UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE

81ST MEETING

FRIDAY, OCTOBER 22, 2004

The meeting came to order at 8:00 a.m. in the Ballroom of the Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, MD 20877, James R. Allen, Acting Chairman, Presiding.

Present:

James R. Allen, M.D., M.P.H., Acting Chairman
Kenneth Davis, Jr. M.D., Member
Samuel H. Doppelt, M.D., Member
Harvey G. Klein, M.D., Member
Judy F. Lew, M.D., Member
Charlotte Cunningham-Rundles, M.D., Ph.D., Temporary Voting Member
Jonathan C. Goldsmith, M.D., Temporary Voting Member
Liana Harvath, Ph.D., Temporary Voting Member
Blaine F. Hollinger, M.D., Temporary Voting Member
Matthew J. Kuehnert, M.D., Temporary Voting Member
Kenrad E. Nelson, M.D., Temporary Voting Member
Keith C. Quirolo, M.D., Temporary Voting Member
George B. Schreiber, Sc.D., Temporary Voting Member
Michael D. Strong, Ph.D., Non-voting Industry Representative
Linda A. Smallwood, Ph.D., Executive Secretary

2004-4074 T2

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

8:34 a.m.

DR. SMALLWOOD: Good morning, and welcome to the second day of the 81st Meeting of the Blood Products Advisory Committee.

I'm Linda Smallwood, the Executive Secretary. I will be reading a brief announcement that pertains to the proceedings for today.

This brief announcement is in addition to the Conflict of Interest Statement read at the beginning of the meeting on yesterday, and it is a part of the public record for the Blood Products Advisory Committee Meeting on October 22nd, 2004.

This announcement addresses conflicts of interest for Topic 3. Drs. Charlotte Cunningham-Rundles, Jonathon Goldsmith, Liana Harvath, Matthew Kuehnert, Kenrad Nelson, Keith Quirolo and George Schreiber, have been appointed as temporary voting members.

The Food and Drug Administration has prepared General Matter Waivers for the special government employees participating in this meeting who required a waiver under Title 18, United States Code Section 208.

Dr. Michael Busch is employed by Blood

Systems. He has contracts, is a researcher, speaker and an advisor for firms that could be affected by the discussions.

Dr. Theresa Smith is employed by the National Center for Infectious Diseases, in Fort Collins, Colorado, and Dr. Susan Stramer is employed by the American Red Cross.

In addition, there maybe regulated industry and other outside organization speakers making presentations. These speakers have financial interests associated with their employer, and with other regulated firms.

They were not screened for these conflicts of interest. At this time I am asking if there are any declarations to be made by any of the participants at this meeting, please do so at this time?

(No response.)

DR. SMALLWOOD: For those who were not here yesterday, I just wanted to announce the tentative meetings, the tentative meeting dates for 2005, for the Blood Products Advisory Committee.

Those dates are March 17th and 18th, July 21st and 22nd, December 1st and 2nd. Again, these are tentative and you will be notified when these dates are confirmed through the normal, appropriate

channels.

At this time I will turn over proceedings of this meeting to the Acting Chairman, Dr. James Allen.

DR. ALLEN: Good morning. We'll start our deliberations this morning by listening to a series of updates. The first is the summary of the Plasma Workshop held August 31st, through September 1st, this year, by Dr. Mark Weinstein.

DR. WEINSTEIN: Thank you, we have the slides, please. You'll be controlling the slides? Okay, thank you.

I would like to review topics that were discussed at the Workshop on Plasma Standards. I will give you a review of the, next slide please. Of the objectives of the workshop, a meeting summary, a summary of the agenda, and some of the highlights that were addressed during the meeting.

And some of our future actions. Can I have the next slide? The objective of the meeting was to obtain information to aide us in the development of regulatory standards for plasma.

Particularly for recovered plasma, including labeling, freezing, storage and shipping conditions. We also wish to review the scientific

data, regulatory requirements and current industry practices, regarding freezing, storage and shipping of plasma.

Another objective was to see whether we could help to harmonize our regulations with those of other regulatory bodies. And fourth objective was to ensure that any regulatory decisions that are made, are based on the science, the need for change and the practicality of implementing any change in regulations. Next slide.

Regarding our, the goals of the, with regard to policy making, we want one to be able to identify the quality of plasma through labeling, that indicates the conditions under which the plasma was prepared, including conditions of freezing.

We want to remove barriers to conversion of plasma collected with the intention of its use in transfusion, to its use in fractionation. Current regulations reduce the flexibility to do this.

While relaxing some barriers, we need to retain some distinctions, but only those that are important. The distinctions that are being considered include labeling that would distinguish plasma coming from a whole blood collection, versus an apheresis collection, product characterization based on intended

use at the time of collection, and conditions of freezing.

We also wish to have our regulatory standards conform to the scientific state-of-the-art. Next. Now to review the agenda of the meeting.

On the first day of the workshop we have a presentation about recommendations of the June, 2003, BPAC, that addressed recovered plasma standards, and we also had an overview of current FDA regulations.

In brief, there was a lack of regulations for recovered plasma, and there was a need to develop specifications for allowable storage conditions and dating periods.

We had a presentation from the consumer community that emphasized the need for high quality plasma products in the United States and internationally.

We also have a very extensive review of the scientific literature that covered the effects of freezing, of rate of freezing and storage temperatures on the integrity of plasma proteins.

The purpose of this review was to help provide us with a scientific rationale for regulations that might be proposed. Next slide, please.

We then had presentations from the international community on their standards and the rationale, and their rationale for freezing, storage and shipping conditions of plasma.

This included standards presented by the Council of Europe, European Pharmacopoeia, Canada and Australia. Representatives of plasma fractionation and blood collection industries, reviewed their current practices about freezing, storage and shipping of plasma, and raised their concerns about the impact of potential changes on their operations.

The panel discussion followed these presentations, which further clarified regulatory and industry positions. Next slide, please. Here are some of the major points that came about from the review of the scientific literature.

And I think these are very important. It gives a frame work for at least the scientific basis of some of our thinking. Loss of factor activity, as reflected in lower product yield, may be regarded as one measure of a reduction in plasma quality.

Loss of activity indicates that proteins are being altered, potentially through aggregation, proteolysis or conformational change. Now is a surrogate marker for proteins that can be altered

during this shipping, freezing, storage process. Factor 8 is currently regarded as the most labile therapeutic plasma protein.

Conditions affecting Factor 8, may affect other plasma proteins in unknown ways. Again the notion that Factor 8, can be considered as a surrogate marker, and that the yield of Factor 8 can be considered as a measure of plasma quality.

I mention that delayed freezing decreases Factor 8 activity in plasma. Preservation of labile components in plasma is optimal up to six hours after donation.

Factor 8 loses about 15 percent of its activity when stored from 16 to 24 hours before the plasma is frozen. An additional losses can occur if it is stored for longer than 24 hours.

A very important point that was raised, emphasized the number of times during the scientific presentation is that the rate of freezing is very important.

Rapid freezing, such as freezing two minus 30 degrees in 30 minutes, gives a better Factor 8 yield than freezing it at minus 30 degrees over a much longer period of time, say three to four hours, or even longer.

Storage within minus 20, to minus 40 degrees, appears to have little affect on product's quality, as long as freezing, as long as the freezing rate is optimized.

It's more important to maintain a steady storage temperature in this range of minus 20 to minus 40 degrees, than an absolute temperature.

And finally it is uncertain whether the time to freeze, way to freeze in storage or shipping temperatures, affect product safety. And this is an area that needs further investigation. Next slide, please.

The chart shows the current U.S. FDA standards for plasma. One of our objectives was to see about the chances of potentially harmonizing our regulations with those of Europe.

I'll point out some of the areas that are in contrast, that are now in contrast with the European standards. First of all, our source plasma is to be frozen immediately upon collection.

It is to be frozen at minus 20 degrees or lower. Our regulations say nothing about the rate of freezing. It can be stored at minus 20 degrees for ten years, and it can be shipped at minus five degrees.

One fact that emerged from the workshop, is that the current shipping of plasma, that plasma is generally now shipped at minus 20 degrees or below.

And so this standard of minus five degrees is not really what is the industry standard at present. Fresh frozen plasma made from whole blood or plasm apheresis, should be frozen within eight hours. It can be frozen, stored and shipped at minus 18 degrees or lower, and stored for a year.

The freezing, storage and shipping temperatures of recovered plasma are not defined. Next slide. In contrast, the European Pharmacopoeia makes a distinction between plasma use to make labile proteins, such as Factor 8, versus the so-called non-labile proteins, like immunoglobulins and albumin.

The time to freeze from collection to freezing, to the time to freeze can be within 24 or 72 hours, depending on the product to be made. And again, this is in contrast to our source plasma which is supposed to be frozen immediately.

Plasma is to be frozen at minus 30 degrees or below, at, if the product is to made, that is to be made is a labile protein. Or at minus 20 degrees or below for non-labile proteins.

Storage and shipping conditions are at

minus 20 degrees or below. For plasma for transfusion, the Council of Europe recommends freezing to minus 30 degrees, within one hour, and storage temperatures at minus 18 to minus 25 degrees, for a three-month dating period, and minus 25 degrees and, below minus 25 degrees, if there is a 24-month dating period.

So the idea of labile proteins freezing to minus 30 degrees, the rapid rate of freezing are in line with some of the scientific data that we heard earlier on in the meeting, this idea of labile versus non-labile proteins is reflected in some of these regulations and standards. Next slide, please.

The fractionation industry presented their perspective on potential changes in the regulations for freezing and storage and shipping of plasma. These summarize a number of the points that were raised by the industry.

Final products manufactured under current storage and shipping requirements, are safe and effective. Increased yield of plasma-derived Factor 8 is not a driver for manufacturing. Yield is not a regulatory issue.

Our current regulations that allow for temperature excursions give flexibility to

manufacturers, changes in allowing for these excursions would limit the availability of plasma for use in manufacturing, and add to compliance challenges.

Changing freezing temperatures would be costly and increase the cost of plasma. And resources spent in changing freezing and storage temperatures, could be better spent elsewhere. Next slide.

The blood collection industry also presented their perspective on proposed changes. There was a wish not to change the definition or expiration date of source plasma.

Most plasma is used to make non-labile proteins. Factor 8 activity decreases the time to freeze, but there's no change in its efficacy. There is no reason why preservation of Factor 8 activities should drive the standards, since it is a small part of the market.

Manufacturers specify the requirements of plasma according to procedures they have already validated. FDA should focus its efforts on donor safety, donor qualifications and good manufacturing practices.

Labeling can indicate expiration date, anticoagulant time to freeze, freezing and storage

temperatures. And finally, there's no compelling reason to change requirements for freezing and storage.

The next day, meeting, next slide, please. The second day of the workshop, we had a review of concepts of regulations, what regulations of the covered plasma.

And we had presentations by FDA, the blood industry, the plasma industry, and this was followed by a panel discussion. Next slide. This slide summarizes some of the points made at the June, 2002, BPAC meeting and FDA proposals for recovered plasma.

First of all, it was recommended that FDA should develop standards for recovered plasma. FDA proposed the term component plasma to replace the terminology recovered plasma, because recovered plasma has a negative connotation.

Component plasma would be defined as plasma that is collected manually or by apheresis, either separately or concurrently with other block components from donors who meet all whole blood donor suitability requirements.

Source plasma would be distinguished from component plasma by defining source plasma as being frozen immediately after collection.

Questions were raised at the 2002 BPAC meeting, about having a ten year expiration date for component plasma, and developing a time to freeze standard for plasma used to manufacture labile derivatives.

Again, reflecting the scientific evidence that was available at the time. It was hoped at that meeting that a workshop would provide data to address the questions. Next.

This slide shows some other AABB proposed standards for recovered plasma. These proposals were derived in conjunction with America's blood centers, the American Red Cross, ECA America, the Canadian Blood Services, the Department of Defense, European Blood Alliance and *(8:53:25).

PPTA, for the most part, endorsed these recommendations, although they questioned a recommended two-year dating period for recovered plasma. AABB proposed the name change for recovered plasma to be plasma for manufacture.

The donor qualifications would be the same as for allogeneic whole blood, including the qualifications associated with infrequent plasma apheresis donations.

Plasma for manufacture would be prepared

from plasma separated from whole blood, infrequent plasma apheresis or by converting plasma for transfusion to plasma for manufacture.

The expiration date is recommended to be two years, and the label should state frozen within X hours after phlebotomy and that the plasma should be stored at minus 18 degrees and colder.

Next slide. There were some additional comments, AABB proposed that freezing within a certain, a specific time frame not be specified because there are multiple types of products that can become plasma for manufacture.

The fractionator can decide what plasma is best, what is best for the manufacture of its product, based on the labeled time to freeze. And short supply agreements would not be necessary.

Regarding our future activity, last slide, please. This workshop was only one opportunity to collect information about standards for plasma. We will continue information gathering through one-on-one discussions with industry, particularly regarding confidential or proprietary information.

And policy proposals will be developed through a public dialogue process of notice and comment. We are preparing a docket site together and

share comments about this workshop, and I anticipate that that docket will be available in the very near future.

The web site for this conference, that will give you access to the slides and transcript, and notice of the docket opening, is at www.fda.gov/cber/whatsnew.htm. Thank you.

DR. ALLEN: Thank you very much. Comments or questions from the Committee with regard to the workshop report? Just to clarify with regard to the proposed name change, if I understand the process correctly, you're going through a decision making process, which, as you indicated on the last slide, will be open -

DR. WEINSTEIN: Correct.

DR. ALLEN: - for public comments? Also, you've not yet made a decision on that?

DR. WEINSTEIN: That's right. I will just, for whatever it's worth, I will just make one simple comment. And that is I tend to agree with the FDA proposals, at least the component, the term component plasma to me, seems to be more descriptive than plasma for manufacture, which sounds as though it's primarily being collected for manufacturing purposes. Other comments or questions on this report?

MS. GREGORY: Kay Gregory from AABB. I just want to explain why we did not particularly care for component plasma.

In our way of thinking, we normally talk about components as being things that we are preparing for transfusion to patients. And we wanted to distinguish this plasma, which is going to somebody else to do something with, from the components that we're working with and the terminology that we're used to working with throughout our industry.

DR. ALLEN: That's a good rationale, thank you. Okay. We will move on to our, thank you very much, Dr. Weinstein, move on to our second update, which is a discussion of the draft UDHQ, Uniform Donor History Questionnaire Acceptance Guidance, review and public comments by Judy Ciaraldi.

MS. CIARALDI: That's pretty good. Good morning. Before each donation, blood and plasma donors are asked questions concerning their medical history and their high risk behavior.

This is because FDA has stated, in regulations and in guidance documents, that donors must me certain criteria and the donors are asked these questions to determine if they are eligible to donate.

Historically, the blood centers have been responsible for developing their own questionnaires. In the '50s, AABB, formerly known as the American Association of Blood Banks, but now known as AABB, developed their own uniform donor history questionnaire that was used be most, or many, if not most, blood collection centers.

And the number of infectious diseases increased and other problems that are associated with transfusion increased, so did the complexity of the questionnaire.

A task force was created from multi-organizations to review, evaluate, revise and streamline the AABB questionnaire. The task force submitted their questionnaire to us for your review.

We completed the review of the full length materials, and published a draft guidance document accepting it as a tool to collect donor information consistent with our regulations and recommendations.

Today I'm going to discuss the comments to the docket for the draft guidance document. Next slide, please. The donor questionnaire process has been discussed at several BPAC meetings, as you can see.

In the early '90s, the FDA commissioned a

report, a study by the American Institute of Research, to look at the donor interview process, and their results were presented at two meetings of the BPAC.

Later on we discussed validation of donor questions and the task force got a chance to present their materials at two BPACs. Afterwards we discussed our review process and then the abbreviated questionnaire and the self-administered questionnaire was presented and discussed.

We at FDA, really thank the BPAC for their attention to this particular topic. Next slide, please. In June of 2002, FDA did discuss its review process of the task force materials. This is a graphic representation of the review time line for the full-length questionnaire.

Just to highlight a few points. In May of 2001, we received a full-length questionnaire from the task force that they asked us to review. This review was conducted by six individuals within FDA, the different offices in FDA.

It took us four months to complete this review, and at the end of four months we submitted comments back to the task force.

In March of 2002, we received the revised full-length and six additional documents to complete

a full questionnaire interview process. This particular review was very complex, very broad. It included eight FDA individuals and four of your BPAC colleagues, for a total of 12 on the review team.

In spite of the complexity and broad nature of this review, we were able to turn the review around and provide comments to the task force within seven months.

After some exchanges back and forth, to get extra clarifications and revisions to the questionnaire, in July of 2003, we were able to inform the task force that we had completed review on the full-length questionnaire.

In addition, we were deep into the development of the draft guidance document, accepting it as a tool for screening donors.

We were preparing the draft guidance document during the rest of 2003, and in the beginning of 2004, when in March of 2004, the task force called us and asked us, if necessary, to delay a little bit the publication of the draft guidance document, because they wanted to insert a new validated question, into the questionnaire and they wanted to make sure that we had the most current version included in our draft guidance document.

They submitted those materials to us in April of 2004, and we finished the review very quickly and were able to say that we were now done. At the same time, our draft guidance document was published.

The total review time for the full-length questionnaire, in FDA's hands was 13 and a half months, in the task force's hands 14 and a half months, independently of each other.

So this was a very big project by both parties. Next slide, please. The draft guidance document was published April 23rd, 2004, with a 90-day comment period.

The draft guidance includes information about the development of the task force materials and our FDA acceptance of it. It also includes reporting instructions for licensed blood establishment that want to implement the new questionnaire.

The task force materials are included in the guidance document as attachments. Next slide, please. More specifically, the draft guidance document states that FDA believes that the task force materials will assist both licensed and unlicensed blood collectors in complying with donor eligibility requirements.

It also states that licensed blood

establishments may report, in their annual report, if they are going to implement the questionnaire without modifications or with more restrictive modifications.

And we are also recommending the self-administration of this donor history questionnaire be reported in the annual report. On the other hand, if blood establishments wish to modify it, as otherwise mentioned, they would have to send that in to us as a prior approval supplement, so that we would have an opportunity to review it.

Any new questionnaire that has undergone major revisions by the blood establishment, have not undergone this FDA review like the one that we are accepting.

We also stated in the guidance document that blood establishments should report to us as a change that's being affected in 30 days supplement, if they would like to implement this process using a computer-assisted interactive procedure. Next slide, please.

There were 11 comments that were submitted to the docket as of last week. Four came from industry groups representing both the blood and the plasma industry.

One came from a task force themselves.

Three came from blood collection centers and blood collection, blood suppliers. One came from a university hospital.

One came from a computer-assisted donor history software vendor, and one came from a private citizen. Next slide, please. We received some positive comments to our particular draft guidance document.

These included their appreciation of FDA's acceptance of the donor history questionnaire material from the task force, including that they would be allowed to self-administer it.

The also appreciated the annual reporting category, if they implemented without modifications. There were no dissenting comments on the prior approval category for major modifications.

One commentor asked if we could expedite the CBE30 supplement review category for the implementation of the computer-assisted process.

Just to respond to this, all changes being implemented within blood establishments, come with some level of risk. And it is the responsibility of the blood establishment to minimize this risk by following good *(9:05:58) and process validation before these procedures are implemented, regardless of

FDA approval. They also asked for clarification on what we meant by without modification, and what was required or recommended for using the accompanying materials.

The things like the education materials, medication list and so forth, that the task force developed. More specifically, they wanted to know if they must use a flow chart format that the task force had prepared for the follow-up questions.

We discussed this a little bit. We haven't completed our full evaluation of the comments, but we did discuss this, and we agree that some of those materials that were prepared by the task force, do contain formats that it is important for the blood establishments to keep.

Specifically, the questionnaires themselves. But some of the other documents, a blood center may use a different format that is consistent with their procedures.

Comments also asked us how to submit comments or concerns that they may have to the attachments. Now the DHQ materials belong to the task force themselves. They are the property of the task force.

And they have changed control

responsibility over them. So comments about the attachments or the materials themselves, should be forwarded to the task force. Next slide, please.

The comments included, whether or not FDA would discuss new questions with the task force before we put them into draft or final guidance documents.

We would like to do this whenever our policies allow. We have been discussing internally about one possible way to develop new questions is to conduct focus groups, whenever our resources and time permit.

One comment asked us to change our donor eligibility regulations to allow the position to evaluate close contact with hepatitis and then the Medical Director would determine deferral.

Right now the regulations do not allow for this flexibility. Questions or comments like this, in anything dealing with changing our regulation, is beyond the scope of the draft guidance document accepting the questionnaire.

A couple of comments asked us if we could accept the abbreviated questionnaire in our guidance document. At FDA's request, the task force is continuing studies on the abbreviated questionnaire.

Once their revised product comes into FDA,

we will need to review it, and this process will delay the publication of the questionnaire.

There were several concerns about a comment in the task force material, a standard or a need to complete the full donor history questionnaire, but before determining eligibility. In other words, if a donor answered a question early in the interview process, that would defer them, why would they need to complete the rest of the questionnaire.

That standard is not an FDA requirement or recommendation, but it is included in the task force materials. So this particular comment was forwarded to the task force.

And all comments contained questions or comments having to do with clarification of information that was contained in the attachments themselves.

Because the attachments are the property of the task force, all of these were forwarded to the task force for their evaluation. And we don't consider them relevant to the content of the draft guidance itself. Next slide, please.

There were several concerns stated in the comments to the docket. The donor history questionnaire contains questions related to issues not

currently recommended or required by FDA. These include a history of cancer, transplant graft and questions about pregnancy.

FDA had stated in its draft guidance document that it will allow these non-required, non-recommended issues to be omitted from the donor history questionnaire if the blood establishment so chooses.

This is because FDA does not have the legal authority to require or recommend industry standards where we've not come out in our own document stating such. Next slide, please.

We also got some concerns that FDA did not require or more strongly encourage the use of the task force materials, and we also stated that we would allow blood establishments that had previously approved questionnaires, to use those even though they were not tested and validated to the extent of the task force materials.

Again, the FDA does not have legal authority to require this particular standard and require use of the task force material. Also, FDA does not have the authority to rescind previous approvals in the absence of data showing a potential risk to the public health.

The task force is comprised of participants from all the major blood establishments, to ensure that it would be used widely.

And I think this is the hope of the task force and that's the reason they composed or constituted the task force with those members. Next slide, please.

The process of preparing the final guidance includes evaluating all the comments and revising the document, if it is necessary. We also are going to consult the task force about revision to their materials based on the comments that came to the docket.

We've informed the task force that we should review these materials, because our guidance document states that this is the version that we reviewed and have looked at and agree with.

We have informed the task force, also, that we feel this review is going to be much more streamline and involve only the three liaisons to the task force committee.

Lastly, we will prepare the guidance document according to our regulations. The time to complete this process will depend on the complexity of the changes that are needed to be made to the draft

guidance document. Thank you very much for your attention.

DR. ALLEN: Very nice summary, thank you. Any questions or comments with regard to the donor history questionnaire?

(No response.)

DR. ALLEN: Okay, I know that, at least my perspective is that this is a very important step forward and I look forward to it being completed. I do have one quick question.

Has the task force or people working with the task force, discussed updating of the history questionnaire as new guidances come out. We discussed *(9:13:02) virus yesterday. There was an update in the last couple of years on, to try to detect symptoms of West Nile Virus and so on, which I know will probably come up again later this morning.

But as these new issues come up, is there a way that the organizations that comprise the task force propose to try to handle that and add another uniform question to the questionnaire to keep it uniform?

MS. CIARALDI: The answer to that is yes. They are, they have discussed it and they're still discussing the most efficient way to do that. It is

the, and Kay Gregory is a member of the task force, so she can finish up where I've left off.

But they have, they want to make sure that the integrity of the questionnaire, that it's been validated and all the questions on it have been tested. They want to keep that integrity.

So, as new issues come up, they want to have the opportunity to find a mechanism to quickly test them. And then incorporate them into the questionnaire so they are developing of that process.

I'm not sue it's been 100 percent finalized, but they have been actively discussing it. It's important to them as well.

DR. ALLEN: Do you want to make a comment on that process?

MS. GREGORY: I think Judy summarized it very well. And we're actually sort of testing the process by testing the abbreviated questionnaire in some additional ways, so we'll know whether the process works very well or not, and we may need to modify it if that's the case.

DR. ALLEN: Good, I'm glad the issue has been addressed. Dr. Epstein.

DR. EPSTEIN: Let me just mention one concept that has been discussed as a possible way

forward. Which is that as a new issue emerges, where there appears to be a need to screen the donor for medical or risk history, that we might provide guidance to blood establishments to defer donors for that risk, but not to frame a specific question.

We would then have a process whereby questions were validated independent of that guidance, and then only later integrated into the uniform donor history questionnaire, as they were validated in their own right, and in the context of the questionnaire.

So in essence, a two-tiered process is, you know, one concept that can be pursued.

DR. ALLEN: Thank you. Any other, yes?

DR. SCHREIBER: Does this uniform donor history questionnaire also apply to the source plasma, or is there another activity going along parallel, and that's a naive question.

MS. CIARALDI: The questionnaire that is currently in our guidance document, could be used by source plasma, there's no restrictions on it.

But the source plasma industry has determined that because of some of the differences in donor eligibility criteria, that they have separated into their own committee and they're working on their document.

They had submitted a first draft to us, and we finished our review and have submitted those comments back to them, and they are working on those revisions that we've asked them to look into.

DR. SCHREIBER: Thank you.

DR. ALLEN: Okay, thank you very much. In our third update for the morning, is FDA's current thinking on monitoring weight in source plasma donors, Linda Alms.

MS. ALMS: Good morning, I'm Linda Alms, a Consumer Safety Officer in the Division of Blood. Next slide. The issue that I'm going to speak briefly about is the tracking of the ten pound weight loss over a two month period of time in source plasma donors.

Tracking of the ten pound weight losses in donors over a two-month period of time, is considered a cumbersome process by industry, and it's an outdated and ineffective procedure to reduce the risk of HIV in plasma products. Next slide.

Tracking donors for ten pound weight losses over a two month period of time, commenced following CBER's revised memorandum dated December 14th, 1984.

As stated in the memorandum, the existing

cumulative records of each source plasma donor's weight should be examined to assure that any weight loss of ten pounds or more, in less than two months, is detected.

The December 14, 1984 guidance, was superceded by a memorandum dated February 5th, 1990, which also includes the statement requiring the tracking of the weight loss for ten pounds or more over a two-month period of time.

A subsequent memorandum, dated April 23rd, 1992, addresses the additional possibility of HIV2 exposure, but no longer made mention of the ten pound weight loss, tracking obligation of the source plasma donors.

This memorandum does not specifically state whether the February 5th, 1990 memorandum was to be superceded. However, the current guide to inspections of source plasma establishments, revised April, 2001, still requires that the source plasma donor's weight be examined to ensure that any weight loss of ten pounds or more, in less than two months, is detected. Next slide.

Since the early 1980s, improved testing technology has reduced or eliminated the predicted value of weight loss tracking with respect to

HIV/AIDS. Although, unexplained weight loss remains a general indicator of possible ill health.

Source plasma donors are currently weighed at each donation, in order to determine how much plasma to obtain. These weights are recorded in the plasma donor's records and they are available for review as deemed appropriate by the center's medical staff. Next slide.

Current requirements pertinent to source plasma donor eligibility includes the following, 21 CFR 6040.63(a), states the suitability of a donor for source plasma shall be determined by a qualified, license physician or by persons under this supervision and trained in determining donor suitability.

Such determination shall be made on the day of collection from the donor by means of a medical history, tests and such physical examination as appears necessary to the qualified, licensed physician.

And as stated in 21 CFR 640.63(b)1, each donor shall be examined by a qualified, licensed physician, on the day of the first donation or no more than one week before the first donation, and at subsequent intervals of no longer than one week.

Therefore, FDA's current thinking is that

it's appropriate for the active tracking of ten pound weight loss among source plasma donors, to be performed at the time of the annual physical, and that other donor informational materials should be harmonizes with those in places for the whole blood donor eligibility. Thank you.

DR. ALLEN: Thank you. Comments or questions on the, this presentation?

(No response.)

DR. ALLEN: All right, thank you very much. I understand that we do have a request for an open hearing statement from the Plasma Protein Therapeutics Association, is that correct? Okay.

Please come to the microphone, I need to read the public hearing announcement, so if you'll bear with me for just a second, and then if you would introduce yourself and make your statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making, to ensure such transparency at the open public hearing session of the Advisory Committee meeting.

FDA believes that it is important to understand the context of an individual presentation. For this reason, FDA encourages you, the open public

hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the companies or groups payment of your travel, lodging or other expenses in connection with your attendance at meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship.

If you choose not to address this issue of financial relationships, at the beginning of this statement, they will not preclude you from speaking.

MR. PENROD: Thank you. Good morning, my name is Josh Penrod, I'm a salaried employee of PPTA, so that I hope that suffices as my disclosure.

The Plasma Protein Therapeutics Association is the international trade association of standard setting organizations for the world's major producers of plasma derived an recombinant analog therapies.

Our members provide 60 percent of the world's needs for source plasma and protein therapies.

These include clotting therapies for individuals with bleeding disorders. Immunoglobulin is to treat a complex, a complex of diseases in persons with immune deficiencies.

Therapy is for individuals who have alpha one anti-trypsin deficiency, which typically manifests as an adult onset emphysema and substantially limits life expectancy. And albumin, which is used in emergency room settings to treat individuals with shock, trauma, burns and other conditions.

PPTA members are committed to ensuring the safety and the availability of these medically-needed life-sustaining therapies.

PPTA welcomes the efforts made by the Food and Drug Administration in reviewing the necessity to monitor, at each plasma donation, records for the donors weight measurements over a two-month period of time for the purposes of detecting an unexplained ten pound weight loss.

The recommendation to monitor donor weight, using measurements obtained to determine the amount of plasma that can be donated by the donor, was instituted prior to the development of tests able to detect HIV infection.

We agree with FDA that such monitoring

today does not add a margin of safety with respect to HIV/AIDS. For source plasma collection centers, the repeated review of these weight loss records, over a two month period, rather than adding to the protection of public health, has instead become an onerous and difficult task that frequently results in auditing pitfalls rather than protecting the plasma donor or the plasma supply.

PPTA agrees with the FDA assessment of the utility of new and improved testing technology such as NAT. We also agree with the FDA that unexplained weight loss could be an indication of poor health, that we would add that it could indicate a change in physical activity, dietary habits, employment or season.

FDA has focused on the usage of the word unexplained as being the operative turn in this analysis. But this predisposes that any weight loss has one cause, and it is either explained or not.

This binary approach may be suitable for determinations of objective testing criteria and standards, but it distal, surrogate marker, such as the weight loss tracking, which never was truly determinate of a disease state, is not subject to such an interpretation, due to its inherent subjectivity.

We also agree, in large part, with FDA's historical review of the blood memoranda issued over the past 20 years, given today by Ms. Alms and its briefing materials to the committee.

And the recommendation is contained therein. He weight loss tracking criterion is contained only in the current guide to inspections, which is categorized as a level-two guidance, and is not subject to comment before implementation.

Our reading of these past memoranda, is that while the April 23rd, 1992, memorandum, quote, did specifically state whether, did not specifically state whether the February 5th, 1990, memorandum was to be superceded, close quote.

We would like to point out that the April 23, '92 memorandum, states that it replaces the February 5th, 1990 memorandum.

Since the February 5th, 1990 memorandum is replaced by the later memorandum, the earlier memorandum should be considered to be superceded. We also not that the 1984 and 1990 memorandum are not generally available to the public on the FDA web site, which indicates that they are, in fact, concerned by the Agency to be obsolete.

PPTA appreciates the efforts of the Agency

in this regard. We also encourage the FDA to continue review of the regulatory requirements and recommendations that do not add to the safety profile of product manufacture, plasma donation or public health.

While PPTA supports requirements and recommendations that can add measurable improvements to donor health and final product safety, outdated, valueless requirements add burdens without benefit.

PPTA supports the FDA's review of requirements that had become obsolete and FDA's efforts to examine the regulations and the guidance criteria to limit efficiency and do not generate enhanced safety.

On behalf of PPTA and our member companies, I thank the committee for hearing us this morning, thank you.

DR. ALLEN: Thank you, any questions or comments on the statement, Dr. Epstein.

DR. EPSTEIN: Well, Josh, you may be right on a technicality, but the compliance program document made it perfectly clear that it was still an FDA policy to monitor the donor weight.

And I think FDA is concerned that if source plasma establishments are in fact weighing the

donor then never to examine the weight records is not appropriate. And we feel that we're providing significant flexibility and reducing burdens by recommending or proposing to recommend that this be done only at the time of the annual physical, and as a general, medical matter.

In other words, that's then within the domain of medical discretion, how to deal with weight trends. So, you know, I would just caution you that because the '92 memo did not make specific mention, didn't mean it was dropped.

Our intent in that memo was to supercede the previous geographic referrals for HIV2, recognizing that we now have testing for HIV2 and well as HIV1. And perhaps there is an omission in not capturing, you know, all previous recommendations.

But the compliance program makes clear that we have not desisted from that recommendation.

MR. PENROD: We do appreciate the flexibility we've been given, thank you. Although I think we'd have to debate for another day, the role of the compliance as policy making documentation.

DR. ALLEN: Dr. Goldsmith.

DR. GOLDSMITH: I was just concerned about your third paragraph statement in which you refer to

weight loss as a subjective measure. Is there any kind of a system for, and showing the accuracy of the scales at the donor center. Is that why you refer this as subjective?

MR. PENROD: Well, we think weight loss is a measurement of weight loss, rather than of necessarily being symptomatic of HIV. I'm not sure I understand you.

DR. GOLDSMITH: Well, you say that weight loss is a subjective measure. Weight loss is an objective measure if the balances have been checked for validity.

MR. PENROD: Well, weight loss certainly is objective.

DR. GOLDSMITH: Right.

MR. PENROD: However, the extent to which you are using it as a surrogate for another disease state and its interpretation of the meaning of the weight loss within that context is open to subjectivity.

DR. GOLDSMITH: But it is a general part of medical practice to assess the health of individuals by monitoring their weight over time. So I guess it would seem to be appropriate to use it in this context, even though it's not good for HIV, it might

be good for something else.

MR. PENROD: Well, we're not abandoning weight loss or weight measurement. Thank you.

DR. ALLEN: All right, thank you. At this point the public comment section is closed, this session is closed. We will move on to our open committee discussion, the third topic for BPAC for this meeting, FDA's current thinking on donor deferral for potential or documented infection with West Nile Virus.

As we will hear, you know, we are in our second or coming to be close to the conclusion, I hope, of our second season of screening with nucleic acid testing for West Nile Virus.

We've learned an awful lot and we'll hear the updates and recommendations for changes in practice. Our first introduction and background will be by Dr. Nakhasi from FDA.

DR. NAKHASI: Thank you, Dr. Allen. Good morning. I sort of sound like a broken record. Every BPAC I'm up here and presenting you the update of the West Nile, but I think I hope next time we'll have that, you know, we will see how it turns out to be.

Well, I that the topic of discussion is today's, is the, we would like to see if we can have

our *(9:31:23) on the donor differential for potential and documented infection of West Nile Virus. The next slide, please.

The issue today is on the table is under concentration, updating our current guidance on West Nile, based on the recent reports that extended *(9:31:41), which came out from our, that schedules them under INDs to revise the current deferral period which is in the current guidance physician and the revised one on May of 2003, from 28 days to 56 days for blood donors.

We want the positive screen by NAT or reported symptoms of headache and fever. Also we would like to, the question on the table is to revise the guidance to have donors which are deferred with either the positive test, screening test for West Nile, or suggestive symptoms to be entered after testing negative by ID-NAT on a follow-up blood sample prior to re-entry after 56 days.

Now, next slide, please. Just to, a quick and brief background, but because Dr. Alan Williams will give a detailed background about what the current guidance talks about and how the questions have been changed and that, you know, what we would like to change and we'd like to make the changes and also the

question is on the table, which, you know, he will be asking at the end. Just to re-orient you about the current recommended donor deferral criteria, they are based on the donor deferral based on the reactive NAT results.

Currently, if a donor sample is tested positive on individual donation, FDA recommends a deferral of 28 days, which is based on the known longest period at that time, which was known at that time, which was the in 1950s, and so, you know, cancer patients, and that was based on that, on 28 days at that time.

This was before the testing was initiated. And what is happening under this, currently under clinical trial and IND donors are asked to enroll in a follow-up sample, those who have tested positive.

And then they are re-entered based on documented IgM conversion, seroconversion and additionally a negative NAT result after 28 days is required for donor re-entry.

In some cases, you know, if you want to re-enter the donor earlier, before 28 days, it is retested, the individual sample and donation, and if it is negative it is re-entered after 28 days.

Or, if it is positive, then the donor is

deferred again for 28 more days. Next slide, please. The next criteria is based on donor deferral based on the West Nile symptoms. This is basically on the potential, again, based on the known knowledge at that time having the extended period, you know, donor period of 28 days.

The potential donors with medical diagnosis of West Nile infection, including diagnoses based on symptoms or laboratory results are deferred for 28 days from the onset of illness or 14 days after the conditions are resolved.

The other question is also asked regarding the previous symptoms are included as part of the current donor selection criteria. This was based on the hypothesis -- not hypothesis. This was based on the thing that during the -- some of the transfusion-transmitted cases which were negative on NAT later on to show that they had symptoms reported to be symptoms before or after the donations.

So in that question, what is happening is donors are asked about the fever and headache in the past one week and if yes, they are deferred for 28 days from the day of interview.

Next slide, please. So that's the current guidance. Now, during the last year's study and

testing and this year some of the testing done, ARC and BSL studied West Nile RNA dynamics in a number of reactive blood donors from 2003 epidemic.

They followed. The follow-up was to determine the rate of disappearance of RNA as well as the seroconversion of IgM and IgG. What they found out, surprisingly, is that in rare cases, some of these West Nile viremia may last up to 49 days and that in those cases, RNA it coexist with both IgM and/or IgG.

So that sort of raised our flags that the virus can be found as long as 49 days, even though it is very rare. But you will hear more about the mean days of duration of viremia from both ARC presentation and BSL presentation by Sue Stramer and Mike Busch.

Next slide, please. So the questions to the committee are, do the available scientific data support extending the currently recommended default period of 28 days to 56 days: one, for blood donors, the positive West Nile NAT screening test; and, two, for blood donors who report symptoms of headache with fever in the week before donation?

Next slide, please. The next question would be, do the scientific data support a recommendation to obtain a negative result by ID-NAT

prior to reentry of blood donors who are different either on the basis of reacting to NAT and/or on the basis of symptoms?

Third is to the committee. Are there other alternatives that should FDA consider regarding criteria to reenter donors who are deferred for West Nile based on that or symptoms? So those are the questions which Dr. Alan Williams will present at the end of the discussion.

Next slide, please. So quickly to update you, but you will hear the more expanded, extended update from CDC. Just to reorient you while you are listening to those presentations, as of October 19, 2004, we have this year so far 2,151 cases and 68 deaths.

Forty-seven states are endemic for West Nile virus, and there was one case reported, one case of transfusion-transmitted case, in Arizona. This happened before the ID-NAT was instituted in that region because, as you remember, this year, as soon as the native area became hot, that means that you found more cases, you know, a lot more than four cases in certain regions, the blood establishment changed from Mini-Pool NAT to ID-NAT. So this case happened before the ID-NAT was instituted in that, just 12 days before

the ID-NAT was instituted in that.

And, as we confirm with NAT, the IgM reactivity donor recipient follow-up, you will hear more about this case from Dr. Theresa Smith's and Dr. Jennifer Brown's presentations later on.

Next slide, please. So now how do we stack up in the interdiction of the asymptomatic donors since we started testing in the ID West Nile NAT by Mini-Pool NAT as well as ID-NAT now this year in certain areas?

Last year, 2003, in last year, 2003, 880 West Nile presumptory donors were reported to CDC ArboNet. Underlining the CDC's ArboNet, there are more than those cases, approximately 1,000 cases, which found the blood establishments.

As of October 19, 2004, this year, we have 191 presumptive donors. And, you know, look at the comparison between the two numbers, even though the year is not over yet, again officially reported for CDC ArboNet using both Mini-Pool as well as ID-NAT. Then this testing, ID-NAT testing, started in May '04.

Next slide, please. So what are we doing? We are still continuing working closely with the test kit manufacturers to see how we expedite the test licensure. And we are still continuing to participate

in biweekly, this year biweekly at least, meetings of the task force established by the blood community and blood bank community, which includes CDC, NIH, and coordinating and monitoring the infection throughout the year.

Next slide, please. So today's agenda will be as follow. First, the summary of the 2004 epidemic will be presented by Theresa Smith and Jennifer Brown. And the duration of viremia and experiences with the NAT testing, both Mini-Pool and ID-NAT, which is going under IND, will be presented by Mike Busch and Susan Stramer. And the current thinking on the deferral extended and donor deferral guidance will be talked about by Dr. Alan Williams. And the questions will be again presented to you by Alan Williams.

Thank you very much.

ACTING CHAIRMAN ALLEN: I am extremely impressed. You wrapped up right at the zero second. Excellent.

I have just one quick question. And I suspect that this is information that will come out later. But if you know it, you reported the number for both 2003 and 2004, the number of presumptive viremic blood donors. Do you have a rough estimate of

the proportion of presumptive positives that are confirmed?

DR. NAKHASI: I think that Theresa and Jennifer will talk about that.

ACTING CHAIRMAN ALLEN: Very good. Any other questions or comment on this introduction before we move to the full presentations?

(No response.)

ACTING CHAIRMAN ALLEN: Thank you.

As introduced, our next speaker summarizing the 2004 epidemic is Dr. Theresa Smith from CDC. Welcome.

DR. SMITH: Thank you. And I appreciate the opportunity to talk to you about what we know so far about the 2004 epidemic.

B. SUMMARY OF 2004 EPIDEMIC

DR. SMITH: Go ahead and go to the next slide, please. I will quickly go over the virology of West Nile virus, the epidemiology from 1999 to 2004, some of which you have seen last year during this update. We'll go on to the 2004 update and blood donation surveillance events.

During these two portions of the talk, I am going to be underlining the fact that the data that you're getting is not the last word. We are still in

the midst of transmission. We are still in the midst of gaining surveillance information.

Next slide, please. West Nile virus is a flavivirus in the Japanese encephalitis sera group. West Nile virus and St. Louis encephalitis are the two members of this serogroup that are found in the United States.

These organisms are primarily bird pathogens. And they amplify in avian host. That means that an infected mosquito that causes an infection in a bird has a great deal of change between how infected material goes into the bird versus how much infected material is available in that bird once it has a full-blown infection.

The common method of transmission amongst nature is from birds to mosquitos to birds. Mammals are a dead end host for this virus with only low-level viremia occurring within mammals before an illness onset.

Next slide, please. I think that you are fairly familiar with some of what has happened over the last few years.

Next slide, please. But you might not be familiar with where some of the data is coming from. ArboNet is a national arbovirus surveillance system

that is a Web-based passive system begun in 2000. It includes 57 area health departments that report to the Division of Vector-Borne Infectious Diseases in Fort Collins. They report mosquito, bird, horse, and other animal surveillance data, including the year, state, county, and date of collection of the specimens.

For human cases, state and county of residence, clinical illness, and onset date, age, sex, race, ethnicity, and risk factors for developing West Nile virus infection are collected, including the questions of blood donations and receipt.

The next few slides I think you're familiar with and I will go through quickly. They will show you the spread of West Nile from 1999 through 2004. One of the aspects I would like to concentrate on is the difference between the map that you saw at this time last year and the map that we then created once we had all of the data in for this year.

If you would show the next two slides? Next, please. Next. Next. Next. Here is what you received last year about this time. Next slide, please. And you can see that by the time we had received all of the data for 2003, we had added two new states. Idaho and Nevada now have activity in

this slide. It has become a fuller, more dense slide. And areas that originally had only non-human West Nile virus activity now were showing human cases, which are in red. Thank you.

Next slide. Here is our most recent as of the time of the printing of these slides set of data for 2004. As you can see, this is as of September 27th. And I would like to point out again that not only is transmission still occurring, so, too, is reporting quite a bit behind that as well.

Next slide. The 2004 surveillance update I'm going to again take use of the numbers of last year and compare them so you can have a basis to understand this year's numbers.

Next slide, please. In 1999, there were 62 human cases of West Nile virus disease in the United States; 2000, there were 21; 2001, 66; 2002, 4,156; 2003, 9,862.

I want you to note that in each of these cases, these are the reports that we received with an onset before December 31st of that year. That contrasts with what data you will be receiving today.

Next slide, please. If we look at what we had at the time of the printing of these slides, there were 4,137 cases of human West Nile virus illness that

had been reported to CDC. And, again, thinking of the previous slide, this is only 42 percent of what we ended up understanding had occurred during that year.

At the time of your report last year, you were told that there were 36 states and the District of Columbia that were affected. West Nile meningitis and encephalitis had had 1,153 cases reports. West Nile fever had had 2,414 cases reported. There had been 80 deaths, with a median age of 79 years.

Eight states last year had over 100 reported cases. Almost 90 percent of the reported cases occurred in these states. That included Colorado, South Dakota, Nebraska, Wyoming, Texas, Montana, North Dakota, and New Mexico.

Now, if we contrast this to roughly the same period this year, we had at that same period 1,784 cases. If we assume that this is, again, not quite half of the cases for this year, it would appear that we are not going to have quite as many cases this season as last season.

However, we do already have 39 states and the District of Columbia affected: meningitis and encephalitis cases number 632, West Nile fever cases number 721. There have been 56 deaths at the time of this report, with a median age of 75.

At the time of this report, 3 states had had over 100 reported cases, accounting only for two-thirds of all of the cases: California; Arizona; and, once again, Colorado.

Next slide, please. Here you see the West Nile virus human cases by week of onset, 2003 in pale blue versus 2004 in burgundy, I guess. And you can see that in 2004, we had an earlier rise in the number of cases and that through the beginning of July. There were actually more cases per week of onset than there were in the previous year.

Next slide, please. For the blood donation surveillance events, I am again going to go ahead and show you some maps comparing what you learned at this time last year to what the ultimate reality of the 2003 season was.

Next slide, please. Here is what you were shown last year with 495 donors reported as of September 17th in 2003. You can see that they are predominantly central. There is some crowding in Nebraska-South Dakota.

Next slide, please. By the end of the year, it has become much more dense throughout the Midwest. And you now have coast to coast events.

Next slide, please. Here, as the

information we had on presumptive viremic donors as of October 4th, 2004, you can see that we are already coast to coast but not particularly dense in the number of cases that have occurred in any one area.

Next slide, please. Last year at this time, there were 495 presumptive viremic donors reported in 20 states. This turned out to be approximately 60 percent of the ultimate total that were reported to the CDC, which was 818. The top four states for reporting presumptive viremic donors were Colorado, Nebraska, South Dakota, and Kansas.

This year, at roughly the same period of time, we had 157 presumptive viremic donors that had occurred in 20 states again. The most common four states for reporting were California, Arizona, Texas, and New Mexico, in this case an entirely new set, as opposed to the West Nile virus illness in general.

Next slide, please. How have we done in terms of our ability to prevent transfusion-associated transmission? Well, we have decreased both our numbers as well as the viremic load of the donations that have been affected. In 2002, plasma from 16 implicated donations had virus titers ranging from 0.8 to 75.1 plaque-forming units per milliliter, with a median of 10.5 plaque-forming units.

In 2003, plasma from four implicated donations had virus titers ranging from 0.06 to 0.5 plaque-forming units per milliliter, with a median of 0.11 plaque-forming units per milliliter.

This year, at the time of this report, we had one implicated donation with a viral titer of approximately a .12 plaque-forming units per milliliter.

Next slide, please. I'm going to give you a summary. And immediately afterward, I'm going to give you more information through Dr. Jennifer Brown. Overall what we have seen is that widespread West Nile virus activity has covered almost all of the continental United States, with New York, the original site, still reporting human cases. There has been continued westward expansion with human cases reported from all states except Alaska, Hawaii, Maine, and Washington.

The concentration of presumptive viremic donors has occurred in those areas that have the highest concentration of infection rates in general. We do continue to investigate possible transfusion-associated transmissions. And we have not seen this year that our West Nile virus transfusion-associated transmission rate is at zero.

Next I would like Dr. Jennifer Brown to give you the update as of earlier this week. Thank you.

DR. BROWN: Thank you.

So as Dr. Smith pointed out, we are continually receiving new surveillance information. And I put a few slides together just to update you on what has been happening over the past couple of weeks.

These data are current as of October 19th, which was Tuesday of this week. And as of that day, there were only three states left that had not reported any West Nile virus activity in 2004: Alaska, Hawaii, and Washington State.

In the Northeast, we have seven states that have reported West Nile virus activity in birds, mosquitos, or in horses but have not reported any human cases in 2004.

Next slide, please. So the current human case count is 2,151. And those cases have been reported from 40 states and the District of Columbia. About 35 percent of these cases have been cases of West Nile neuroinvasive disease and about 41 percent have been cases of West Nile fever, but there's a substantial number of cases that have not yet been classified. So we will be looking for those case

classifications to be updated as we receive more information from the health departments that are doing those investigations.

Sixty-eight of those cases have been fatal so far. The median age of the decedents has been 74 years. And no one under the age of 43 has died as a result of West Nile virus infection.

Next slide, please. So here is a map, to give you a visual. You can see that we have had a quiet year in the Northeast in terms of human cases, but that does not mean that West Nile virus has been absent from those areas. We have evidence of transmission in birds and mosquitos in all of those states that are colored in green.

The states that are colored in blue are states that have reported human cases. And, as you can see, Washington has reported neither ecologic activity nor human cases, but with newly reported ecologic activity and human infections in the State of Oregon, it seems likely that either late this season or next year, we will start seeing some West Nile virus activity in Washington State.

Next slide, please. So this is the top ten in terms of reporting of human cases in 2004. And, as you know, California, Arizona, and Colorado

have reported the highest numbers of human cases. They currently account for about 62 percent of that 2,151 cases that have been reported so far.

One of the things that I wanted to point out to you as you look at this slide is that several of the states shown here are states that have experienced epidemic activity in past years but are still continuing to report substantial numbers of cases.

In particular, Louisiana and Illinois are states that were foci of the epidemic in 2002. Each of these states reported hundreds of cases in 2002 but then continued to report substantial numbers of cases in 2003 and 2004.

So, for me, this illustrates the need for continued vigilance, even in areas that are not currently experiencing epidemic levels of West Nile virus activity.

Next slide, please. As of Tuesday, we had 191 presumptively viremic donors reported to CDC from 23 states. And, as Dr. Smith reported to you, the highest numbers of donors had been reported from California, Arizona, Texas, and New Mexico. Three of those presumptively viremic donors had gone on to develop West Nile neuroinvasive disease or meningitis,

encephalitis, myelitis, or other CNS pathology. Forty-five have gone on to develop symptoms of West Nile fever.

Next slide, please. This is the presumptively viremic donor map updated as of Tuesday. It's not much different from the one Dr. Smith showed to you. The one thing that has been added is that a green triangle marks the county of residence of the transfusion-associated transmission case that was reported in the September 17th MMWR.

Next slide, please. I do have a little bit more information to report to you. We have learned of a second probable case of transfusion-associated transmission. That is still under investigation by the State of Michigan.

The donor was an Illinois resident who donated blood in Iowa and subsequently became ill. The donation was nonreactive by Mini-Pool, reactive by individual donation testing. The donor has seroconverted.

The platelet recipient is a Michigan resident and does reside in an area where there is West Nile virus transmission. And the recipient has not developed symptoms of West Nile virus infection but has seroconverted.

Next slide, please. The question that everyone is asking us at CDC is, what is going to happen in 2005? There are only a few things that we can say with any degree of certainty.

Next slide. First, human cases will continue to occur in areas where West Nile virus has already been identified.

Next slide. Second, the geographic range of West Nile virus will continue to expand through the movement of infected birds.

Third, epidemics will occur in areas where conditions are favorable. But, unfortunately, we can't tell you right now in the Fall of 2004 where areas of epidemic activity will be in 2005. And that's why on the next slide we see that surveillance is critical for early identification of epidemics. That's why it's so important for us to look for West Nile virus activity in birds, mosquitos, horses, and blood donors, and to look for human cases as well because that's the way that we learn where epidemics are developing. And hopefully we can learn about them in time to implement public health interventions.

Next. And, finally, I'd like to conclude by showing you the faces of some of the people that are responsible for the collection and analysis of

ArboNet data. Some of them are shown here, and some are shown on the next slide with the ArboNet team.

Dr. Smith and myself are both available to field your questions if there are any.

ACTING CHAIRMAN ALLEN: Thank you both.

Yes, Dr. Lew?

MEMBER LEW: Since we know reporting is what I consider the tip of the iceberg, what do serologic studies show in terms of how many people will actually be infected every year? And when do you think you will reach a point where the majority will be --

DR. BROWN: Well, we know from past years' serosurveys that have been conducted in areas of epidemic transmission in the Northeast, in New York City, and Connecticut; in Louisiana, where an epidemic took place in 2002; in Rumania, where a West Nile virus epidemic occurred in 1996.

Population-based serosurveys conducted after West Nile epidemics in those areas showed that overall at a population level, the seroprevalence of infection was no more than two to three percent. And so it's unlikely that at this point, even in areas that have previously experienced West Nile virus epidemics, that we have reached a level where

background immunity in the population would be adequate to protect against future epidemics or future infections.

ACTING CHAIRMAN ALLEN: It does seem that we've got a slightly different pattern in the United States than we have ever been aware of in any other country. New York now is in its sixth year of reported cases, even though it was a fairly small number of human cases this year.

So we may find that if you consider the United States as a whole, we may become an endemic country for continued West Nile virus activity.

DR. BROWN: Oh, certainly. One of the things that we can say with certainly is we will continue to see cases of West Nile virus. What remains to be seen, since the virus is so new, we are still learning about its ecologic behavior.

And so what we don't know yet is whether it will fall back to a level of endemicity where we will only see sporadic cases, as we do with St. Louis encephalitis, punctuated by irregular and unpredictable outbreaks, or whether we will continue to see what we have seen so far, which is sporadic cases in some states, modest levels of activities in others, and epidemic levels of activity in still

others. We will just have to keep watching to see what happens.

ACTING CHAIRMAN ALLEN: One other question just for clarification. Of the total reported human cases, that includes the asymptomatic virus-positive people if you become aware of them as well as those with West Nile fever and West Nile meningoencephalitis?

DR. BROWN: No. That's a very good question. ArboNet -- when we discuss reported cases, we are referring to the case definition for West Nile virus disease that has been developed by the Council of State and Territorial Epidemiologists. And that case definition refers only to symptomatic cases.

We track presumptively viremic donors separately. So the mechanism for tracking donors allows us to track people who are asymptomatic, but when I reported those 1,251 cases, those are only cases that meet the national case definition for West Nile virus illness. So an asymptomatic donor would not be included in that count.

The donors that did, those 48 donors that did, go on to develop neuroinvasive disease or West Nile fever, they are included in that overall case count. So that's why we present the case count

separately from the donor count.

ACTING CHAIRMAN ALLEN: Okay. There was still a, however, category. If you add up the meningoencephalitis and the West Nile fever, that still doesn't total 100 percent, however. Are those just not classified yet?

DR. BROWN: Right. Those are not all asymptomatic donors. Those are cases that have not -- their clinical syndrome has not yet been classified. And they're still under investigation by the state health departments that are tracking them.

ACTING CHAIRMAN ALLEN: Thank you.

Dr. Doppelt?

MEMBER DOPPELT: I just had a question to follow up to that. On one of those slides, I think you said it was 35 percent had neuroinvasive disease. So depending upon how you're counting, what's the *n*, the number infected? So I assume that that means that the total percentage of neuroinfected is not really different this year than last year or not?

DR. BROWN: That is hard to say. Thirty-five percent of the cases that have been reported to us have been classified as neuroinvasive illness. Because so many of them have not yet been classified, it's difficult to say. That's kind of a

moving target.

It's difficult to say what the final -- what proportion of neuroinvasive disease cases, how much they will contribute towards the total number of cases reported. And, as you have pointed out, the proportion of neuroinvasive disease cases as a proportion of the total number of cases reported is not the same as the proportion of neuroinvasive disease cases as a whole of the entirety of people who are infected.

We think that about one in 150 West Nile virus infections will result in neuroinvasive disease. So it's not that 35 percent of everyone who is infected with West Nile virus gets neuroinvasive disease. The actual number is quite smaller.

ACTING CHAIRMAN ALLEN: Dr. Lew?

MEMBER LEW: Have you had a chance to see of the people who fit in the definition -- in other words, how good is your definition for West Nile for reporting when you have ability to test that they actually are positive? I mean, has it been validated some, the definition that you have?

Just like initially with the HIV epidemic, there was criteria to make the diagnosis. But then later we have testing.

DR. BROWN: Yes. The case definition that we use ha two components. One is the clinical component, and one is the laboratory component. And so in order to meet the case definition, a case must first meet the clinical criteria for diagnosis.

But then they must also have one of the laboratory criteria for diagnosis. And these laboratory criteria we are very comfortable have a very high positive predictive value for being cases of West Nile virus illness.

ACTING CHAIRMAN ALLEN: Dr. Williams?

DR. WILLIAMS: Alan Williams, FDA. Pertinent to the questions being posed to the Committee today, of the two presumptive transfusion cases under investigation, the first my understanding is the donor did not report having any symptoms prior to the donation. Do you know what the situation is with respect to the second donor under investigation?

DR. BROWN: I only have very limited information about that case, but it is my understanding -- and I'll ask Dr. Smith to jump in if she knows more, but it's my understanding that this was a case where the donor became ill following donation and the investigation resulted as a result of the donor notifying authorities.

ACTING CHAIRMAN ALLEN: Dr. Nakhasi?

DR. NAKHASI: Hira Nakhasi, FDA. Dr. Allen, I just wanted to have clarification of what Jennifer Brown said. You know, you were asking, do you think in Europe or other countries, why the U.S. now is sort of developed and Peter has it.

There was a paper last year in *Science* where they described the differences between the mosquito population here in the United States and Europe is different. So that's why the difference possibly could be, that they have much more endemic, they have become better or worse of that. And you have the better -- you know, you have epidemic currently going on.

And because other of the differences are hardly because the European population and the U.S. population more or less are the same basically.

DR. BROWN: That is a very good point in that the differences in the mosquito populations could be one factor that influences the behavior of West Nile virus in the United States. That may be one thing that makes West Nile virus different in the U.S. than in Europe.

DR. NAKHASI: Yes.

ACTING CHAIRMAN ALLEN: Okay. Dr.

Kleinman?

DR. KLEINMAN: Yes. Steve Kleinman. I have one comment and one question. The comment is more for the Committee, just to be clear that the number of positive donors reported to CDC through ArboNet or whatever, AlterNet, whatever it's actually called, are actually fewer than the number of West Nile virus donors that will come up in the next several presentations because not every state gets the report and reports it on to CDC.

So that's just a comment, although I think it is interesting that the relative proportion of cases dropped significantly in 2004, both in CDC's data and in the blood center data.

My question is a more general one. Have you seen or have you been able to assess the effect of mosquito-spraying programs on the progress of West Nile? I know it's a county by county or state by state decision, but what is sort of the general climate of whether effective places spray for mosquitos or not?

DR. BROWN: At CDC, we do feel that mosquito control is an important component to West Nile virus case prevention, but it is very difficult to do a scientific assessment or to quantify the

degree to which cases can be prevented by spraying. That is because mosquito abatement districts tend to vary by community.

And in order to answer that question, you would have to find two mosquito abatement districts with different vector control programs, but those two communities would have to be similar in every other way. It is extremely difficult to find that set of circumstances where you could answer the question of whether it was only the mosquito control that was making the difference in cases.

So we are looking, our entomology group is looking, at ways to answer that question, but it is very difficult. That being said, we do feel that vector control is a very, very important part of case prevention, especially in epidemic areas.

DR. KLEINMAN: Yes. And do you have a sense on at the community level how frequently communities are actually doing this versus not spraying or is that just so individual that it is hard to answer?

DR. BROWN: That is another thing that tends to vary a lot by community. In Maricopa County, for example, in some residential areas, there was a high degree of resistance and some political

resistance as well to doing aerial application of insecticide, where in some more rural areas, it's no problem at all.

So that's another thing that varies from community to community. And that's another reason why it makes it so difficult to do scientific studies to try to quantify the degree to which this is effective.

ACTING CHAIRMAN ALLEN: We are getting a little afield here in terms of spraying. And I realize the relationship. I personally would love to continue the discussion.

We have got a schedule to adhere to. We will take questions from two other people at the microphone and any others from the Committee directly.

DR. BUSCH: Yes. Mike Busch from Blood Systems.

Of the two cases breakthroughs, probably breakthroughs, issues, one of them, as you indicated, is reported to MMWR. It was a Blood Systems case where we had our system to turn on individual donation NAT, but it basically was not completely ready to operate in early June. The epidemic started earlier. Had that system been in place, we're confident that that donation would have been screened by ID-NAT and interdicted.

The second case you mentioned, you indicated that it was ID-NAT-reactive. Was that ID-NAT performed by the test of record at the blood center? And also I think, to my knowledge, all of the transmissions from prior years and this year have been IgM-negative. Was that additional case tested for serology?

DR. BROWN: I do not have the personal familiarity with that case to be able to comment, but perhaps Dr. Smith.

DR. SMITH: Hi there. We are in the midst of getting this one settled. So I'm afraid that we haven't shared all of our information. We tried to give you enough to let you know that this has occurred. So I apologize that I haven't given Jen all of the information she could share with you.

This case came through during a time when the blood bank was doing Mini-Pool testing. There had actually been no positive Mini-Pools. So there was no trigger that could have been sent off to switch to ID-NET. And in retrospective testing of the plasma, it was IgG-negative.

DR. FITZPATRICK: Mike Fitzpatrick from America's Blood Centers. Just one question.

You stressed the importance of

surveillance on prediction and looking at what has happened with the epidemic. A number of states and counties have stopped surveillance of birds, and I just wondered what the impact of that is on your data and what the future holds for those areas that are no longer doing that surveillance.

DR. SMITH: Many places have chosen to stop surveillance for birds this season and will reinstitute that in the spring. Once you have a positive bird, it doesn't gain you more information to have more positive birds in any one particular county.

I don't know of anybody that has said that they will not be accepting for a new season reports of dead birds that they would want to check.

Thank you.

ACTING CHAIRMAN ALLEN: Dr. Lew?

MEMBER LEW: Just as a follow-up to what Dr. Williams had mentioned. And I can stand for clarification, but my understanding is about one in 150, as you mentioned, or one percent or less has encephalitis, 20 percent with West Nile fever-like, but the vast majority of people with West Nile infection are asymptomatic. So that is going to be a problem.

DR. SMITH: Also, for the clarification of

the numbers, currently this is not a disease that is required to be reported. So we're not going to get 100 percent of the neuron base of numbers or 100 percent of the West Nile virus fever numbers, which is also going to make the percentages then different. In the coming year, meningitis and encephalitis will be reportable.

Thank you.

ACTING CHAIRMAN ALLEN: Thank you, Dr. Smith and Dr. Brown, for a very nice update. I hope both of you will be available later in the day if people want to engage you in discussions or we could go on for hours.

Our next presentation we're going to get back more directly to blood collection center experiences, duration of viremia, and experience with individual NAT testing, Dr. Michael Busch from Blood Systems.

DR. BUSCH: Thank you.

C. DURATION OF VIREMIA/EXPERIENCE WITH ID-NAT

DR. BUSCH: This is a project that obviously involved lots of collaborators to characterize both the index donation and the serial follow-up samples as well as some other studies correlating viremia with the total infection rates in

the population. So, again, the collaboration by several companies as well as Blood Systems. And this was supported by NHLBI and CDC and Blood System Foundation.

Next slide. Actually, the insights into the natural history of West Nile virus I think are able to be significantly enhanced and expanded with the implementation of donor screening because, really, for the first time with donor screening, we're detecting humans within the acute viremic phase of infection and are able to then follow them to understand better the evolution of viral immune markers and pathogenesis questions.

So, really, we're very interested in further studying these issues, both with respect to the donor screening and deferral policies we're talking about today, but also I think we're generating data that has insights into the diagnosis of the infection in clinical populations and also the pathogenesis issues.

So I am going to summarize for you four studies that we have been doing relevant to the question of viral dynamics. The first is just analysis of the index donations, the yield donations themselves, then a study where we have correlated the

yield of Mini-Pool NAT with the cumulative incidence of West Nile virus in a particular state, an epidemic region.

Of relevance to this discussion, this analysis has allowed us to estimate the duration of the window period that Mini-Pool NAT detects. That, in turn, actually allows one to use that understanding of that window period to estimate total infection rates in the population.

The next analysis is a study that Blood Systems did where we did a large amount of individual donation NAT testing of samples that had been Mini-Pool-negative from 2003. By analysis of that data, we have been able to estimate the lengths of the window period that is detectable by individual donation that prior to Mini-Pool-detectable levels of viremia as well as the subsequent windows that are detectable by ID-NAT with antibody, either IgM or IgG.

And then, finally, an analysis of the sero follow-up data from about 180 viremic donors in a determination of the lengths of the window periods to both seroconversion and to persistent detectable NAT reactivity by replicate individual donation NAT.

Next slide. So in terms of the index donations, all of the data I will be presenting is

based on Blood Systems laboratory screening using the GenProbe platform in 16-unit Mini-Pools.

The viremia levels were determined with a target capture real time PCR assay developed at Chiron. And the serology is based on focus technology assays.

Next slide. So at Blood Systems, we screened -- this is all data from 2003 -- 680,000 donations, 230 confirmed viremics. Of those, you can see about 80 percent of them were detected by Mini-Pool NAT and 18 percent were detected either through the retrospective or prospective ID-NAT testing.

If you look at the index donations in terms of their antibody status, overall 20 percent of the viremic donations that we picked up had antibody in them but a very different rate of antibody depending on whether the units were detected by Mini-Pool NAT.

The Mini-Pool NAT screened units, only eight percent had IgM-detectable; whereas, the samples that were ID-only that were missed by Mini-Pool but detectable by individual donation NAT, the vast majority, 75 percent, had IgM antibody, indicating that most of those were in the post-acute viremic

phase as IgM was developing.

Next slide. This is just a conceptual window phase evolution of the primary viremia. I don't know if anybody has a pointer. No. So, in any event, the overall viral load of the Mini-Pool yield donations, which we're calling stage 3 here, the samples that are detectable by Mini-Pool NAT, are about 2,300 copies median, mean of 37,000 copies. And you can see that there are some lines drawn that represent the limit of detection of Mini-Pool NAT, which is about 80 copies per mL; whereas, if you test the samples individually, the viral load can be as low as 5 copies per mL and be detectable.

Next slide. This shows the distribution of the units that were detected by Mini-Pool NAT, either with IgM, on the left, or without IgM, on the right. So what you can see is that the samples again, all detectable by Mini-Pool NAT, that had IgM had a very low viral load. The median was 198 copies per mL; whereas, the samples that lacked IgM had a much higher viral load. So these are the tail end.

In fact, if we go back one slide, please, you can sort of see that what we're picking up with Mini-Pool NAT, the vast majority of them are prior to IgM seroconversion, but we pick up a small portion of

units that are on the down slope of viremia, so have low viral load in the presence of IgM.

Next slide. Next slide, please. So the next analysis I'm going to summarize is the correlation of Mini-Pool yield to infection rate in the population. This is a study that was done through the Reds Program, where all of the donations from North Dakota that had available aliquots, which had been screened by Mini-Pool NAT and actually also screened by individual donation NAT, we went back and we performed IgM testing on all of the available samples. And then we analyzed the data, the weekly data, of Mini-Pool NAT yield over time. We had 28 Mini-Pool NAT yield units.

Next slide. And then again we performed IgM testing on about 4,000 samples to understand over the course of the epidemic how was the IgM conversion evolving. We also went back about nine months later and sampled another 1,000 donations from this same region. And we performed both IgM and IgG testing on those collections about six months out from the epidemic, from the exact same donor pool.

Next slide. This slide is a summary of the results of that testing. Again, from North Dakota, we are starting over here in July and running

through October. And then we come back in May of '04 and have additional data six months later.

You can see the goal here is the Mini-Pool yield occurring. So we begin with some early yield of viremic donations. About two or three weeks later, we begin to see IgM conversions accruing in the population.

And then after Mini-Pool yield has completely disappeared, the IgM rates in the population begin to plateau. And they end up peaking at 5.2 percent. So this is the infection rate in the donor population that corresponds to this yield of Mini-Pool NAT that was observed in that same donor pool.

When we went back six months later, the IgG rates were 5.3 percent, so essentially identical to the early IgM rates. But by that point, the IgM in the donor pool had waned to 1.1 percent. So IgM, a transient marker, had begun to disappear. These numbers here give us the total infection rate in the population.

Next slide. A couple of observations from this. I think that, as you can see, IgM really comes up a little bit later than that, so wouldn't be an early marker, a good screening tool for the early

viremic phase. It peaks three to four weeks after detection with peak IgM rates about four times the Mini-Pool NAT yield peak rates.

If we are concerned about a tail end low-level viremia, actually, IgM could be argued to have some value because it is picking up all of the convalescent infections. And, as you will see later, ID-NAT itself even performed individual donations but only once, is not able to detect all of the low-level viremic subjects. So some people are coming in at the tail end of the epidemic who would be detectable by IgM but have viral loads that might be so low that even individual donation NAT wouldn't pick them up.

Next slide. Late in the epidemic, if we were to screen for IgM, we'd lose a lot of donors. Over five percent of donors in a high-activity region would be seroreactive. And, yet, the risk of these units is extremely small, if any.

After six months, IgM rates have dropped to 20 percent of their peak. However, what that tells us is that IgM screening in a subsequent year would still have some tail of prior year seroreactives coming into the next year epidemic. So it tells us that it's very difficult to use IgM or serology in general to estimate risk once you have seen an

epidemic in a prior year.

And then, finally, even in a highly endemic region, as discussed earlier, the vast majority of donors were never infected. So there's still clearly going to be a susceptible population and, therefore, a potential need for continued screening.

Next slide. From an analysis of that relationship between the Mini-Pool yield data and the total infection rate in the donor pool, David Wright at Westat was able to derive the length of the Mini-Pool window period. And that's 6.9 days with a confidence bound shown here.

This is a very important parameter to understand because it, in turn, allows us to benchmark off the length of the Mini-Pool window period to estimate the lengths of other window periods.

It also lets us use that window period and national Mini-Pool yield data to estimate total infection rates in the population. In fact, we have estimated that during this year by compiling the national data for Red Cross and CDC, that something in the range of 750,000 people were infected with West Nile virus in '03 based on the Mini-Pool yield data in the country and the length of this window period.

Next slide. I'm just going to skip this. This is the statistical modeling that was needed to derive that window period estimate from that relationship between the Mini-Pool yield over time and the seroconversion rate.

Next slide. Okay. The next study I want to summarize -- and this will all tie together at the end -- is our large-scale retrospective testing study. So this was work that was done with strong encouragement from FDA in 2003.

When we realized the epidemic was so massive and there were some breakthrough transmissions, we began to save samples from high-yield regions that had been negative by Mini-Pool NAT but, again, from regions that had high yield. And these samples were tested by individual donation NAT.

If they were reactive, we immediately tried to retrieve any untransfused product, confirmed that the donors were infected based on both analysis of the index sample and follow-up of the donor, and then collaborated with CDC in terms of investigation of recipients, who were transfused with units that came from donors who were ID-NAT-only reactive and confirmed positive.

Next slide. So overall we tested 23,000

donations that had been Mini-Pool NAT-negative by individual donation NAT. And in the three areas which had high activity, we picked up 30 viremic units. Toward the end of the year, we also turned on prospective ID-NAT in the Dakotas.

Once we started to see the data showing significant low-level viremia, an additional 4,000 donations were tested prospectively, yielding an additional 17 viremic donations.

Fourteen of these 17 were ID only, meaning that they were negative when retested at one to 16 dilution. So three of these would have been picked up by Mini-Pool. So we have 14 plus the 30. So we had an overall 44 additional infected donations that year detected by ID-NAT.

Next slide. And this is data, then, showing the evolution of the detection over the course of the two-week intervals over the course of the epidemic, specifically focused on North and South Dakota, where every donation was tested, essentially every donation was tested, by both Mini-Pool and ID-NAT.

What you're seeing here are stages of the infection. So the blue bar is units that were detectable by Mini-Pool NAT. This light blue bar here

is the units that are detectable only by individual donation NAT but have no antibody; and then the units that have IgM only, low-level viremics; and then those that had IgM and IgG.

You can see that at the beginning of the epidemic, you have these low-level viremics without antibody, the ones that we know can transmit that are seen actually kind of throughout at some low rate.

But what is striking is you get this high Mini-Pool yield, but then as the epidemic is moving along, you begin to see large proportions of the viremic donations are ID-only units in the presence of antibodies. So these are these convalescence infections that still have very low-level viremia in the presence of antibodies.

Next slide. By analysis of the number of cases in each of these stages -- so in this Dakota region, we had 79 Mini-Pool yield units. These are the number of front-end antibody-negative ID only with IgM only and ID only with IgM and IgG.

And using the 6.9 days that we derived earlier, we can estimate the lengths of these other window periods based on the relative frequency in this sort of serial cross-sectional analysis that we picked up units in these stages. You can see that these are

fairly brief periods.

Overall in this fairly comprehensive analysis, only 66 percent of viremic units were detected by Mini-Pool NAT, but the majority of those that weren't detected were antibody-reactive and we believe probably had neutralized the virus.

Next slide. So this just takes that 6.9 days that we had derived earlier from the cumulative NAT infection rate IgM data and uses that to estimate the lengths of these earlier window periods, the .55, .65, and 2.29 days.

Next slide. Okay. The next analysis is the follow-up of the donors, the last analysis. And what we're looking at here is enrolling the donors per the IND into the follow-up study. It included a symptom questionnaire, which you will hear about later today, and approximately weekly sampling.

The follow-up was to continue until the donors had converted their IgM and tested negative by single ID-NAT. The follow-up included RNA by TMA quantitation and IgM and IgG. And then a subset of over 60 of the panels were further tested to better understand the low-level persistent viremia by performing five additional replicate TMA assays, individual donation. And a number of these panels

were also studied for additional antibodies, including plaque neutralization, by CDC, Rob Lanciotti.

Next slide. Overall 182 of our about 230 donors enrolled in the follow-up study. You can see that the follow-up averaged about 15 days to the first sample, but a number of the donors did come in fairly early on to let us look at early events, an average of 2 and a half specimens per donor.

Just one factual point, which is that at index donation, there were 140 of these 182 who were negative for IgM on the index donation. On the first follow-up lead, 81 percent of them had converted their IgM. In a second follow-up lead, the remainder had converted their IgM. So 100 percent of the people who enrolled into follow-up converted their IgM on follow-up.

Next slide. Just one example. What we're looking at here is the viral load of the index donation dropping to negativity on quantitation, the antibodies kicking up the IgM, the IgG. And here is plaque-neutralizing activity. In every case, plaque-neutralizing activity was observed concurrent with the development of IgM antibody. So the antibody is effective at neutralizing virus in an *ex vivo* mixing type analysis.

What you see down here are the percentage of the six replicate TMAs that were performed on all of the serial bleeds. And you can see that the viremia is detectable out to here. And then as you out in time, only a small proportion of the six reps may be reactive.

We had examples in our data by the singlet follow-up TMA of people who were negative and then came back for another bleed and were positive. And so we were seeing flip-flops that were of concern.

By doing the six replicate TMAs, we no longer had any of them. We could basically show that what was really going on was just a waning viremia and that it was the probability of detecting that low-level viremia that led to an occasional negative followed by a positive. But by doing the multiple reps, it was all a smooth transition down in viremia.

Next slide. Just another example.

Next slide. So the analysis of that data was done by David Wright using what's called interval-censored longitudinal analysis modeling. And what we looked at was the time from the index donation to IgM and IgG seroconversion as well as the time to loss of RNA from the index donation by a singlet TMA assay and also the times between these differen

seroconversion and RNA loss events.

And then for the subset of 56 cases that we did the 5 replicate TMA assays on 580 follow-up samples, we were also able to look at time from index to loss of RNA by 6 replicate TMAs, so a more sensitive quantitation of detection of viremia.

Next slide. This just shows these window periods. So this is these people are being detected at some point in the Mini-Pool NAT yield window phase. We're assuming on average they're being detected in the middle of that period. And then this is the time, 3.4 days to IgM, 7.6 days to IgG, 11 days to loss of RNA by singlet ID-NAT, but an additional 6 days if we do the 6 replicate ID-NAT assays. So these are the critical parameters.

Next slide just summarizes the statistics around these estimates. I don't have time to go through these, but you have them in your handout. And you see confidence bounds. These confidence bounds are confidence bounds around the mean. So this is how accurate is this average time from Mini-Pool NAT positivity to IgM?

For this discussion, the most important parameter is down here, how long after Mini-Pool positivity to negative ID-NAT, again 11.2 days, or to

negative 6 replicate ID-NATs, an additional 6 days? And if you want a 99 percent inclusion bound, then you would take the standard error times 2.3. And you end up with about 31 days to negative RNA by singlet TMA from the index donation date.

Actually, if you add any replicates reactive, this gets out to about 38 days. So this is the outer limit of detectable viremia, even doing six replicate TMA assays.

Next slide. Then this is just rolling it all together. One interesting observation actually Steve Kleinman noted is our estimates for the length -- this is the data I showed earlier based on the retrospective testing at Blood Systems. And the window periods are a little bit shorter here than we derive by following the donors longitudinally.

This may relate to some symptom-based self-deferral after the people have gone through primary viremia. They may be less inclined to come in and donate blood because of symptoms. And, therefore, that's why we're not seeing as many donors and this window period is not imputed to be as long based on the rate at which donors give in this tail end viremic phase compared to what is seen when we actually follow viremic donors prospectively.

I don't think these differences are probably statistically significant, but it suggests that there may be some symptom-related deferral occurring after the primary viremia, which is what is understood. The symptoms are all believed to occur after the primary viremia and reflect the immune response.

Next slide I think is just conclusions. Oh, just the important question of lookback, how many of these units are infectious. In our large ID-NAT study collaborating with CDC, we had 27 confirmed viremic donations that components were issued and potential recipients exposed. Twenty-one of those were low viremic antibody-positive, 6 antibody-negative.

Unfortunately, despite extensive testing and work by CDC, we were only able to ascertain recipient outcome in four cases. Two of two recipients that got ID-only IgM-negative units were infected, and zero of two recipients of a donor who was ID-only and IgM and IgG-positive were infected.

So, despite the extensive retrotesting to trigger additional lookback, there were very few outcomes defined. Really, the other idea, and it's in progress, is to look at animal inoculation studies.

There's primate studies being planned by CDC and Darin Maria with Harvey Alter.

We've done some recent Murine knockout model -- next slide -- I think last slide -- just -- this is a model where these mice have been genetically engineered to lack certain immune response functions, interferon and alpha beta receptor knockout.

These mice are extremely susceptible. Unlike wild-type mice with 100 plaque-forming units, you only get a proportion dying. These knockout mice are extremely susceptible down to .1 plaque-forming units kills these mice and they have rapid outgrowth of viremia.

So we did infuse -- Michael Diamond infused 500 microliters of plasma from five of our units times two into these knockout mice. And we were able to show transmission in this model using one of the breakthrough transmission cases, the Nebraska case from last year.

So we're continuing to study this model to put in the IgM reactive units or do mixing studies, adding early seroconversion samples to these infectious units to try to further determine the infectivity of these convalescent donation samples.

Next slide. So in summary, you know, I

think what we've seen is that we're seeing a logical progression of conversion of antibodies, both IgM, IgG, and plaque neutralizing activity immediately after the viremic donations.

The low level viremia, though, is persistent in the setting of the antibody for about 11 days and it actually extends another six days if you do multiple replicates. And this critical question still remains, are any of these infectious? Again, to our knowledge, there's never been a transmission linked to any of these seroreactive low viremic units.

Thank you.

CHAIRMAN ALLEN: Thank you, Dr. Busch, for a very elegant presentation. A lot of data collected under sort of make the rules as you go kind of a situation. Very nicely done and saved a number of possible transfusion-transmitted cases in the process.

Comments, questions from the Committee? Dr. Klein?

MEMBER KLEIN: Mike, you make the point that there is really no scientific evidence that there has been any transmission by any of the cases that have endogenous IgM antibody. Do you think that the passive antibody studies that are being done really are going to help you in that regard given the fact

that with other diseases total prevention of infection with passive antibody is contrasted with endogenous antibody is questionable?

DR. BUSCH: You mean a high titer -- the immunoglobulin prep that's being developed? I mean it all depends on when you give it. In animal studies, you know, if you give it before you expose, you can neutralize.

If you give it literally, you know, concurrently or within hours of the inoculation, you may be able to either, you know, abort infection or suppress the viremia that occurs with infection.

So, yes, so I doubt they'll be proven to be effective. You know the majority of people during the primary phase are completely asymptomatic. So the only way you'd pick them up is with nucleic acid screening. So it's to me by the time you would identify a case clinically, they've already seroconverted themselves.

MEMBER KLEIN: I'm also thinking about whether that would help you in terms of saying that well maybe some of these IgM-positive infections would be infectious. And I'm not sure that demonstrating the path --

DR. BUSCH: Right.

MEMBER KLEIN: -- of antibody does or doesn't --

DR. BUSCH: Yes.

MEMBER KLEIN: -- is going to help you there.

DR. BUSCH: Exactly. The other problem we're realizing now after we've sort of worked with Michael Diamond on this mouse model is these animals are markedly immunosuppressed. So if we show -- you know we may not see when we add antibody to a viremic donation and then we put it into an animal that's completely immunosuppressed, the ability to clear and eradicate that complex virus may not exist. So --

CHAIRMAN ALLEN: Yes, Dr. Kuehnert?

MEMBER KUEHNERT: You mentioned that through your data approximately, I think it was 33 to 38 days duration of viremia from the time of donation, and -- but you also sort of passed through quickly one slide that showed one particular donor that seemed to be beyond that.

And I wonder if you'd comment if that is an outlier or what were you --

DR. BUSCH: Right --

MEMBER KUEHNERT: -- showing in the data.

DR. BUSCH: -- that's -- right. We had

one donor who was initially -- it was one of these flip-flop cases where we had a sample -- I forget exactly but something like 30 days it was negative but the donor happened to come back in like at 42 days, you know, before we had the results on the prior donation that would have said you don't need to come back anymore, they came back and got another bleed.

It was reactive on one of two initial reps. We went back and tested that six more times. And one of six additional reps was reactive. So it was overall, I think, five more times, so two of seven reactives overall.

And that is the outlier case. And this distribution of the length of the tail of viremia, again the modeling currently assumes a normal distribution. Clearly there will be some people who may have, you know, for whatever reason, a longer tail of viremia.

MEMBER KUEHNERT: But it was just the one?

DR. BUSCH: But again, if you look at that case, there were long bleed intervals between that date -- so it was like 30 to 42 days. And then the donor came back again like at 70 days and was completely negative. So when in those intervals, you know, viremia was resolved --

MEMBER KUEHNERT: Okay. And the other question I had, and I'll ask Sue this also, about a question that came up earlier about presumptive viremic donors and how many of those are confirmed. I wondered if you could comment on that.

DR. BUSCH: Well, it's an interesting issue because if you screen through Mini-Pool NAT, and then you resolve the individual donation, they had to have had a fairly high level of viremia and virtually 100 percent of repeat reactives, which we do all the time. We do an initial and then we repeat it, which is the definition of presumptive viremic.

Virtually 100 percent of donations screened through Mini-Pool NAT are confirmed of presumptive viremics. If you are screening by ID-NAT, again if it's repeat reactive, it has a virtually 100 percent probability of confirming.

But we also -- a lot of the donations that are picked up by ID-NAT that are real are initial reactive only. When we repeat it, it's negative.

And that's because what we're picking up is this extremely low level of viremia that is stochastically detectable by the initial -- it was fortunate we got it once but, you know, that tells you there's -- and the other factors, there's a lot of