it is easy to say we should have no-fault. It is hard to do it, and it is really in that context that I recommend that you

read the response of the Secretary to that advisory committee recommendation.

This was written on July 26 of this year. "Dear Dr. Kaplan: in regard to your second recommendation," Dr. Shalala wrote, "The Department continues to feel that compensation issues are the responsibility of Congress."

[Slide.]

"The Administration stands ready to assist Congress as it considers such recommendations or legislation." This was, in fact, a reiteration of the Secretary's testimony on October 12, 1995 before Congressman Shays. The summary, then, is that, current policy, we have the competing frames of the same question which often present those in, if not irreconcilable but at least strongly competing, words.

The solution that has been proposed is not over the political horizon yet. That has led us to the discussion of alternatives.

[Slide.]

One of those alternatives has been what is called, rather than defined as, the precautionary principle. The precautionary principle was published by the European Union on February 1 of this year. The best legal statement of it is here--it is in an environmental context--"Where there are threats of serious or irreversible damage, lack of full

scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."

[Slide.]

Again, a problem with the precautionary principle is that it is not well-defined in European or any other law. It is one of those things that we all understand, kind of like group theory, but can't put our fingers on it. The principles that are enunciated by the European Union on February 1 were the application of the precautionary principle should be proportional to the chosen level of the protection, nondiscriminatory it its application, consistent with similar measures already taken, based on an examination of the potential benefits and costs of action or lack of action, subject to review in the light of new scientific data, and capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment.

I think that you will see where I am going with this talk is that there has certainly been some progress towards discussion of these principles but that progress has been, by no means, sufficient for action.

[Slide.]

I am sorry that screen does not have all of this because, as I alluded to, the Rio Conference on the

Environment was one statement of the precautionary principle. The European Union's statement does not define it explicitly but there is what I am going to call a more stringent form.

Dr. Epstein, who was, really, the leader of our efforts to get to this point, suggested that the principles that underlie blood safety could be ranked on the order of stringency. Stringency is also an evolving concept but I think you will get what Dr. Epstein had in mind when you read what Mr. Justice Krever wrote about the precautionary principle. This is also on the table, so to speak.

This one says, "Preventive action should be taken when there is evidence that a potentially disease-causing agent is or may be blood-borne even when there is no evidence that recipients have been affected. If harm can occur, it should be assumed that it will occur. If there are no measures that will entirely prevent the harm, measures that may only partially prevent transmission should be taken." Another definition that is on the table.

[Slide.]

The discussions that took place on August 24 have been distributed to the advisory committee. I did bring 24 copies of it. It will be posted on the advisory committee's website as soon as my deputy returns from travel because he knows how to do it and I do not.

That failing, that is the direct phone to my office. That is my fax. And that is my E-mail. Those will be available outside the room afterwards.

I think the one piece of the discussion that I specifically want to bring to the Blood Products Advisory Committee's attention is on the next slide.

[Slide.]

These are seven criteria for blood policy. This is a very tight abstract of Dr. Epstein's presentation to the committee and does not do that presentation full justice but is what got into the ABC Newsletter. It is a very accurate reflection of a summary slide.

This is pretty much where we are in our own thinking. I, again, thank Dr. Epstein for the formulation and praise it. Acceptance of risk is a political decision. Acceptance of cost is a political decision. Decision-making must be transparent if it is to obtain public endorsement. Decision-making must include both risk assessment and risk communication. Decision-making must include ongoing scientific input.

Blood-safety decisions should be considered in an international context and, finally, individual contributors to blood safety decisions should independently articulate the scientific, economic and political bases of their recommendations.

There is far more thought behind these seven commandments, is what we are calling them informally, behind Dr. Epstein's back. I recommend them to you for your thoughtful consideration.

[Slide.]

The question, however, of whether or not a sufficient foundation for blood policy can be identified is being debated, not only within blood policy but within broader realms as broad as law. That will be coming into our decision-making process; can you really find a set of principles that you can enact a sound policy.

The argument on the left side is one of the several competing--lists a few of the major competing principles. The argument on the other side, which is cut off and really shouldn't be, because it is the argument not only of Mr. Justice Holmes but of current legal scholars like Richard Posner who are arguing for scientific or ad hoc adjudication of political issues.

Most of you--the lawyers--will recognize, "The life of the law has not been logic. It has been experience, the felt necessities of the time, the prevalent moral and political theories, institutions of public policy, avowed or unconscious. Even the prejudices which judges share with their fellow men have had a good deal more to do than the syllogism in determining rules by which men should be

governed."

So the ultimate debater here is whether or not we can come up with a set of principles. It is definitely worth trying. But there are bright people who think that we are not going to succeed.

[Slide.]

Where the first challenges for this effort will be coming; the first will be in November. We expect that there will be a meeting convened by the WHO of its Global Collaboration for Blood Safety. The general agenda items are harmonization of blood-safety practices in developed countries and promotion of blood-safety practices in the developing ones and, in January, where I suppose the rubber hits the road locally, where we have agreed that the advisory committee should take up the issue of how the government should respond to the current debate over universal leukoreduction.

The last and very substantive point that I want to make to this advisory committee is that the review by the department's Advisory Committee on Blood Safety and Availability is, by no means, a review or a second guess of the deliberations of this advisory committee.

We have made it very clear that there is a delineation of roles and the role of the advisory committee, whatever it may be, is not to second-guess scientific

decisions of a scientific panel. We will continue in dialogue with you to assure that our roles are complementary and not competitive.

I would be glad to answer any questions that anybody would like to have about them and apologize for running over a little bit. I am done.

DR. HOLLINGER: Any questions?

If not, thank you, Steve.

The next update is on factor VIII and von Willebrand factor standards. Dr. Chang and Dr. Kirschbaum.

Factor VIII and vWF Standards

DR. KIRSCHBAUM: Hi. I am Nancy Kirschbaum from the Laboratory of Hemostasis in the Division of Hematology.

Oh; that is Dr. Chang's talk.

Do you just want to go?

DR. CHANG: Thank you, Mr. Chairman.

[Slide.]

For the next five minutes, I would like to give you a brief introduction on the work in progress toward the first international standard for von Willebrand factor concentrates.

[Slide.]

My name is Andrew Chang. I work in the Division of Hematology, CBER, FDA. I would like to first start to give you a message that is the good news, actually. The

first international standard for von Willebrand factor concentrates will likely to be available by the end of the next year.

[Slide.]

I would like to give you a brief, very brief, introduction on the process we have carried out for this first international standard. We carried out this project in two phases; phase I is the initial characterization and phase II is the production and calibration phase.

In phase I, we selected five von Willebrand factor concentrates from five different manufacturers. There are three organizations actually involved with this study; CBER, FDA and NIBSC. SSC stands for Science Standardization Committee which is under the International Society for Hemostasis and Thrombosis.

The goal for this study is to try to reach agreement based on the scientific study to select two candidates which are suitable for the international standard. The second phase is production and calibration. We decided to take two candidates into the phase II study and filled 5000 ampoules for each candidate and then had a panel of about twenty international laboratories around the world in the calibration.

By the end, we will select one, the best one, as the standard.

[Slide.]

Where are we now? We have completed the phase I study and we presented our selection process to the SSC, Science Standardization Committee, in May of this year. We are very happy the committee accepted our selections for two candidates.

We are now on the second phase. That is the production and calibration. We have already filled one candidate. We have 5000 ampoules ready for calibration. The second one is on its. way. We already have the material and are ready to fill.

We also distribute a survey form to about thirty laboratories around the world. We sent it out last month and so far we have received sixteen of them committed to do the calibration studies. The calibration will be carried out against the WHO Fourth International Standard for factor VIII and von Willebrand factor plasma. We envisioned that, by the end of the study, we will have at least three potencies which can be assigned to this standard; that is, the von Willebrand factor level, von Willebrand factor ritocetin-cofactor activity, and the collagen-binding activity.

The final report for this project will be presented to the Expert Committee of the Biological Standard which is a committee under the World Health Organization in

Geneva in October of next year.

[Slide.]

So, in conclusion, we have completed the phase I study and we selected the two candidates. They are accepted by the SSC Committee and we are now under the production phase and are ready to distribute the candidate for multicentered international-wide calibration. Hopefully, I think very likely, by the end of next year, we will have this first international standard for von Willebrand factor concentrates available basically for the world.

Thank you very much.

DR. HOLLINGER: Thank you.

Dr. Kirschbaum?

DR. KIRSCHBAUM: I guess I will reintroduce myself. My name is Nancy Kirschbaum. I am a senior staff fellow in Laboratory of Hemostasis in the Division of Hematology.

[Slide.]

Thank you for inviting me to present an update on the development of Mega 2, which is the new U.S. working standard for determination of Factor VIII activity.

[Slide.]

Mega 2 is being developed to replace the dwindling supply of Mega 1 which is the current U.S. Factor VIII working standard. Phase I, in the development of Mega 2,

was devoted to choosing a suitable candidate. This was achieved through an international collaborative effort.

The candidate that was chosen met stringent criteria of molecular integrity, linearity of dose response, stability and consistency of results within assays, between assays, and, importantly, between the two currently used test methodologies of the one-stage APTT assay and the chromogenic substrate assay.

The candidate that was chosen is a plasma-derived concentrate. During phase II, the final fill of 100,000 vials was performed with direct participation by members from our laboratory of hemostasis. This particular final fill was subdivided into two and these two sublots were lyophilized in separate machines.

So, because of that fact, we conducted extensive testing in our laboratory of hemostasis that demonstrated the equivalence of the two sublots.

[Slide.]

Currently, we are collaborating with the European Pharmacopoeia and the National Institutes of Biological Standards and Control to organize the final phase of the development of Mega 2 which is the assignment of potency. Forty-five laboratories from around the world have been invited to participate.

The testing will involve the comparison of potency

values determined for the candidate against current international standards. The ones that we are going to include in our study are the WHO Fifth International Standard, the WHO Sixth International Standard and the European Pharmacopoeia Current Working Standard.

In addition, a preparation of Mega 2 that has been filled in ampoules will also be tested for consideration as an international working standard. Testing will also involve the comparison of potency values determined using the two current test methodologies--that is, the one-stage APTT assay and the chromogenic substrate assay.

[Slide.]

Finally, we plan to compete testing and data analysis so that the new Mega 2 standard will be ready for distribution next year.

Thank you.

DR. HOLLINGER: Thank you. Any questions for Dr. Chang and Dr. Kirschbaum?

The next update; Dr. McCurdy will give us an update on the blood supply. Paul?

Blood Supply Update

DR. McCURDY: Good morning.

[Slide.]

At the last meeting of this committee, I provided an initial brief description of what we have been doing.

[Slide.]

There have been, as I mentioned last time, for a number of years attempts and recommendations by a number of different groups that we do find out something about the blood supply in the United States. It has been deplored that we know more about widgets than we do red cells and platelets.

When the situation came up that it was necessary to defer donors who spent more than six months in U.K. from 1980 to 1996, and we were concerned about what might happen to the blood supply, at the request of the Surgeon General, the Heart, Lung and Blood Institute contracted with the National Blood Resource Center to provide data on the blood supply.

Initially, we selected a sample of twenty-seven blood centers around the country. These were selected to be representative of the country as a whole, although there was a bit more of a concentration in larger cities than small rural centers primarily because one of our goals was to detect shortages as they occurred or immediately afterwards, and big cities are more vulnerable than small rural centers.

Twenty-seven were selected. Six centers were not able to participate and were replaced, and we had one late dropout. The final sample, therefore, was twenty-six.

[Slide.]

This slide is a simplistic cartoon because I discovered that more people than I had originally thought were confused about what was released and made available for distribution, what the inventory level was and what was shipped or actually used. What we are doing at the present time is getting information from the blood centers, from the sample of blood centers, on what was released for distribution and we are getting information on inventory the first and third Wednesdays of each month.

We do not have information on what was actually shipped from the blood centers and, more importantly, we hope to get information from a sample of hospitals about what was actually used. So keep in mind that that level of inventory depends not only on what is put in but what goes out at the bottom.

[Slide.]

These are a graph of the red-cell products released from October through August. As I mentioned last time, we did not get information from all centers from the very beginning. Some were phased in as time went on and, until August, we did not get information from every center every month. So we did a quick and dirty extrapolation from the number that actually supplied to the total.

In August, we did get information very promptly and from all twenty-six centers, and they are all to be

congratulated for that effort.

[Slide.]

The next slide shows a regression line that I calculated. The increase in blood made ready for distribution from October through August is significant at a p less than 0.01. I am not quite sure what that means other than, perhaps, blood centers were able to cope with any loss of donors due to phasing in the variant CJD deferral period.

[Slide.]

This is what happened to the inventory. I started the inventory slide in January because the retrospective inventories, starting in October, there weren't enough centers and we didn't think we could rely upon those data, although it looks, perhaps, as though there is a progressive downward trend on that.

[Slide.]

When one calculates a regression line, one can get a negative slope. But the p-value of this slope is being different from zero probably because the variability is not significant.

[Slide.]

The final slide shows information on the inventories by blood group. I am not sure how to interpret this yet. We have got, on this slide, the O's and the A's, O's being characteristically in short supply all the time

and A's being pretty adequate. But we do get that information and we will be looking at it as time goes on.

Thank you.

DR. HOLLINGER: Thank you, Paul.

There is a person who would like to--Derrick Robertson from the Hemophilia Treatment Centers would also like to give us an update a little bit on the supply issue. Is Derrick Robertson here?

No? I guess that was an interesting comment that he had.

Any other comments about the supply issue? Yes, Paul. Do have a comment for yourself?

DR. McCURDY: I might comment that this really does not speak to the issue of shortages which have been widely reported in various different media, particularly the newsletters of the blood-banking organizations. With the supply or the information about the blood put on the shelf, one would suggest, but you can't prove, that there may have been some increased demand over this period of time in order to generate the shortages.

DR. HOLLINGER: Thank you.

The final committee update is on donor questionnaire. Dr. Lee?

Update on Donor Questionnaire

DR. LEE: Good morning committee members and Dr.

Hollinger. I am here to not necessarily give you the full update on the donor questionnaire streamlining process but simply to give you a very brief background and introduce Dr. Joy Fridey to give the update.

As Dr. Zoon mentioned this morning, the issues presented here are always controversial and important, and the donor interview process is no exception. Blood safety and availability, at present, starts with selecting the right donor.

We intuitively know how important the interview process is in safety and availability of blood, yet it has been unclear for many years as to exact role of the donor interview in assuring safety and availability. There has been ongoing internal discussion at the FDA for many years as to how we might improve this.

The agenda of today's BPAC, especially the one after lunch, speaks to our ongoing efforts in trying to improve the current interview process and the questions used in selecting the right donor. More recently, the FDA has charged the blood industry to get together as group to analyze this in a more concrete fashion in an effort to improve the donor interview process, particularly the questions used in selecting the right donors.

Dr. Joy Fridey has graciously chaired this group. Dr. Joy Fridey will now give the update as to what the

recent accomplishments have been from this task force, multiorganizational task force, led by AABB and give some specific goals as to what it is intending to do in the near future including a joint FDA-AABB-sponsored workshop currently scheduled for October 16 at Lister Hill Auditorium on NIH campus on streamlining the donor questionnaire.

Dr. Friday? I don't see Dr. Fridey. I see Ms. Kay Gregory. So I will now have the pleasure of introducing Ms. Kay Gregory.

MS. GREGORY: Thank you. There was a mixup in communication and Dr. Fridey thought she was going to be presenting tomorrow. So I will try to fill in for her in the meantime.

The American Association of Blood Banks has established a new multiorganizational task force to evaluate and develop recommendations to simplify the uniform donor history questionnaire including consideration of an abbreviated version for repeat donors. The task force appreciates the opportunity to make this advisory committee aware of its activities. We hope that this meeting will also provide an opportunity to let the public and those with a special interest on donor screening know the activities of the task force.

The task force was formed in response to information from the Food and Drug Administration that the

agency would like to see a simplified questionnaire developed perhaps sometime in 2001 and would prefer to have a single initiative supported by the entire blood banking community.

The task force, as you have heard, is chaired by Dr. Joy Fridey and is composed of representatives from the American Association of Blood Banks, American Blood Resources Association, America's Blood Centers, the American Red Cross, the Center for Disease Control and Prevention and the FDA. We will shortly be joined by representatives of NHLBI and the Armed Services Blood Program Office.

The task force is intended to be the core group guiding the effort. But each organization will be active participants assisting the task force with tasks such as identifying member centers to pilot questions and generate additional information or data as needed. It is vital that we include everyone in this effort including donors.

The task force charges are; to reevaluate the scientific validity of all FDA requiring infectious-disease questions in view of the most recent scientific data including current testing technology; to identify and reword questions for which the wording may represent comprehension difficulties for average individuals--for example, do not meet the eighth-grade reading comprehension guidelines for written materials; to identify questions that can logically

be grouped together and simplified; to reorder questions as appropriate and to evaluate methods and develop recommendations for administering the questionnaire, oral, written computer-based questioning, methods of handling recurring questions, et cetera; and, finally, to submit the document and proposal for its use for FDA approval when we finish the process.

The task force will utilize pilot studies and other methods of obtaining information as appropriate. This is an active task force. It was organized in June and has already met three times by conference call. Subcommittees have also had numerous conference calls. Sometimes, I have talked to this group at least three or four times in one week.

Activities currently underway include planning, as you have heard from Dr. Lee, for a joint AABB-FDA workshop to be held October 16. We have also distributed a survey to obtain information about questions currently in use to selected blood centers, hospital blood banks and plasma-collection facilities.

We have begun an AABB review of AABB-generated questions. There are some questions that we asked that were generated by us and not necessarily by the FDA. If we are going to look at everything, we need to look at what we have done, as well.

Finally, the FDA is compiling information about questions most frequently cited in error and accident reports that they receive. And then FDA is also putting together a list of nonnegotiable question items. These are things that they believe are critical and must still be covered somehow in the questionnaire, although not necessarily using the exact wording that we are currently using.

Again, I thank you for the opportunity to speak today. The task force is excited about the opportunity to accomplish meaningful change and plans to provide regular progress reports.

Thank you.

DR. HOLLINGER: Thank you, Kay

Any questions? I think that concludes the updates for the committee at this time. I want to thank the individuals who have presented these updates today.

So we are actually back on time, but I will tell you we will probably get out of time before long.

We are going to start the first open committee discussion, which is a very important--all the topics, actually, I think at these meetings here are important. This is another one. This one is on HIV p24 antigen testing of plasma for fractionation, the potential criteria for discontinuation.

Dr. Hewlett is going to give us an introduction and background to this proposal.

I. HIV p24 Antigen Testing of Plasma for Fractionation

Potential Criteria for Discontinuation

Introduction and Background

DR. HEWLETT: Thank you, Dr. Hollinger and good morning everyone.

[Slide.]

The topic for discussion this morning is the potential discontinuation of HIV-1 p24 antigen testing of source plasma.

[Slide.]

The specific issue that we want to focus on today is whether FDA should permit manufacturers of plasma derivatives to replace HIV p24 antigen testing with the licensed minipool NAT method that has equal or greater sensitivity.

[Slide.]

By way of background, I think would all agree that there has been a dramatic and vast reduction in the transmission of HIV by blood and blood products during the past decade primarily due to the implementation of sensitive tests for viral antibody antigen and, more recently, nucleic acids under the IND mechanism and, in the case of plasma derivatives, the use of effective viral removal and

inactivation methods.

[Slide.]

The major sources of remaining risk are from window-period donations, viral variants that are not detected by currently licensed assays, atypical seroconversions and laboratory-testing errors. According to recent reports, donations during the window period constitute at least 90 percent of the risk. Therefore, measures to close the window period could further reduce the low residual risk in HIV transmission by blood and plasma.

[Slide.]

In 1994, FDA held a workshop to discuss the potential application of nucleic-acid-based methods to donor screening for HIV. It was felt, at the time, that, although these methods were clearly very sensitive, they were not ready for implementation on a large scale.

It was subsequently decided, in 1996, that p24 antigen testing could be adopted as an interim measure for interdicting window-period donations until more sensitive methods become available. Despite the effectiveness of viral clearance and inactivation procedures in the manufacturer of plasma derivatives, FDA recommended donor screening for HIV p24 antigen for plasma for fractionation as an added safeguard since such testing would limit the virus burden that may be present in a plasma pool for

fractionation.

[Slide.]

Subsequent to implementation of HIV p24 antigen testing, the industry actively pursued development of nucleic-acid testing, or NAT, for screening blood and plasma donors. NIH awarded a contract for development of NAT to screen individual donations of blood and plasma. At this time, however, due to the high costs and the labor intensity of NAT, there was interest in testing minipools of plasma rather than single units and, by 1997, some manufacturers in Europe had voluntarily instituted NAT on minipools.

At about that time, the European Union had issued a directive that, by July 1, 1999, HCV RNA testing would be required in Europe for all plasma for fractionation and that the requirement for HIV-1 RNA testing would follow at a later date.

In the U.S., testing of minipools was first introduced as an in-process control test for plasma for fractionation. However, the FDA position to regard pool-sample testing by NAT as a form of donor screening and a European directive which applied to both source and recovered plasma provided impetus for rapid development of minipool NAT for all blood and plasma donations.

FDA has taken the position that all NAT tests used to screen blood and plasma are subject to regulation as

biological products under the licensing mechanism.

[Slide.]

Since NAT screening of donors was expected to improve blood safety while not interfering with current measures of safety, FDA permitted the clinical study of this investigational technology on a large scale under an approved IND. Such large-scale studies would be necessary to demonstrate the efficacy of NAT primarily because the frequency of window-period donations is low.

At the present time, virtually all source plasma and whole blood collected in the U.S. is being tested by a minipool NAT method for HCV and HIV-1 under an approved IND. FDA has not yet licensed a NAT method for use in screening of donor blood and plasma including source plasma.

[Slide.]

With the implementation of NAT for detection of window-period donations, the question of replacing HIV p24 antigen testing by NAT has been raised by many investigators. Since both tests are for direct markers of the virus, it has been suggested that it may be feasible to replace p24 antigen on the neat sample with minipool NAT if it is found to be of equal or greater sensitivity.

At the BPAC meeting held in March of last year, FDA defined criteria for discontinuation of p24 antigen and replacement by minipool NAT.

[Slide.]

I will now briefly summarize the criteria that were presented at the time. First, the sensitivity of the NAT method should be equal to or greater than that of p24 antigen testing for the window period. This could be established by testing all available and properly stored repository specimens that are p24-antigen-positive and antibody-negative and commercially available seroconversion panel specimens in the pooled method and the neat p24 antigen method.

Second, frequencies of NAT and p24 antigen positivity in antibody-positive and negative specimens should be evaluated in prospective studies. Third, NAT and p24 antigen should have equal sensitivity for detection of the major HIV-1 subtypes. Finally, weakly reactive p24-antigen-positive specimens should be reproducibly detected by the NAT method on multiple days by multiple operators and for multiple kit lots and instruments.

[Slide.]

FDA also indicated that the NAT method would have to be licensed before it could be used to replace the antigen test. FDA has published guidance on the validation of NAT methods to screen plasma donors. Among the major considerations for the sensitivity of NAT on pools is analytical sensitivity of the NAT method on the pool and the

original donation as well as the pool size tested.

FDA has defined a proposed sensitivity limit for licensure of 100 copies per ml for the pooled test and 5000 copies per ml for the original donation. FDA has not specified pool-size limits, thereby allowing manufacturers to set these limits based on the analytical sensitivity of their specific test. Source plasma donations are currently being tested in pools ranging from 96 to 1200 donations.

[Slide.]

To establish sensitivity criteria whereby p24 antigen can be discontinued, it is important to understand the early dynamics of HIV infection and to establish and determine a relationship between detectable levels of viremia by p24 antigen versus minipool NAT.

Recent data, which will be presented later on in this session and more in detail at the upcoming AABB meeting, and which was shared with us by Mike Busch and his coworkers, indicate that in studies where 146 serial specimens from 48 HIV plasma-donor panels were characterized by tests for HIV RNA, p24 antigen and HIV antibody, the mean viral load at the time of p24 antigen seroconversion was estimated at around 10,000 copies per ml.

Based on this estimate, NAT method should be able to detect a minimum of 10,000 copies per ml or less in order to replace currently licensed p24 antigen tests.

[Slide.]

In regard to plasma for further manufacturer, it is important to note that viral-inactivation methods provide an added measure of safety. Since the end of 1987, there have been no transmissions of HIV by albumins, immune globulins or clotting factors. Heat treatment used in albumin production has been shown to inactivate the infectivity of HIV-1 by around 7 logs, which is a least 3 logs more virus than the maximum concentration reported in the plasma of infected individuals, which is around 10^4 infectious units per ml.

The Cohn-Oncley method used to manufacture immune globulins can remove greater than 10^{-5} infectious doses of HIV per ml which is at least 11 logs greater than the maximum circulating infectious doses per ml.

So, based on the rationale and criteria outlined above, FDA is seeking the recommendations of the BPAC on the potential discontinuation of HIV p24 antigen testing and replacement by a NAT method for plasma collected for fractionation.

[Slide.]

As outlined above, the two major considerations are; one, that a NAT test is of equal or greater sensitivity than the p24 antigen test and, second, that viral removal and inactivation methods validated to remove and inactivate

circulating levels of HIV detected by p24 or NAT are in place for plasma collected for further manufacturing.

[Slide.]

So, at this point, I will go ahead and read the questions for the committee. I will put them up again at the time of the discussion.

The first question is, "Do the committee members agree that HIV-1 p24 antigen testing of source plasma may be discontinued if, a), it is demonstrated that a particular licensed NAT method can detect HIV at a level of 5,000 copies per ml or less in a unit of plasma even if the donor sample is tested as part of a pool."

The second part of the same question, "Comparative studies of the NAT method versus HIV-1 p24 are consistent with the hypothesis that the NAT method is of equal or greater sensitivity including the ability to detect major subtypes."

[Slide.]

The second question is, "If committee members disagree, we would like you to comment on an appropriate alternative."

Thank you.

DR. HOLLINGER: Thank you, Indira, for that nice summary of what we are going to be discussing.

I think we will just move right now on. Dr. Busch

is going to now give us some initial data here, and then we have several presentations afterwards.

Mike?

Presentation

DR. BUSCH: Thank you.

[Slide.]

I would like to take a moment to also acknowledge Blaine's leadership on this committee. He has dribbled his way through all these problems. Many of you may not know that Blaine was actually on the basketball team with Wilt Chamberlin at Kansas, about the year I was born.

Blaine is actually an amazing person in that every time, for example, these committee meetings, when I would send him material, and recently was a good example, about two or three weeks before. Now, FDA is quite religious about getting material out to committee and, within two days of sending that stuff out, I have about a four-page E-mail from Blaine critiquing the data and with comments and corrections on the material. So he is a very conscientious leader here.

[Slide.]

What I was asked to do is to review the issues around p24 antigen in the blood and plasma-donor setting. My presentation will review the data briefly about what really led to the introduction of p24 antigen. I think it

is an interesting brief review, particularly how we actually got into plasma-donor screening for p24 antigen.

Then I will briefly summarize data that you will hear in much more detail later, the actual experience with p24 antigen, particularly in the whole-blood sector, because I think it was surprising in terms of the yield being substantially lower than predicted and some explanations around that.

The most important part of the talk is really the analysis that Indira alluded to, trying to understand the relationship between viral RNA levels and antigen levels during the early what we call ramp-up phase of viremia, the pre-seroconversion phase, in order to get quantitative data to base a decision to discontinue antigen on, in terms of what level of sensitivity should a nucleic-acid test achieve in order to confidently detect any antigen-positive units during the window period.

Then I also added a little bit of data, at Indira's request, in terms of the issue of viral subtypes, both with respect to the distribution of non-B clade infections in the U.S. donor setting and the sensitivity of the NAT assay system's two different subtypes.

[Slide.]

So just briefly, there were early studies--actually, Sue Stramer, who is now at the Red Cross was, I

think, the first to publish in JAMA a major paper showing the detection of p24 antigen in early seroconversion using plasma-donor seroconversion panels. Those panels remain a mainstay of our understanding of early dynamics of viremia.

But this led to the clear evidence that, at least in the plasma-donor sector, individuals could give blood in an antigenemic phase detectable by p24 antigen tests prior to the development of antibody tests.

That led to the initial concern around the potential that antigen testing should be used to screen the blood supply and led to two large-scale national studies to evaluate p24 antigen. This was back in the late '80s. There was a national study led by Harvey Alter that tested over half a million donations on-line. It was actually a very large, the largest at that point, clinical trial.

Now, of course, NAT has long surpassed this. But over half a million donations were screened in parallel with standard serologic tests and p24 antigen and no antigen-positive antibody-negative donations were detected in this study.

The second study, and these two papers were published back-to-back in the New England Journal of Medicine, was a study of high-risk donations given to the Transfusion Safety Study just prior to the availability of the HIV antibody assay.

There were 200,000 donations to this repository. What we did was to select about 8,500 that were from donors who were the right age males in zip codes which had the highest prevalence of HIV. The rationale here was that we were going back to a time late in 1984 when the rate of new infections in the communities were much higher than in 1989 and, therefore, we were selecting a population of antibody-negative samples that theoretically would have been enriched for early infections. Yet, we found no p24-antigen-positive donations.

So, these two studies at the time led to the interim conclusion that antigen testing did not seem to have any value for whole blood or blood donor screening. Over the subsequent several years, three case reports were detected in the U.S. of antigen-positive antibody-negative units through back testing of donors who seroconverted. These were associated in several cases with HIV transmission.

So these were some anecdotal cases that suggested that these earlier studies may not have been adequately sized.

Then work from Ken Nelson, actually in Thailand, demonstrated significant yield of p24-antigen-positive antibody-negative donations in the blood-donor setting in Thailand. In fact, in Thailand, they introduced p24 antigen

screening.

If you extrapolate this to the U.S. donor setting, you would actually estimate about five to ten infections per year might be detected in the U.S. donor setting based on relative prevalence rates.

Finally, the REDS modeling approaches sort of began to look at the issue of antigen screening. Based on the duration of the antigen window and the incidence in the U.S. donor setting, estimates of about five to ten antigen-positive antibody-negative donations per year were projected.

[Slide.]

This is an interesting slide that was some of the early model data based on seroconversion panels just to give you some illustrations. At the time, we had probably about 30 or 40 of these panels that were analyzed to estimate the duration of the antigen-positive antibody-negative window.

As you will see, in many panels over the next, probably, several days, the typical pattern is really very consistently observed with a ramp-up of viremia, RNA load increasing, then p24 antigen, and then the antibody tests. The green here is the new or third-generation assay which has actually been around for now ten years in blood screening--at the time, new--that pick up the early IgM response.

So you can see, in many of these panels, there is increasing signal in the more sensitive third generation antibody tests. These tests have been estimated to close the antibody window by about two weeks compared to the earlier IgG-sensitive assays.

So the improved antibody tests were thought to have made a dramatic impact on safety and, indeed, did. But, nonetheless, the data was suggesting that there was an antigen-positive spike estimated at about five days prior to antibody.

But one other thing this slide illustrates that we didn't understand at the time is that people don't donate at a consistent pattern over this period of early HIV infection. Again, these are plasma donors who are eligible and usually give twice a week. This was a slide that was made back in the early 1990s before we knew the problem of the yield being not as high as we now realize.

What this shows is that these donors often give twice a week, twice a week, and then they skip a week; again, twice a week, twice a week, skip a week; twice a week, twice a week, skip a week. This is consistently observed across these panels that these plasma donors do not give as frequently during the antigenemic spike.

We will come back to this because we think this is the explanation for the lower-than-predicted yield of p24

antigen testing.

[Slide.]

So, in any event, through the modeling estimates, we have estimated that the period of time prior to antibody that is p24-antigen-positive is approximately six days, and then there is about a five-day viremic pre-antigen phase. It is these numbers that led to the predictions of about five to ten infections per year by combining this six-day antigenemic window phase with the incidence rate of new infections in the whole-blood-donor setting, one can estimate the rate at which people would give during this transient seroconversion window period. That ends up being about five to ten per year.

[Slide.]

The other data that was addressed, and there was a BPAC meeting back in the 1994 time frame where all of these data were reviewed, the new evidence of case reports and the yield projections. At that time, also, in hindsight probably a mistake, there was data presented on the cost-effectiveness of p24 antigen screening derived by Jim AuBuchon based on the projected yield of five to ten antigenemic donations per year which would prevent ten to fifteen infections at a projected cost range of $3 to $5 per unit, or probably in the range of $60 million per year.

Out of that analysis, Jim derived cost-

effectiveness estimates for both antibody testing and antigen testing. You can see that antibody testing is really quite cost-effective, about $3,000 per quality life year, relative to the usual benchmark of $50,000 considered procedures that are medically indicated.

In contrast, p24 antigen at the time was estimated to have a cost-effectiveness of $2.3 million per quality life year, well out of the window of usual public-health measures. That data was presented to BPAC.

[Slide.]

In addition, there was concern about what is called the magnet effect, which is the concept that if there is a new, better test available in blood banks, could you actually recruit high-risk people who are seeking that test at a rate that would actually offset the benefit of the test, the idea that this was of concern early on in HIV in the context of anti-core testing.

But, in any event, there was evidence that there were donors who were infected who were seeking tests, both HIV positive donors and seronegative donors, based on surveys. We knew that the antigen test would only reduce the window partially, perhaps 30 to 50 percent. So if you more than doubled the rate of high-risk donors, you could actually have a negative impact on blood safety by adding a test that would only reduce the window period in half.

At the time, though, the REDS group did a formal analysis that was published which actually concluded and, again, presented to the BPAC was the conclusion that it was extremely unlikely that any kind of magnet effect could offset the benefit of window-period closure with respect to adding the antigen assay.

[Slide.]

So, finally, at the BPAC meeting in June, 1995, this kind of all came to a head. At that meeting, after all of the data I just summarized was presented, there was actually a vote of 9 to 6 recommending against licensure of p24 antigen. This resulted in an immediate backlash. Congressman Shays who was in charge of the oversight committee of FDA at the time wrote a letter within a month that explicitly indicated that the estimates that were presented were gross underestimates of yield.

Somehow, he derived estimates of at least 50 to 100 per year would be interdicted and that it was inappropriate and outside of the FDA's mandate to have considered cost-effectiveness data and that there was too much industry influence on the committee.

This led, within the next several weeks, to basically complete revision of the membership of the committee with all blood-banking members being excluded, considered as industry representatives. Then, a month

later, FDA issued their memorandum.

Now, up to this point of the FDA memorandum, all of the discussion that I was involved with and was aware of was focussed on the need to implement antigen potential need in the whole-blood sector. As Indira mentioned, there had not been a transmission of HIV by a plasma derivative in over eight or nine years. So everyone--at least I--assumed that the issue of plasma derivatives was safe as a consequence of the inactivation procedures and that the discussion around adding p24 antigen was limited to the blood-donor sector.

But, when the memorandum came out, it extended the requirements to plasma donors as well. That is really the issue we are talking about now, which is considering eliminating an assay which, in some context, was never even indicated in the first place.

[Slide.]

The next comments are just in terms of, briefly, the experience with yield. Again, I think you will hear a lot of data from the plasma industry as well as Sue Stramer for the whole-blood sector that will give you much more detail. But the bottom line in whole-blood screening is that the yield has been significantly less than predicted.

We have, I believe, detected five antigen-positive antibody-negative donations now in approximately five years

of screening. So that is a rate of about 1 per 10 million, which is significantly less than the predictions of about 5 per 10 million. This reflects, in part, the declining incidence of HIV in the whole-blood sector but also what I alluded to earlier which is a bias, and that people probably do not give during that antigenemic phase of infection.

There is also no evidence of a magnet effect, no evidence of a change in rate of HIV-positive donors giving during the pre- and post-introduction of antigen screening. The assay has performed relatively well in terms of specificity but a 0.02 percent repeat reactive rate still translates into thousands of donors being deferred annually in the whole-blood sector.

In addition, one of the problems that Sue will present is that we observed a moderate rate of donors who were positive, not only on the screening assay, but neutralized, meaning they were thought to be true infections. But, in fact, what we have realized is that the assay is prone to false neutralization, false confirmation, these donors are RNA-negative and are negative for other studies to see if there might be some new or unknown retrovirus present.

[Slide.]

Just a few comments here. As I indicated, we overestimated yield. The bottom line is the models assumed

a steady-state rate of donations during these phases of primary viremia. But, in fact, what we now appreciate, through some formal analyses, is that that is not true, that there is a bias in that the rate of people giving during the per-seroconversion phase of HIV is significantly lower than the rate that these people give during other stages. So, looking at individuals over time, the immediate pre-seroconversion phase, they tend to self-defer.

This is probably related either to symptomatic events of primary HIV syndrome or to risk behavior or to the fact that we take temperatures of people at donation and primary HIV during the antigenemic spike is often a febrile phase.

[Slide.]

Now I am going to shift gears and present some summary data on the modeling of RNA versus antigen. As Indira summarized, RNA tests are now routinely performed for HIV and HCV, both in the whole-blood and plasma-donor sector. They have been phased in over the last two years. Retrospective studies have shown that the viral load the p24 antigen cutoff is about 10,000.

So, theoretically, any minipool NAT system that can detect greater than 10,000 copies should be greater than the capacity of p24 antigen. I will show you a lot of data to support that.

In addition, as you will see from several speakers, I am sure, extensive prospective studies that have monitored the ability of these NAT screening programs to detect p24-antigen-positive samples have demonstrated consistent detection, both of sort of real-world antigen positives that are being screened in parallel but, also, a number of programs have conducted external control assay runs where every single run includes p24-antigen-positive controls that are literally set at the cutoff of the antigen assay.

I am sure you will see data later that will show that these are consistently deleted through minipool NAT screening.

[Slide.]

What I want to present is a recent analysis that we have done in the context of the REDS study group. Ebi Fiebig is the person who did the biostatistical analysis on this. It is based on 146 donations that were given during the pre-seroconversion phase from 43 seroconverting plasma donors. These were plasma donors identified and collected through the Alpha Therapeutics Program and the repository of these plasma units was coordinated by Bioclinical Partners.

These donors were screened prospectively by p24 antigen using the Ortho/Coulter assay and the antibody tests were performed both with Abbott and Genetic Systems on all

of these panels.

The PCR data is from NGI. It is both qualitative and quantitative, but the data I will be compiling and showing is based on their quantitative PCR assay. In the more refined model that I will show, there were 146 antigen-positive antibody-negative donations that were analyzed. We actually truncated that dataset because, at the top end of the antigen spike, the RNA loads begin to flatten out.

So, as we are trying to more precisely model the cutoff and the relationship during the ramp-up phase, the analysis was limited to 94 RNA-positive samples in the ramp-up phase. Those were then analyzed using a model that David Wright at Westat developed called the multivariate longitudinal regression model.

[Slide.]

This just illustrates the kind of panel data. You saw some earlier. Again, what we are focused on now are samples that are given during this very brief period when RNA load is ramping up and we are looking at the relationship on a sample-to-sample basis of the RNA load versus the antigen level.

[Slide.]

This is actually an earlier dataset but it illustrates that when you do a lot of these panels, you can then compile the data from a lot of these panels on a single

time line, either through extrapolation or other methods. You can get a sense, then, of the difference in the ramp-up rates of viremia and then, after seroconversion, all of these people ramp down their viremia. But we are focussing here on this early ramp-up phase of viremia.

[Slide.]

The first thing we did was to simply divide these samples up, these 146 samples, into those that were RNA-positive only versus those that were p24-positive. This is what is called a "box and whisker" plot which is just a distribution of the RNA loads, the concentration of RNA, during the RNA-only phase versus the p24-antigen-positive phase of seroconversion pre-antibody.

What you see here are the summary statistics. Most important for this discussion is the viral load distribution during the antigen-positive phase. The critical question to the committee is how good do RNA tests need to be so that we can be completely confident that any antigen-positive samples could be detected if we were to discontinue the antigen test.

What this analysis indicates is that the median RNA concentration during the p24 antigen-positive antibody-negative phase is 140,000 genome equivalents per ml and, most importantly, the lower bound of the 95 percent confidence interval, if you will--the lower 2.5 percent

inclusion limit is 7,300 copies.

So if we have an assay system that can detect 7,300 copies of HIV RNA, we can be confident, from a statistical perspective, that that would detect 97.5 percent of antigen-positive antibody-negative samples.

Interestingly, these 85 specimens that have been derived from these selected plasma-donor panels represent something in the range of 20 years worth of whole-blood screening in terms of the rate of detecting antigen-positive donations.

[Slide.]

We have also done a more sophisticated modeling, as I indicated, based on these 94 samples during the ramp-up phase using this statistical model. This is what is called a "spaghetti plot," which is plotting out the RNA loads over time from the first positive RNA sample datapoint for these 94 panels.

From this analysis, you can derive a slope for each of these seroconverters based on the RNA load increase over time. From that slope, you can derive a doubling time, which is the estimate of the rate at which viral load increases over time. That is estimated at 21.5 hours. So, in other words, the concentration of HIV RNA increases in plasma two-fold approximately every 21 hours.

[Slide.]

What we looked at a moment ago was the distribution of RNA concentrations of p24-antigen-positive versus negative. Another approach to get at what sensitivity should a test have in order to be comfortable discontinuing antigen is to try to estimate the cutoff at which all these seroconverters would break the p24 antigen cutoff level.

In order to do that was this more sophisticated model, but basically the simple way to show this is to express the concentration of RNA against the signal-to-cutoff level of the p24 antigen assay.

So, in this graph, what we have done is to express, on the X axis, the p24 antigen signal-to-cutoff. It is actually the log. So zero is when each of these seroconverters break the cutoff of p24 antigen. Then, this is the log of RNA concentration. So this is a regression plot of the RNA load relative to the p24 antigen signal to cutoff.

The intercept of this regression plot tells us the level of RNA at the point of p24 antigen seroconversion for each of these seroconverters.

[Slide.]

The next slide summarizes the statistics on this regression analysis. The bottom line is that the p24 antigen assay cutoff, and this is based on the Coulter test

and we have done this for the Abbott test as well and it is actually slightly higher, is almost exactly 10,000 genome equivalents per ml.

So, again, so long as an assay achieves an RNA screening system, achieves the sensitivity of 10,000 genome equivalents per ml, it would detect antigen-positive seroconversion samples at the point where they actually achieve cutoff of the antigen assay. So this is really a much more rigorous sort of approach to address the question of what level of sensitivity should an RNA system achieve.

[Slide.]

Based on this analysis, I feel comfortable and I think the FDA recommendation is even somewhat conservative, that a p24 antigen test really should have a sensitivity of at least 10,000 copies in order to recommend discontinuation of p24 antigen and should, theoretically, if it can achieve that sensitivity, detect additional yield beyond p24 antigen.

As you heard, I think FDA's requirement or proposal is that systems achieve at least 5,000 genome equivalents per ml, so they have sort reduced the level to be more stringent.

[Slide.]

I want to just briefly talk about HIV subtypes. There is concern that these unusual subtypes, at least in

the United States, may begin to traffic into the U.S. As you will all, I am sure, know, the major subtype that seeded the epidemic in the U.S. was what is called clade B infection, group M, clade B. That still amounts for the vast majority of infections in this country and, most importantly, the vast majority of new continued spread of infections is clade B.

But, over the last five years or so, there has been documentation of non-B-clade infections including group O and HIV-2 in the U.S. Virtually, all of those infections were imported, meaning that they were individuals who had moved from or military personnel who had been stationed in regions of the world where these non-B infections are prevalent.

They were infected in those countries and then moved to the United States. So, again, we are talking here about window phase so the real issue is what are the incident infections, the newly transmitting strains. Again, a number of studies have shown that virtually all of the new infections going on in this country remain clade B infections.

[Slide.]

We have, under the support from the Center for Disease Control, conducted a fairly large study to monitor for unusual subtypes of HIV in the U.S. donor setting. A

paper is in press next month in Transfusion and will be published that characterizes the rate of unusual subtypes actually going back to samples from that early transfusion safety study testing samples from hemophiliacs who were infected in the very early 1980s from donors who undoubtedly were infected probably in the late '70s, moving on the very earliest infected donors found from TSS, 97 donors found through that repository as HIV positive and then continuing on to more contemporary samples from donors enrolled in the CDC surveillance study, 400 donors from '93 to '96, and then recently updated with an additional 265 donors from '97 and '98.

You can see that, in terms of non-B-clade infections, none were detected in these early samples, but we did begin to see a small percentage, about 1 percent, of HIV-infected donors in the last two periods of time are determined to be infected with non-B-clade infections. We have seen some As and some Cs.

These are all individuals who have actually come to the U.S. They were infected in Africa and came to the U.S. so were not acquisitions here. They are more concerned with the antibody tests than window-phase detection but it does document that we are beginning to see, and there are other studies in other settings as well that are documenting--beginning to see infections by these unusual

subtypes in the United States.

So we do need to be proactive and assure that the tests are detecting these subtypes.

[Slide.]

The next couple of slide will just summarize, for several of the assay systems, the capacity of these new TMA and other kinds of PCR assays to detect subtypes. This is some data that was shared with me by GenProbe. GenProbe has, in their clinical trials, evaluated a large number of both tissue-culture viral isolates as well as clinical specimens from different subtypes of HIV, all HIV-1.

[Slide.]

In this analysis, where they looked at the CBER subtype panel, they diluted--CBER has a panel of non-B-clade infections. These were diluted down to identify the endpoint at which the assay goes from positive to negative. So, in each of these slides, you will see kind of two lines that really flank the endpoint where the assay is consistently detecting these samples as positive compared to the next dilution where it begins to miss some.

The viral load is estimated at each of these endpoints. What you can see is, across each of these clade infections, that the TMA assay is able to detect HIV at dilutions that are equivalent in viral load to the range of 10 to 80 or so viral genome equivalents per ml. So these

assays do have high sensitivity to these variant infections.

[Slide.]

Additional data from GenProbe looking at some even more unusual subtypes, group O infection, some recombinant clade infections that have been recently characterized, and H. Again, they ran these at both 300 and 100 copies per ml inputs and they had 100 percent detection of I think this was 20 replicates both in their combination multiplex screening assay as well as in the discriminatory test, so excellent sensitivity to these HIV-1 subtypes.

[Slide.]

Finally, similar data that has actually been submitted for publication from Roche on their HIV-1 donor-screening assay system. They actually had a number of viral particles that were actually--the concentration was actually characterized by EM particle count, so very precise estimation of the concentration of virus.

What we are looking at here is viral concentrations ranging from 20 up to 200 genome equivalents or particles per ml and then they are looking at different--this is actually a shortened version of their table just showing two representative viral isolates for each of these different subtypes.

What you can see--this is this bolded kind of area here--is the endpoint of detection. You can see that they

consistently detect in the range of 30 to 75 genome equivalents per ml, they begin to get 100 percent hit rates. So, again, both the major whole-blood screening platforms, either GenProbe and Roche systems, both seem to have excellent sensitivity to HIV-1.

Both systems are HIV-1 specific. They do not detect HIV-2. But this is very reassuring data in terms of the concern around subtype detection.

[Slide.]

I think the last slide, just a conclusion slide. What I have tried to summarize is a kind of history and then to explain that I think, in fact, our early projections were slight overestimates of yield in addition to cost effectiveness needs to be revised because the yield was so much lower that the cost effectiveness, at least in the whole-blood sector would now come in at around $10 million per quality life year.

We have had some unexpected problems in terms of false-positive neutralization but, most important, I do believe that the minipool match screening platforms that are in place, both in the plasma and whole-blood sector, do make p24 antigen redundant and that we should recommend discontinuing this test so long as these systems achieve the sensitivity standard recommended by FDA.

Thank you.

DR. HOLLINGER: Thank you very much, Mike.

Are there questions now from the committee of Dr. Busch while he is here? We can always bring up other questions later.

DR. SCHMIDT: Blaine, just to mention another relationship between the antigen and the FDA, the original report on the no findings in 500,000 donors was presented at a conference, a big conference, set up by the Institute of Medicine. The real reason we got it set up that way was we were trying to get the Institute of Medicine involved in decision-making processes so there would be another big voice out there that the FDA might listen to even though they didn't have to.

Somebody got up in the audience and said, "Well, if you just found one in those 500,000, maybe we could set up some sort of system in the Institute of Medicine for evaluation in the future," but the whole conference fell through for that reason, that nothing was found.

DR. HOLLINGER: Any other comments to Dr. Busch?

Mike, just a question--I don't want to dwell on it because of the numbers and the time that these specimens were collected. I think a real important question is not always just 97.5 percent and so on, but how many specimens were actually below 5,000. I saw one that is 596 that was in there, but how many other specimens were in there that

were below the 5,000 level.

These are specimens collected over twenty years, I understand, in many cases. They are specimens representing about 200, 300, samples of seroconversion specimens. Of those that were antigen-positive, that were in the seroconversion period--that were antigen-positive and antibody-negative, how many were actually below 5,000?

DR. BUSCH: I would need to look at that. I think I do have the dataset here so why don't I look into that. There was only really one sample that was an outlier. In fact, one seroconverter, as you noticed, had sort of three values over time where that particular seroconverter had a lower RNA to antigen ratio in their viral particles over seroconversion.

There was one datapoint that may have approached that 5,000 limit, but let me confirm that.

DR. HOLLINGER: Okay. I am always concerned about outliers also because I am never sure about that sample and so on.

Dr. McGee?

DR. McGEE: On your regression slide where you give the 10,000 point estimates, were the numbers in parentheses the 95 percent confidence intervals?

DR. BUSCH: Yes; I wish you hadn't noticed that. That was a confidence bound around the point estimate of the

cutoff intersect.

DR. McGEE: The lower estimate for that was well below 5,000.

DR. BUSCH: Right. It is important that you recognize that. On the other hand, it is important, I think, that we put into context what we are saying there. One, this is a statistical estimate of the point in time. What we are trying to get at is, for all these different seroconverters, there is this five-day period or so or antigen-positive antibody-negative ramp-up viremia.

For each of these seroconverters, we are trying to back estimate the exact concentration for RNA at the point where they theoretically--that moment where they cross through the level of RNA to achieve antigen. What we are talking about is the confidence bound around our back projection of that intercept.

To me, it would be ultraconservative to expect that a system could detect every possible--and, again, the numbers, the panels, et cetera, are not sufficient, perhaps, to get a more precise estimate around that intercept.

DR. HOLLINGER: Toby?

DR. SIMON: I just want to clarify. The question that we have is to demonstrate that the particular licensed NAT method can detect HIV at a level of 5,000 copies per ml. That is the question before the committee. Based on your

presentation, are you asserting that it should be 10,000 instead of 5,000?

DR. BUSCH: There were two numbers that I think are critical. One is the 10,000, which is the estimate of the cutoff level based on these seroconversion panel analyses, the level of RNA at which different seroconverters cross through the cutoff of p24 antigen.

The other analysis was much simpler but perhaps much more straightforward and logical which is simply looking at the distribution of the RNA load among all the antigen-positive samples that were available. That had a lower, 2.5 percent, confidence inclusion bound of 7,500 copies.

So I think the FDA proposal of 5,000 is the appropriate one. It is also, I think, an achievable one. It is below both of those lower bound estimates.

DR. NELSON: If there were an outlier that was below that, presumably what you are saying is that outlier would also be probably negative on p24 antigen test. I remember, there was a single case report in the JAMA a month or two ago where there was an antibody-negative transmission.

I can't remember what the NAT and--presumably, that person was negative on both p24 and NAT. I think what you are saying is these two measures sort of travel

together, isn't it?

DR. BUSCH: No; I think that is incorrect. That JAMA paper, those samples were RNA-positive antigen-negative in that seroconverter. The RNA tests are much more sensitive. If you are asking a head-to-head comparison, RNA wins out hands down. What you saw there was all of those other samples that were only detectable by RNA.

So RNA buys us much more window-period detection than antigen. But, in order to drop a test, I think we are asking a somewhat different question; are we absolutely confident that antigen will not miss anything that RNA might have detected. On a head-to-head comparison, RNA wins hands down.

DR. NELSON: I asked the question just to get to the outlier issue; in other words, the outlier would also be an outlier for p24, I suspect.

DR. HOLLINGER: Although I think, Ken, that that outlier was p24-antigen-positive.

DR. BUSCH: Right. Again, it is theoretically possible, and that one case suggests, that in some cases, it is probably an issue of the primer pairs not accurately amplifying up a particular sequence. But, in some cases, two specific assays, you can have, theoretically, levels of detectable p24 antigen that break cutoff whereas the amplification assay fails to amplify the RNA.

Theoretically, it could be defective viral particles or something like that. But, more likely, it is the primers. Again, that particular case was based on the NGI system. We actually haven't run that sample with the other platforms.

DR. HOLLINGER: I think we should not also forget, as Dr. Hewlett put up there, that there are other viral-inactivation-removal factors here for the plasma industry also.

Paul?

DR. McCURDY: Mike, one of the take-home messages I thought I got from that JAMA article was that pooled RNA might not pick up samples like that one. Is that correct or am I misremembering?

DR. BUSCH: That is correct. We will be talking later today a little about the issues around NAT and individual versus pooled. Individual donation would further close the window for HIV by about four or five days. So there are definitely good examples of samples, as that illustrated, and that are infectious, that are only detectable consistently with single-donation NAT.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: I guess it is important to recognize here that we are talking about minipool NAT at this time versus single-unit antigen at this time. It is not an

accident that the standard that FDA put forward for minipool NAT resembles the current sensitivity of antigen.

The fact of the matter is that what we were trying to do--in other words, when the question presented itself, how shall we set a standard for minipool NAT. We decided that it should be at least as good as what we were currently doing, which was antigen screening.

The goal was not to overreach the currently available technology. So now what is going on is--that was all done in prospect. Now we have datasets that we can examine since we have had experience with the minipool NAT. So, in essence, we are really asking the question, did we set the standard in the right place.

It is important to bear in mind that we have clearly focused today's decision only on plasma for further fractionation where there is the safeguard of viral inactivation. The goal in screening for p24 was to make sure that there was a limit set on the viral burden that can enter a fractionation pool.

What we are really asking is if you now do that with minipool NAT, is that sufficient or do you still need to do antigen besides. I think the way we have to look at it is whether we have achieved an equivalent sensitivity standard.

It is not necessarily the case that they have to

be identical on all samples tested. It just has to be the case that, overall, it is as good or better. I just thought it was important to point out that we may have a more stringent standard in mind when this question reemerges for whole-blood screening because you are not going to have the backup of viral inactivation.

So it is comparability overall and a reason we are at the margin, comparing the two sensitivities, is because we tried to set the sensitivity requirement for minipool NAT at the level of antigen sensitivity. It looks like we got very, very close.

DR. HOLLINGER: Thank you, Mike. We appreciate that review.

Now, we have several presentations from a variety of groups. I would like to ask you to keep on the time that you were asked to stay with. The first one is Andy Conrad from NGI. Andy?

Open Public Hearing

Presentation

DR. CONRAD: Good morning.

[Slide.]

I am here today to present the data, and my associate from Alpha, Chuck Heldebrant, will also present some of the secondary data from a follow-up study, about a prospective study we conducted on pooled plasma to determine

whether or not the polymerase chain reaction in these pools could detect HIV-positive samples prior to p24 testing of individual samples.

[Slide.]

So, basically, we understood that the blood-derived products had the potential to transmit virus and had in the past. We wanted to see, under the system where donations are currently tested for a variety of antibodies and antigens, if we could use, as well as the p24, pooled PCR to detect the HIV at an equal or earlier time point.

[Slide.]

Basically, that was our goal, the demonstration of the plasma-pool testing system could beat the p24.

[Slide.]

So it was a prospective study. It included 342,729 donations from approximately 48,000 donors collected randomly over a three-month period. Individual samples were tested for anti-HCV, HIV antibody, HIV p24, HBV s antigen as well as ALT levels. So the standard tests were performed.

Samples from new donors--in other words, donors that were just applying, had all these tests done prior to the time that they were pooled in PCR but samples from repeat donors or qualified donors were just immediately pooled for PCR. So you will see that some of these donations have the possibility of being positive for these

other markers because they were PCRed prior to being screened out for those other markers.

[Slide.]

Under our IND and our subsequent BLA and PLA submission, the mean sensitivity of this assay, with 95 percent confidence, was 3.1 virions with a 95 percent hit rate of 5 virions. So, in a pool of 512, you are talking about detecting individual samples with around 2,500 copies of HIV. This becomes important later but you will see why.

[Slide.]

Essentially, for the last time, I will explain how we do this. We use automated robots called Tecan devices. I am sure you have all seen this many times. This is just what the Tecan looks like. Essentially, 512 samples are placed on the deck of this machine and the machine pipettes them into a sort of a complex structure.

[Slide.]

Essentially, what that structure is is that, in groups of eight, they are put into rows, layers and columns. So each row, layer and column pool will have 64 components.

[Slide.]

Essentially, what the model of this is is a giant cube. You can't see the little black lines of the cube because my slide is bad, but it is a giant cube. You test all 512 members of the cube. If it is negative, then you

can infer that all 512 members are negative or at least below the cutoff of 2,560 that I just described to you.

If it is positive, by testing the row, layer and column, you zero in on the positive sample. So, essentially, to resolve a positive pool, it takes 25 PCRs instead of 512 to pick out the positive fellow. It works if there are two, or if there are three. It doesn't matter, the number. It gets a little complicated if there are many more than that.

[Slide.]

So the rule, again, is if the master pool is found negative, then all its components--and it is 25; I skipped ahead there. This is essentially what the assay looks like. It is a series of membranes with nucleic acids bound and probed on them. You can see that it is fairly digital, that a positive is a positive and a negative is a white space. It is a dark band if it is a positive and the computer reads these and does the analysis, picks out the row layers and columns. It is fairly automated.

[Slide.]

The results of the study. Eighteen of 348,000 donations were found to be positive for PCR for HIV. Of these donations, ten were both antibody- and antigen-negative. That means they were pre-p24-positive. Eight of them were positive for either antibody or antigen, so they

would have been excluded by the current system.

These eighteen donations came from only four donors. The donors in the plasma industry can donate quite frequently and, in the time it took for the donors to be rejected through the process, they had donated several more times, as you can see. So there is about 1 in 12,000 donors were found positive by PCR.

If you sort of take out the eight, it is probably 1 in about 20,000 would have been negative for antibody and antigen.

[Slide.]

We endeavored to enroll these donors into a follow-up study to sort of see what we could get, see how their seroconversions progressed. From the two donors enrolled, we got four of the ten donations. From the two not-enrolled donors, we got six donations.

[Slide.]

Here is the story of each of those four donors. Because they donated so many times, we saw a story. This is an interesting thing, and Mike Busch, I have got to talk to you about this a little bit, because, in real time, in real samples that were collected and were rather fresh and in under fairly stringent conditions, here is the p24 status of those individuals that we tested donations.

What you can see here is, here is the pool at 512

if it was resolved naturally. If we had already found the donor and this was a follow-up study, we diluted at 512 just to see if it would still have been positive or would continue to be positive.

The most important number, I think, is over here, on this Donor No. 1, on the draw from 72997, he was positive in the naturally detected pool. It was actually positive one donation before that with 20,000 virions, but he had 750,000 virions. This is an anomaly that sort of violates the extrapolated graphs that we have been seeing.

In this case, the person turned positive here at about 60,000 virions.

[Slide.]

The next slide is the other two donors. This was one of the eligible donors. Actually, we caught him positive a little bit lower than we would have expected to have caught him positive. Instead of 2,500, we caught it at 20. But that is the 95 percent detection, so that was a natural--and we never got him to follow up. He vanished, so we never found out if he would ever go p24-positive. He was repeat-positive on PCR.

The final donor, again, converted to positivity around--it was negative at 40,000 copies and who knows when he turned positive because there was a gap in between those days. So, at some point, he would have turned p24-positive

lower than that.

But those are the numbers. And so we were alarmed to find out that there were actually cases when the HIV viremia was fairly high and the p24 on individual donors was negative. So what we did at this point is we said we should go back and look at all of our donors in the past, in a retrospective study, that had ever turned HIV positive, get all of--because what happens is they donate so frequently that we probably have huge panels of this material.

So we went back to a retrospective study.

[Slide.]

What we did is we got 347 potential HIV donations that came from people we know later had an HIV seroconversion. What this complicated graph sort of shows is that we looked at what would happen if we tested those by individual PCR, by pooled PCR, using p24 with Coulter or Abbott, or the antibody test.

What you can see is that, indeed, there were 41--here, there are 36 cases which would have been detected if you use individual PCR. However, here there are 41 cases that would have been missed if you used the antigen test alone. If you would have used the antibody test alone, it would have been 88 cases that would have been missed.

So, essentially, it shows that, indeed, individual sample PCR is the best. Chuck Heldebrant will talk to you

about "best" as far as detection. But with the plasma hold, it is probably unimportant and Chuck will demonstrate that.

[Slide.]

The next slide is just a different way of showing this same thing. Graphically, basically, what you see is the difference between the undiluted, the diluted, pooled PCR.

[Slide.]

I think the next slide is the easiest way to actually see. I think this is the most important message. It is a two-by-two table. This is PCR-positive, PCR-negative. There were 145 cases that were PCR-positive and none that were PCR-negative whereas, if it is Coulter-positive, Coulter or Abbott-positive, there were 81 cases totally in this retrospective of these donations that were found to be negative.

I think that that is an incredibly important thing. There was not a single case that PCR failed to detect before p24. In the whole retrospective or the prospective study, we did not find a single case when p24 brought anything. And this is a pool of 512. So I think that is a pretty significant statement about the efficacy of the p24 in comparison with NAT testing.

[Slide.]

Anyway, those are the conclusions. There wasn't a

single case during the clinical trial where the p24 individual testing detected a donation prior. The specificity of the pooled PCR, and that is important because I think the specificity also is in question about the p24, how many false positives, there was not a single donor identified during the course of the trial or in subsequent trials that was false identified using the polymerase chain reaction.

The beautiful thing about the matrix is that, as you test the primary, and then you have to go down to smaller and smaller pools, you are essentially really reverifying any result. It is very hard to get a false positive. You might get some of the PCR reactions, but that doesn't, then, translate all the way to the donor.

Then there were 81 donations that were not detected by p24 but that were found by pooled PCR in the combined prospective and retrospective study we conducted.

[Slide.]

I would just like to thank all my colleagues at National Genetics and at Alpha Therapeutics. Thank you.

DR. HOLLINGER: Any questions for Dr. Conrad? Andy, I have one and it has to do with the level of sensitivity because that really gets back to what maybe can or cannot be, to your confidence that you are going to be detecting. You mentioned that, at a level of 5, there is a

95 percent hit rate. That means 5 percent are going to be missed at that, presumably, if I understand that correctly. I will ask my statistician over here to help me on that.

DR. CONRAD: It sounds about right to me.

DR. HOLLINGER: If that is correct, where are you at 100 percent? At what level are you at 100 percent, because that gets back to the pool size, basically.

DR. CONRAD: The question is complex because what we do is we take multiple mls of material and prep it out. So when you see that it is 5 copies per ml, we also run it with more reactions for the HIV, so it really is a matter of how much you actually sample.

Although we can detect five copies per ml, I think the statistics show that at around 18, it was 100 percent detection. That, again, translates here. But, remember, Blaine, the important thing about that is it is sort of an interesting statistic in there because you saw the one that we caught below the level. So there is going to be a continuum in there.

The important thing, and I think you will see later, is that with the hold in the subsequent donors, there is a system by which you could guarantee, because the HIV sort of increases fairly rapidly. It is a matter of catching it, getting it out and at least identifying that donor.

So, although the numbers for the 100 percent detection is a weird math--and Chuck Heldebrant can talk a little more about it because it was a statistician who did it for us. I think is was around 18.

DR. HOLLINGER: But, at 18, that would mean that you would really, then--to get 100 percent, you really need a pool size of about half of what you are doing, so instead of 512--to pick up 5,000.

DR. CONRAD: Yes; at 100 percent. See, the 100 percent statistic is weird. They don't like that statistic. They think it is very hard to derive. They do these strange curves and I think that they are inaccurate at 100 percent.

Dr. Epstein?

DR. EPSTEIN: The negative p24s at very high antigen load raise the question whether your p24 assays were adequately sensitive in the trial. Can you just comment on the controls and did you use any external control reagents.

DR. CONRAD: I will tell you that, during this trial, it was not us doing the p24, it was an FDA-licensed laboratory for Alpha that was conducting these, certainly under the auspices of their licensure and following the package insert.

In addition, what we did is we took the ones--if they used Coulter, we would use Abbott. In those particular

samples, for some reason, we used both kits on them and found them to be negative. We subsequently retested them at NGI. So, again, we followed the package insert. I don't know what the unique situation is.

I want you to know that those particular samples are separate. It is a split off the plasma leader. There are two tubes dangling off of it and we took one of each. So there may be issues about how they were stored or used, but certainly neither kit detected them.

DR. HOLLINGER: Mark?

DR. MITCHELL: Does that mean to imply that there are some times when you get a positive test but you can't trace it back to an individual donation and can you explain why that is?

DR. CONRAD: Early on, in the trial, and this was done back in 1997--we are now seasoned, salty veterans of the pooling wars and so it doesn't happen as much, but early on, the decks of the Tecans--we had the samples arranged on the deck in an interesting way, that the head of the Tecan would pass over the already pipetted samples.

I think what was happening is there occasionally would be a remnant on the outside of one that would drip in. There were four cases of that in the 596 pools that we did. There were four cases where we could see that there was--for example, an antibody-positive HCV sample and it dropped into

another sample. We could prove that with genotyping and sequencing.

So we switched the configuration of the Tecans and it dramatically reduced that problem. But most of it was sample-sample contamination that occurred on the deck of the Tecan. It happened a lot in HBV early on in the IND because the donor centers needed to handle it.

But the nice thing about is you can ask for a backup sample and identify it that way or it won't prove out in the row, layer and columns if the pool gets contaminated the same way. The row, layer and columns won't line up. So it is very easy to see when something is anomalous and then you can just test to find out where it happened. It was 4 out of 596 times--early. It was in the first month.

DR. HOLLINGER: Thanks, Andy. I appreciate it.

The next speaker will be Charles Heldebrant from Alpha Therapeutics. Dr. Heldebrant?

Presentation

DR. HELDEBRANT: May I have the first slide?

[Slide.]

I am going to talk about a comparison of HIV-1 p24 individual testing against pooled RT PCR in a source-plasma screening program.

[Slide.]

We approached it from the idea of what are the

criteria to replace individual p24 donation screening with pooled PCR in a source-plasma program. The first criteria is that the HIV-1 PCR test of pooled samples has to be equal or superior to individual p24 and its performance in terms of sensitivity and specificity.

[Slide.]

As Andy alluded to, we conducted a prospective clinical trial and, for new donors, they were screened for HIV-1 p24 antigen and HIV-1/2 antibody and, if positive, were excluded before PCR pooling. For qualified donors, all samples were tested irrespective of their subsequent HIV-1 p24 or HIV-1/2 antibody status.

We screened over 300,000 donations. We used a pool size of 512 for the master pool, which is the first screen. The row, column and layer are pools of 64 and all suspect-positive donations were confirmed by individual PCR.

[Slide.]

In this study, again we tested 345,000 donations. We had 6 PCR-positive p24 and HIV-antibody-negative donations. These units comprised 7 times 10^8 genome copies per ml. The clinical specificity was 100 percent. The clinical sensitivity of PCR was 100 percent. The corresponding sensitivity of p24 antigen and HIV antibody in this sample set was 27.8 percent.

The mean reduction of the window period estimated

through some fairly complex work that was done with Mike Busch and Steve Kleinman is in excess of four days.

[Slide.]

Again, this is looking at the performance of an individual p24 antigen test. This is taken from the Ortho p24 antigen package insert. It shows a donor sample screening of about 300,000 donors. Thirty-three samples found repeat reactive. Of those, 31 were not neutralized. They were Western Blot or PCR-negative and only two of them were truly positive samples. This is a reasonable performance for all of the p24 antigen kits.

[Slide.]

Again, as Andy has alluded to, the proof of the pudding is does PCR detect things that p24 does not detect and vice versa. Again, for undiluted p24 samples, using basically the same data you have seen, there are no instances where a sample is p24-positive undiluted and is negative by pooled PCR. There are a substantial number of cases where the opposite case applies.

[Slide.]

So our conclusions were that, first of all, substituting the HIV-1 PCR test of 512 pooled samples for individual p24 in a donor screening detected virtually all of the HIV-containing donations. It increased the specificity of screening and increased the clinical

sensitivity of our screening.

Our conclusion is that the PCR of pooled samples is superior to individual p24 antigen tests.

[Slide.]

The second criteria is that the performance of the entire screening program and its associated quality systems using the RT PCR with pooled samples has to be equal to or superior to the performance of that same donor-screening system when you use individual p24 as a component of it.

[Slide.]

This is a group of 288 HIV-infected samples, both prospectively identified seroconversion panels and look-back samples including a substantial number of low-titered HIV samples. Of these 288 samples, when they were evaluated with pooled PCR, HIV-1/2 antibody and the look-back inventory hold and qualified-donor standard quality systems, we detected all 288 of those samples.

Similarly, had we used individual PCR with HIV-1/2 antibody, we would have detected all 288. In this group, individual PCR detected 285. There were three samples which were HIV-antibody-positive only. They were PCR-negative and p24-negative.

Pooled PCR with HIV-1/2 antibody detects 252, or 87.5 percent, of the samples emphasizing the need for the look-back inventory hold and qualified-donor standard

quality systems in the overall screening program.

The addition of p24 antigen individual testing to pooled PCR plus HIV-1/2 antibody did not detect a single additional sample. Again, 87.5 percent of the samples were detected. p24 antigen and HIV-1/2 antibody alone detected only 200, or 70 percent, of these 288 high-risk samples.

[Slide.]

Our conclusion here is that the performance of the entire donor-screening program and its associated quality systems, using HIV-1 RT PCR testing of pooled samples, is superior to the performance of that same donor-screening and quality systems using individual p24 antigen test.

[Slide.]

The benefits of PCR testing; the source-plasma program coupled with the qualified-donor standard inventory hold and look-back quality systems decreases the HIV-1 load and manufacturing pools to the practical minimum. Validated viral-inactivation procedures inactivate any remaining HIV-1 during the manufacturing process of all plasma products.

[Slide.]

Why replace individual p24 antigen with a pooled PCR? Increased sensitivity; it detects more HIV-positive donations; pooled PCR, HIV-1/2 antibody coupled with inventory hold look-back and the qualified-donor standard quality systems detects virtually all HIV-positive

donations; and increased specificity.

As Dr. Conrad told you earlier, and I am going to reiterate, the pooled PCR had no false positives. There were no instances where donors were told that they had a positive or a reactive HIV test when it was not, in fact, a true test.

Thank you.

DR. HOLLINGER: Thank you.

Any questions? We move on, then, to Dr. Watson from Aventis.

Presentation

DR. WATSON: Good morning.

[Slide.]

I am going to report on our experience with PCR testing and HIV antigen. We did not design our IND to specifically look at this question but I believe some of the data we have is relevant for your consideration.

[Slide.]

We are going to first summarize what our test system is. We test all serology-negative samples for hepatitis A, B, C, HIV and parvovirus B19. Our first pooled test comes in a pool size of 1,200. With that, we use a research-grade ultracentrifugation step. So this is our test system.

[Slide.]

The results of that test system are summarized on our next slide which shows that, in this system, we have identified four donors and about 3.25 million samples, but those four donors come from 220,000 donors during the time period.

So what we have identified here is approximately two donors per 100,000 donors where we find an NAT-positive and all serology markers are negative. These donors donated six units and the frequency for that is 0.2 when you look at the 3.25 million units per 100,000 donations. That is just a quick summary. Remember that these are all serology-test negative donations.

[Slide.]

The next slide shows a little more in depth the donation history of the four positive donors. I have tried to show the donation prior to the PCR positive and then any subsequent donations. Notice, in the second and third donors, there was approximately one month between the time of the PCR-positive and they came back and it was antibody-positive.

The fourth donor down here has two PCR-positives, no antibody-positive, and that donor never returned, just like the first donor never returned. If you look at the second donor here, and the fourth donor, you notice that there are PCR-positives anywhere from two to four days prior

to where an antigen might become positive if we assume a positive antigen on the next day.

[Slide.]

We then did some panel testing to see, in our pool of 1200, and if we ran that pool, what would we find based upon the serology tests and also based upon the HIV-antigen test. We took the first antigen-positive sample and a sample prior to that on these panels to see what would happen. Again, all of our testing is done in the pool size of 1,200.

If you will notice, PCR found a positive on the same day as the antigen-positive test and we found one pool where we found a positive two days prior to the antigen-positive.

[Slide.]

The next set of panels shows essentially the same results where the antigen test is positive. We have discordant results here so we took the first one where both were positive. Wherever there was an antigen-positive, we found a PCR-positive and, again, one out of three, we found a PCR-positive, in this particular case, four days prior to the antigen-positive.

So, to summarize this, basically, the panels that we have run so far, we have found the PCR-positive signal, even in our test system, to be the same day as the antigen-

positive and, in addition, we found two of the six positive prior to the antigen signal.

[Slide.]

We also ran the HIV FDA panel, which is shown on the next slide, again using our test system by diluting it out because that is our first test. In this test system, we found 5,000 copies positive, the 25,000 and the 250,000. Based upon the data that we have, and I think the data that you are going to see from everyone that is presenting, we believe that the PCR test process used in the plasma industries could be a viable alternative to the p24 test.

Thank you.

DR. HOLLINGER: Thank you, Dr. Watson.

Any questions? If not, we will move on to the next speaker, Barbara Masecar from Bayer.

Presentation

MS. MASACAR: Good morning.

[Slide.]

I would like to thank you for inviting me and I appreciate this opportunity to give you this update from our HIV NAT clinical study.

[Slide.]

First, I would like to start with a little bit of background. We filed our IND with FDA in August of 1999. It is a shared IND with Roche Molecular Systems. We used

the Roche Ampliscreen Microwell Plate method, not the Cobas. we actually started testing in October of 1999, so we are coming up to that one-year mark.

We use a minipool size of 96 individual donations. In our system, that minipool is created, the nucleic acid is extracted and that sample is split. Part goes to HIV testing and part goes to HCV testing.

[Slide.]

A few facts on assay performance in our hands, and I will also give this in copies, since that is what we are talking about today. For the 95 percent test positivity rate for this assay, it is 91 IUs per ml. In our laboratory, that is 10 to 20 copies per ml. That calculates up to detecting individual donations at 8,736 IUs per ml or 1,000 to 2,000 copies per ml in the individual donation.

We also run an in-house control with each assay at 40 copies per ml so we have assurance that we are detecting individual donations at 4,000 copies per ml and above.

[Slide.]

Our donors that are discovered to be NAT positive are divided into three major categories at the time of index donation, that first donation that is positive. The first category, A, is those donors that are positive for NAT only. The second category is those donors that are positive by NAT and p24. And then the third category being those donors

that are positive for NAT, negative for p24 but positive for antibody.

We assume that this kind of correlates to the stages of infection, that those donors in category A are very early in infection, category B is a week to two weeks later, and then category C is after the donors have actually gone through the period of antigenemia and the antibody is now positive. I will get back to those assumptions later.

One thing that is not on this slide is those donors that are positive for antigen only. It is important to this discussion to be able to say are we seeing any false-negative NAT where the antigen is actually picking them up.

[Slide.]

Although that category of donors, those donors that may have a false-negative NAT test with a positive p24 antigen are described in our investigational plan. We didn't really build a process around that starting off to really effectively capture that category of donors. We don't know of any donors to date that fall into that category, but we are in the process of amending our IND to more effectively capture that and to query the plasma centers for that information.

So I don't have any information on donors that could potentially be a false-negative NAT but we don't know

of any in that category to date.

[Slide.]

So what is our data so far? We have screened over 2 million donations. We have discovered eleven donors in category A that are positive for NAT only. We have identified three donors in category B that were positive for antigen and NAT but negative for antibody and ten donors in category C where the antigen was negative but those donors were positive for NAT and antibody.

Going back to our assumptions of where these donors fall in the viremia and the stages of infection, it does fit in pretty well because those donors in category A, we have found are fairly regular donors so we do have recent prior negative donations on these donors.

The three donors in category B were absent from donating, could be the self-deferral situation--I'm sorry; that is category C. In category B, also, they are fairly regular donors but there is a longer gap in donation frequency for those donors in category B. So, typically, for those three donors, they donated on day 1 and then they were gone for two weeks, so they could have gone through the period where they were positive by NAT only.

Then those donors in category C; actually, category C is mostly comprised of applicant donors so they have actually gone through the antigenemic period. The

antigen is now negative and they have come in to donate and their antibody is positive, and the NAT is positive.

We intend to prescreen applicant donors from our studies but we have spotty compliance with those directives. So we do get applicant donations that come in for NAT screening that have not been effectively prescreened by the viral marker test. But, if we do identify them, we attempt to enroll them in follow-up studies.

As far as the follow-up studies go, the most useful perspective information to get from these donors is those that are in category A, that when they come in, they are NAT positive. Can we enroll them and follow them up and see when the antigen becomes positive.

[Slide.]

So for those eleven donors in category A, we do have subsequent donation information on nine of them.

[Slide.]

So we have the nine donors here. Most of these donors actually had subsequent donation information that allowed us to calculate the reduction in the window period. These three donors plus this donor here were actually positive for p24 antigen the next time they came into the plasma center.

Now, the NAT-positive test will defer these donors but it is one to two weeks by the time we can turn the

result around to the plasma center so the donor will continue to come in and donate without knowing that there are positive-sample result is coming.

These two donors, A and C, actually did have one donation in between that was still NAT-positive, p24 negative. We did have three donors that were initially NAT-reactive. They did not come in for subsequent donations. We were able to enroll them, however. By the time they came in which was approximately two months later, the antigen was already negative. We assume it went through a positive and then reverted to negative, but we don't have any data to say that for sure. But now the antibody is positive.

For these donors that we had the subsequent donation information on, we did get donation information that went to when that donor became antibody positive, 9 or 14 days after the initial NAT reactive. And then we had these three donors that we didn't see them again. We had that single subsequent donation. They were antigen-positive and NAT-positive at this donation and then we were unable to enroll them into this follow-up study.

[Slide.]

This is the quantitative data actually on the index donations for these nine donors. You can see that the range is 4,100 to 312,000. As I said, we do run a control with our assay that gives us assurance we are picking up