TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

67th MEETING

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Pages 1 thru 283

Gaithersburg, Maryland
September 15, 2000

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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

67th MEETING

Friday, September 15, 2000

8:00 a.m.

Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Welcome and Opening Remarks

DR. SMALLWOOD: Welcome to the 67th Meeting of the Blood Products Advisory Committee. This is the second day of our meeting here. I am Linda Smallwood, the Executive Secretary. Yesterday, I read the conflict of interest statement that applies to both days of this meeting.

At this time, if there is anyone who needs to make any declarations regarding any affiliation that may be perceived as a conflict of interest regarding this meeting, please do so at this time. If not, then we will proceed. I would just like to remind anyone that is speaking, when you go to the mike, please give your name and your affiliation so that it can be recorded appropriately in the transcript.

At this time, I will turn the proceedings of this meeting over to the Chairman of the Blood Products Advisory Committee, Dr. Blaine Hollinger.

Dr. Hollinger?

DR. HOLLINGER: Thank you, Dr. Smallwood. We have two items, basically, this morning. We first start out with some committee updates on several workshops that have been held and several other issues from advisory committees and updates. Then we go into a session on utility of screening blood donors for antibodies to syphilis. That will take this morning.

This afternoon, we then have something on classification of HLA devices and finally a report of an intramural site visit on the Laboratory of Molecular Virology.

So, having said that, we will start off, then, with a summary of the Workshop on Recruiting Blood Donors, Successful Practices, that was held July 6 to 7, 2000.

Gilliam Conley?

COMMITTEE UPDATES

Summary of Workshop on Recruiting Blood Donors Successful Practices

MR. CONLEY: Good morning. It is nice to be part of the opening act for the main events to follow later today.

[Slide.]

In talking about the workshop that we held in Rockville, it was difficult to fit all of the issues into two days, but we pressed a lot of information in a very tight time frame. So it is even more difficult to do a ten-minute or so recap of that.

I was alarmed, as I was making bullet points, that flying past some of these issues in a bullet point almost makes them seem insignificant. Just keep in mind, please, that each of the bullet points would all warrant a lot more lengthy discussion so, if everybody will regard my

presentation this morning as the Readers Digest Condensed Book that was made from the cliff notes of the meeting, then we will all be in the right perspective for what we are working with.

The committee has got a handout of the summary. I will have a correction to that as I go through--a clarification, really--as I go through the presentation. So, even trying to condense it to a three-page summary, I also made mistakes.

[Slide.]

There were a lot of people, when FDA announced that they were going to have this workshop, wanted to know why the FDA was having a workshop about donor recruitment. I have to say that FDA has always been in support, certainly, of donor-recruitment issues but the Public Health Service at large became much more interested when, in 1999, the National Blood Data Resource Center published a report where they predicted significant blood shortages sometime this year.

In defining why we would be involved, certainly, as a member of the Public Health Service Group, the mission to enhance the wealth and well-being of the public is part of our mission and this workshop fits easily into that. The FDA mission of guarding the safety and efficacy of the blood supply in the U.S., likewise, low supplies certainly will

mean that there are safety issues to be concerned about.

But the most important part of the workshop was really to share proven donor-recruitment strategies.

[Slide.]

These are just the basic facts about the meeting, when it was held, where it was held. It was important to a lot of our participants that, being a government-sponsored workshop, they didn't have to worry about registration fees. So some people on tight budgets could afford to come.

We advertised, as best we could, in the short time frame that we had. It was published in the Federal Register and our colleagues at ABC, AABB and the ADRP--and if you are not familiar with that group, donor-recruitment professionals group, all did the best they could to get the information out.

We especially were appealing for donor recruiters or even donor groups to participate in the workshop. Indeed, about half of our participants at the workshop were donor recruiters and we did have a few representatives from donor groups.

We deliberately limited the time for the speakers in the first day. We really put the pressure on them to bring the most important facts out very quickly and in a short time frame. In our second day, we had discussion groups and we used facilitators for our discussion groups,

again to keep them on track. Each group has a focus task to bring back to the main meeting.

I think this time pressure and this focus and this facilitation kept things on track very well for the meeting. Our speakers, for the most part, all rose to the challenge and put a lot of information in a short period of time.

We also asked all of our speakers to be as fact-based as they could. We wanted people who had observations that showed that what they were reporting on was successful over time. In the donor-recruitment literature, it is easy to find anecdotal stories and we did not want to hear that if we have a donor drive that has a luau theme that we get more donors, unless you had done it repeatedly over a number of years and could show that it made a significant difference in how you were recruiting donors.

So that is what we were looking for. In a way, the two-day session gave us both a set of fact-based presentation and then a conventional wisdom because the people who were there, many of whom were donor recruiters, were in our discussion groups. So we compare, in some ways, the things that have been proven versus the things that people at a gut level think work.

You will see, when I present later, places where there was not clear agreement. Mostly, it was because we could see a difference in some of the presentations and what

people wanted to continue doing.

Ultimately, when we started planning this workshop, our goal was to have a guidance document on donor-recruitment. Again, this seemed to set a lot of people's teeth on edge, the thought that the FDA might start setting regulatory guidance about donor recruitment.

In fact, Dr. Epstein clarified at the opening of the meeting that that was not the ultimate goal, that we don't want to get into this in a regulatory way but in a way to encourage blood donation. So we will get into areas where there was clear agreement between the two days and between virtually all the presenters that are key aspects about blood donation and then we will cover where there is not clear agreement.

[Slide.]

This is the area where I am very nervous because a lot of these bullet points look very simple and succinct, but there is a lot of detail and a lot of information that goes behind them. Successful donor-recruitment programs are multifaceted with demonstrated expertise in customer relations, advertising and marketing, public relations and in management issues. It is a wide spectrum of business and marketing practices that have to be applied well to be successful.

Successful programs exhibit a culture of hard

work, innovation and cooperation, at least the speakers who came forward for us and talked about their program. These seemed to be aspects of their programs.

[Slide.]

Successful programs have all the employees in their organization focussed on blood donation and they are all thanking and encouraging donors. This is especially true among the collection staff, the people who have the most face-to-face contact with the donors. Successful programs emphasize panel recognition and there is a difference between recognition and giving incentives and gifts.

We heard, over and over again, that the long-term donor who is the altruistic donor who is donating for internalized reasons really can be turned off by incentives. But what they are not turned off by are those constant "thank you"s, the encouragement, the celebration dinner for your multi-gallon donors once a year, public recognition of the importance of their altruism and those kinds of issues. That is what we mean by donor recognition.

So it is important that their altruistic behavior be reinforced at each donation and at notable milestones in their donation history.

[Slide.]

When it comes to advertising, successful programs

are keyed to an emotional appeal. They put a human face on both donors and transfusion recipients. Pictures of empty blood shelves don't really cut it. They don't do anything. Those that tell the story of a transfusion recipient or tell the story of a long-term donor, those advertising appeals and campaigns do have an impact.

Advertising campaigns can definitely benefit from partnerships. And we heard about partnerships with sports teams, t.v. and radio stations that have been very successful. Paid advertising, especially, also seems to bring other benefits in that the donor centers establish a relationship with the local t.v. and radio stations. We were told that then, when they have to go on appeal and there are public-service announcements made, they seem to appear in better time slots when you are already also a paid customer. So there is a spinoff benefit.

It was also noted, though, that advertising, although it increases awareness, it does not put a donor in the chair. People don't come flooding to your donor center because they have seen your latest well-conceived, high-impact ad, no matter how much of a human face you put on it. To put a donor in the chair, you still need to ask them to donate and preferably one-on-one face-to-face.

Successful corporate campaigns are those campaigns that are run usually by a large corporation and they work

when you have buy-in and support from the top management of the organization that you are working with. They also seem to have a natural growth pattern in that once a corporate campaign has been successful, the executive officers of that company like to challenge similar companies to do the same thing. And so there is a natural growth pattern to corporate campaigns.

[Slide.]

Successful telemarketing, and telemarketing includes those annoying people that always call you at dinner time to try to sell you something. But blood-donor centers have also used it successfully to call their donors to schedule them for new appointments or to remind them of existing appointments.

These seem to work well when they are linked to a real-time donor database. By real-time donor database, I mean that when I am sitting down as a telemarketer to make my calls, I am not calling you when you just donated at 1:00 p.m. this afternoon and annoying you with an evening phone call.

Instead, I have got real-time data that tells me what your donor history is. Similarly in my database, when I call you, I know, based on your donor history, when you like to donate, where you like to donate. I know your blood group so I know if it is one of the things my inventory

needs.

Not just picking up the phone and calling donors. That is not telemarketing, but a system that is linked to a database where things are tied together with real and important information.

Successful donor education definitely belongs in the schools as early as possible as part of the science and health curriculum. We heard reports on Puget Sound's successful educational program, My Blood Your Blood, that was originally put together with an NHLBI grant and is now being revamped and continuing under the auspices of AABC, but, again, a program that has shown to be very successful and, in the long run, if we want to have donors in the future, we have got to get out there and educate our donors.

Pretty much the feeling of the group was that community education is not as successful. It is nice to get that information out, but where you get the real bang for the bucks is educating the younger potential donor, the child of potential donors, using that education and that recruitment technique where you can.

[Slide.]

We heard heart-felt concern from virtually everybody at the meeting that it is difficult in pressing financial times and competitive times when the reimbursement issues in the hospitals and healthcare have a trickle-down

effect to the blood centers that it is very difficult to put together good programs and maintain good donor-recruitment programs in that situation.

It was very clear that successful programs recognize that donor recruitment is essential. They put it up front and you see the difference in that belief in the funding, staffing and involvement of donor-recruitment people in organizational planning. You know, maybe this should have been my first bullet point because that is the overarching, recognize how important it is, put it up front, support it, integrate it into your entire blood center and you will see a difference.

So the successful programs are the ones that keep the donor and the recipient as the focal point of their purpose and what they are trying to accomplish.

Now into the area where there were discussions and not clear agreement. So if I can see the next slide, please.

[Slide.]

Incentives were clearly an area of concern, confusion and disagreement. First of all, there was data and evidence presented that incentives, and probably the larger the incentive the more the impact, have an adverse impact especially on long-term donation. You may get more first-time donors but for building a cadre of long-term

repeat donors, incentives really don't work.

Yet, despite some of the evidence that was presented at the meeting in the discussions, it was clear that people are reluctant to give up their incentives. Here I come to, in my summary, where you need to make a correction because I mentioned that some states have apparently outlawed incentives. Based on the remarks, as I initially heard them, I said that New York was one of those states, Dr. Linden has clarified for me that, indeed, all that New York State really does is enforce FDA's incentive issues as they understand them.

What the gentleman, Mark Thornhill, who reported said was that they do not use incentives at their Red Cross Center and it was supported by a very conservative approach in New York. I think it is a matter of interpretation but it also illustrates the confusion about incentive issues. There was a strong request that FDA clarify where they stand on incentives and, indeed, work is in progress. It will probably be a guidance for field inspectors that will be publicly available on exactly how to interpret the FDA's stance on incentives coming out later this year.

Incentives are further clouded by the fact that some of the things that we call incentives are also advertising; t-shirts. The gentleman from Florida Blood Services said, "If you are in the Tampa Bay area at any

sporting event, if you look around, you will see our t-shirts."

Indeed, he described the efforts that they do to come up with new and attractive designs, and t-shirts are very important. Again, they bring in the first-time donors. For them, they are also free advertising. So I guess you have to balance those kinds of issues, too, in incentives.

Another area where there is not clear agreement was all about advertising. While some centers reported great success in using paid advertising and recruiting and maintaining donors, there were still many that felt that advertising was either inappropriate or unaffordable for their centers. And so an ongoing debate there.

I recognize that some people are having great success. I recognize that others still have problems with the issue.

[Slide.]

As a spinoff of our discussion about the success of corporate donor-recruitment programs, there was some discussion about whether corporations should be able to realize tax breaks for the expenses associated with those programs. Again, there was a lot of skepticism about that as an issue and, certainly, it is not within FDA purview to say anything about the tax schedule, especially the business tax schedule, but it is not a cheap affair to sponsor a

corporate donor program because usually a lot of the donor-recruitment personnel are coming from your own center.

There may be dinners. There may be awards. There may be incentives that are given out usually which the corporation pays for. Of course, once you open that door, then you get into issues about should they be able to somehow expense the time off for donors to donate and so it was seen as quite a quagmire. I think that is why a lot of the skepticism on that issue.

[Slide.]

Those are kind of the issue-related things. I wanted to present to this group, on the next slide, at least one more issue just because we heard it spontaneously from many different people that, in their blood centers, one of their problems is a conflict between their donor recruiters and their donor operations staff.

What it come down to is if I am bringing in more and more people and then I want you to handle them competently, but you have limited resources to do that, and now, because you have limited resources, you have offended one of the people I recruit so they won't come back again, there is a natural tug here between the two.

What it comes down to is the most successful organizations have integrated the recruiting and encouraging of donors so that permeates the entire organization and it

is part of everyone's job. So, together, they find solutions to resolve the problems while remaining focused on their primary goals.

Some organizations have made this shift to a new approach to an integrated system of recruiting donors. It sounds like many blood centers are still struggling with that change and many of them said that they needed to institute some kind of a culture shift in their own organization.

A lot of information in two days and where do we go next.

[Slide.]

Again, recognizing that donor recruitment is not the area of FDA's expertise, the people at the America's Blood Center have agreed to spearhead the writing of a document about best practices or successful practices in donor recruitment and contact person is on this slide, Susan Parkinson, at ABC.

The reviews that we got from the participants at our workshop were some of the best we have seen at any FDA workshop.

[Slide.]

So I have to, on the next slide, at least acknowledge the speakers. My time is brief so I am not going to read all the names, but these were the people who

came and spoke for us.

[Slide.]

In this slide, you will see the people who facilitated the discussions on Day 2.

[Slide.]

On the last slide, I just have to thank the people that were on the planning committee for the workshop and a special thank you to Susan Parkinson at ABC who was very helpful in identifying people who had successful practices so that we could contact them and invite them to speak at our workshop.

I will be happy to answer any questions.

DR. HOLLINGER: The next item is a summary on Hemopoietic Cells from Cord Blood, Dr. Lazarus.

Summary of Workshop on Hemopoietic Cells from Cord Blood

DR. LAZARUS: Good morning.

[Slide.]

The Cord Blood Meeting was sponsored by the National Heart, Lung and Blood Institute and CBER. It was held at the Mazur Auditorium of the Clinical Center of NIH on August 14 and 15. This was predominantly a scientific meeting as opposed to a regulatory meeting.

It consisted of cord blood bank, clinical transplantation and basic scientific presentations followed by panel discussions which summarized the main points of

each session and gave the audience to ask questions and express opinions.

Several of these presentations included clinical and nonclinical data that were submitted to the docket in response to the FDA requirement for data for proposed Hemopoietic Stem Progenitor Cell Standard that was published in the Federal Register and an unedited transcript of this meeting will soon be up on the web.

[Slide.]

The objectives of the two-day meeting were first to discuss the current status of unrelated allogenic, placental in local blood banking and transplantation and secondly to discuss the scientific issues regarding the characterization of placental and local cord blood grafts and the data supporting development of cord blood-product standards and then, finally, to identify future research directions

[Slide.]

The first session consisted of presentations by representatives of public cord blood banks in the U.S., Canada and an international organization, NETCORD. There was data presented addressing the major issues in cord blood-bank collection, procedures, processing and frozen storage and infectious disease testing, HLA testing, product characterization, shipping and thawing.

[Slide.]

And then the panel discussion at the end of this first session focused on the similarities and differences in cord blood-bank practice among the centers. One of the major differences that was apparent is in the way the various centers perform and report cord blood-product cell counts and by ability and other assays used to characterize the product.

Some of the donorists suggested the development of uniform criteria for product cell counting possibly supported by voluntary laboratory certification programs. Another major area of nonuniformity is in criteria for donor exclusion. All of the panelists were able to agree that, as a minimum requirement, all cord blood units should be characterized with respect to total nucleated cell counts, ABO/Rh type. They should all undergo hemoglobinopathy screening and, of course, HLA typing.

However, a recurrent issue, the optimum level of resolution for the HLA typing remains unresolved.

[Slide.]

The second session addressed essential issues for communication between cord blood banks and transplant centers. The presenters provided information regarding search algorithms used to select the optimal cord blood product for each patient. Among the most important criteria

that fell out were HLA match, cell dose and confirmation that the transplant will be performed under an IRB-approved protocol.

Most of the current systems that were described were automated on-line systems. Web-based systems are being developed and then, interestingly, several multibank cooperation levels were presented.

[Slide.]

In the next session, transplant outcome data were presented describing the effects of HLA disparity, cell dose, recipient age and underlying disease on engraftment and survival outcomes. There was a comparison of pediatric bone-marrow transplants and umbilical-cord transplants from HLA-identical sibling donors. And then data were presented from the New York Blood Center, St. Louis, consolidated data from Duke and University of Minnesota.

Transplant outcomes in 68 high-risk adult recipients were presented and some Japanese data. Basically, the data showed that umbilical-cord blood has been successfully transplanted in hundreds of pediatric patients and a much smaller of adult patients, and that cell dose is the major determinant of transplant outcome while extensive HLA disparity is also very important.

[Slide.]

The next session consisted of other scientific

presentations. Among the topics presented were ex vivo expansion of cord blood and several talks on different approaches to identify and characterize hemopoietic stem cells and their possible correlation with engraftment potential.

[Slide.]

Then, at the end of the meeting, a list of possible standards, standards for cord-blood products, was derived based on the presentations and discussions that had occurred during the two-day forum. The general attitude expressed at the meeting was not resistant to the development of cord-blood products and transplantation and the suggestions that were derived are as follows.

The products should be processed and stored in an accredited lab setting or cord-blood bank and should be collected in accordance with some standards. The donors should undergo infectious-disease screening and testing. Maternal and family history should be obtained and maternal informed consent should be obtained.

The minimum product volume was recommended to be 30 milliliters and the product should be sterile or free of bacterial contamination. The product should be characterized with respect to ABO/Rh, HLA typed at the A, B and DR beta 1 loci. It should be characterized with respect to the post-procession, cell counts and possible viability.

The transplant unit should be selected to be a minimum of three out of six locus HLA match and the suggested cell dose for small recipients, under 50 kilograms, was 2 times 10^7 per kilogram and, for larger recipients, over 50 kilograms one times 10^7 per kilogram recipient body weight.

[Slide.]

Finally, the future research directions were presented. This lists for you some of the suggestions that were made. One is development of voluntary certification programs for cord blood banks. There is interest, of course, in techniques to increase cell dosing and these can include ex vivo expansion combining units and perhaps other strategies that are yet to be developed.

There is interest, of course, in development of DNA-based technologies for infectious-disease and sterility testing and for development of laboratory markers to detect the true hemopoietic stem progenitor cells.

There is interest in pursuing prospective comparative studies of cord blood versus bone-marrow transplantation in pediatric patients and well as consuming and expanding ongoing studies of the efficacy of cord blood for transplantation in adults.

And then, finally, it would be important to investigate the possible multipotentialities of cord blood

cells.

Thank you.

DR. HOLLINGER: Thank you, Dr. Lazarus. Dr. Linden?

DR. LINDEN: On your second-to-the-last slide, you mentioned recommending or saying that products should be stored and collected by an accredited bank. My question is accredited by whom and, if you are referring to private organizations such as FACT and AABB, is FDA considering recognizing private organization and accreditation? Could you please elaborate that issue?

DR. LAZARUS: As I said, the meeting was basically a scientific meeting so, at the end of the meeting, when discussion occurred, there really wasn't a discussion of who should be making the standards and enforcing the standards but rather there was an acceptance of the concept of standards and accrediting organizations.

So who would do it wasn't really discussed.

DR. HOLLINGER: Dr. Stroncek?

DR. STRONCEK: There has been national activity around stem-cell donations and collections for about fifteen years as far as unrelated donors. Cord blood activity really goes back almost ten years. It is probably about five years it has been really popular. I commend the FDA in the battle you fought to get this under some kind of

organization around it. I know it has been a difficult battle, so I would encourage you to go ahead and set up your standards.

We have heard a lot about FACT. I am Chairman of the NMDP Membership Committee and all these organizations are trying, but there is kind of a consensus. They have a consensus on the areas you pointed out, but as far as the tightness of the regulation, it is not there unless the FDA moves forward and comes up with their own standards and starts to handle it like a blood product.

For example, you mentioned cell counts. Cell counts is one area where, as you pointed out, there is huge disagreement on even how to do a cell count, what a cell count means, where that is in stark contrast to the regulation and the care we must use for the reagents we use for ABO typing or for viral testing. These results are very comparable from one center to another across the country.

I can tell you these cell counts are not comparable across the country. As the data suggest, cell count is a critical measure in these outcomes. So I applaud the FDA's efforts and encourage them to move forward and to bring up the basic aspects such as cell counting in cord blood banking up to the same standards we have in blood banking.

DR. HOLLINGER: Thank you. Thank you, Dr.

Lazarus.

The next presentation is on a summary of the Public Meeting on the Regulation of Bone Products. Dr. Solomon.

Summary of Public Meeting on Regulation of Bond Products

DR. SOLOMON: Good morning.

[Slide.]

I am going to be summarizing an open public meeting held on August 2 of this year.

[Slide.]

The meeting was announced in the Federal Register on July 18 and the title of the meeting was Human Bone Allograft Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair. The meeting was held in Bethesda and a docket was set up.

The purpose of the meeting was to provide information to help FDA in clarifying the regulation of human bone allografts under the proposed approach to the regulation of cellular and tissue-based products.

To give you some background, in February of '97, FDA announced a risk-based approach to the regulation of a broad spectrum of cells and tissues where the degree of regulation would be proportional to the risk. Since '97, FDA has published two proposed rules to implement the proposed approach.

They are the registration proposed rule and the donor suitability proposed rule. A third rule on good tissue practice will be published shortly.

[Slide.]

Criteria for determining risk is set forth in the proposed rules. For some products with low risk, there would be no premarket submission, to review and approval of an application and the concerns would be focused on preventing communicable disease transmission, the legal authority being Section 361 of the Public Health Service Act.

In order for a human cellular and tissue-based product to fit into this category, all four of the following criteria would need to be met. The product would need to be minimally manipulated, and I will define some of these terms a little later, not promoted or labeled for any use other than a homologous use, not combined with or modified by the addition of any component that is a drug or device, and does not have a systemic effect, with certain exceptions.

Other products which do not meet all four of these criteria would be more rigorously regulated as a biologic, drug or device requiring a premarket submission to FDA.

[Slide.]

The meeting focused on the first two criteria, manipulation and homologous use. Many comments to the

dockets of the proposed rules had expressed concern that bone allografts would be regulated as medical devices rather than as 361 tissues. FDA asked five questions to focus the discussion. The first asked which processing procedures apply to human bone allograft fall within or outside of FDA's proposed definition for minimal manipulation.

[Slide.]

The definition, as proposed, for minimal manipulation for structural tissue such as bone meant processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair or replacement.

Examples of such minimal manipulation procedures were given in the preamble to the proposed rules.

[Slide.]

Public discussion and comments on manipulation included the following. Some people felt the criterion should be eliminated. Some felt, because the definition was vague, we should repropose it with more specificity and examples. Others felt that the definition should be pertinent for each product type.

Other comments said that preshaping or threading bone, whether in the tissue bank or in the operating room, does not alter its original relevant characteristics. And this was really the main focus of the meeting in that there

is a product called a bone dowel which is a cylindrical segment of bone machined to have threads, like a screw, and used in spinal fusion.

They perform a similar function to metal prostheses and the metal prosthesis are regulated as medical devices, so the concern was that the bone dowels might also be regulated as medical devices. But this comment mentioned that threading, which is done to a bone dowel, should be considered minimal manipulation.

[Slide.]

Others suggested that any process which does not alter the essential microstructural elements of the allograft is a minimal process. Still others felt that the result of manipulation should be more important than the fact of manipulation, that validation to insure that processing does not affect the product was the way to go and, as an example of more than minimal bone products modified by genes, genetic therapy, was felt to be more than minimal but anything less severe than that would be considered minimal.

The second question focused on homologous use, which use of human bone allograft fall within or outside of FDA's proposed definition of homologous use which appears on the next slide.

[Slide.]

By homologous use, we meant the use of a cellular or tissue-based product for replacement or supplementation. And for structural products, such as bone, it occurs when the tissue is used for the same basic function that it fulfills in its native state in a location where such structural function normally occurs.

In other words, the function of the bone in the donor and the function in the recipient were the same, essentially the same. The proposed rule focused on whether the product was promoted or labeled for any use other than homologous use. Examples were given in the preambles.

[Slide.]

Again, the public discussion on this point varied. Some people, again, said, "This is not a good criterion. Eliminate it." Others said it was vague, we should repropose the definition with more specificity and examples, and the definition should be pertinent to each product.

Others pointed out that when an allograft is used in the same manner as an autograft, it should be considered homologous use.

[Slide.]

Others wanted us to tweak the definition a little and say "same basic characteristics" instead of "same basic functions." But the main points that were made were that fusing bone to bone should be considered homologous use. We

are not trying to replace the disc but rather to fuse bone.

These bone dowels, for instance, had a long history of safe and effective use in spinal fusion and there was a lot of literature on them. Finally, the use of bone anywhere in the skeleton or in any orthopedic procedure should be considered homologous use.

[Slide.]

Then we asked what risks to health have been identified and characterized for human bone allograft products. The comments ranged from, "There are no risks," to other comments that said, "We should evaluate risk by looking at what alternatives the surgeon had." The alternatives were either to use an autograft which had much more morbidity than an allograft or to use a metal prosthesis which weakened over time.

However, some people did point out that there were certain risks to using bone in spine, and those included infectious-disease transmission, possible collapse of the bone dowel, non-fusion in the spine, a graft versus host response. One comment suggested that we would do a risk assessment for each product and if significant new risk exists, then we should promulgate additional regulations.

[Slide.]

The fourth and fifth questions were similar. We asked what controls have been identified to adequately

address the risk to health in bone allograft products.

[Slide.]

The discussion pointed out that there are industry standards, the AATP, American Association of Tissue Banks, has industry standards and, also, the ASTM, the American Society for Testing Materials, has standards for the metal protheses.

Also, some tissue banks have elected to become ISO 9001 certified. Other controls in place are peer review of the literature articles and the large body of experience that we have with the products and no reports of collapse.

[Slide.]

Finally, the last question said, "What industry standards are available and what standards will be needed in the future?" Again, the existing standards that were pointed out were those of the ATB. Those are really processing standards and standards aimed at infectious-disease control. Not all tissue banks are members of ATB and those that are not, some follow the standards but others don't.

The ASTM standards, again as I mentioned, are for metal implants. It is not certain whether tissue banks that make allografts hold to these same standards as the metal implants. However, the several orthopedic surgeons and neurosurgeons did point out that they felt that standards

were needed in this area, standards aimed at performance, standards for biologic activity and potency, standards for mechanical performance, standards for processing and determination of bone density.

[Slide.]

Lastly, the perceived advantages of regulation as a medical device were pointed out and the concerns were decreased patient access to treatment, decreased availability and supply, increased cost, increased reliance on autografts or metal prostheses, slowing of ongoing industry standards, development and interference with the practice of medicine.

[Slide.]

Finally, the FDA will take all comments under serious consideration. We are moving forward with the finalization of the first proposed rule, the Registration and Listing Rule, and it is possible that the definitions and criteria would be modified in that final rule based upon the comments that we have heard, both at the meeting and to the previous dockets, and that additional examples would be given in the preamble.

[Slide.]

Next I would like to read a statement into the public report on another matter pertaining to tissues.

DR. HOLLINGER: We really are getting a little

far--I am trying to limit everyone to about eight minutes. We have been going over every time. So could you maybe summarize, then, what you have to say and then we will move on.

DR. SOLOMON: Okay. It is just a one-page statement.

[Slide.]

It has to do with U.K. deferral as it relates to cell and tissue products. Basically, this might be hard to read, but, "The regulations currently in effect for human tissue and transplantation require donor screening and testing for HIV-1 and 2, HBV and HCV. The proposed regulations for suitability of donors of these products would include the above and, in addition, donor screening for the transmissible spongiform encephalopathies including CJD.

"As you know, in November of '99, as a precautionary measure for variant CJD risk, FDA recommended that blood donors who have resided or traveled to the United Kingdom for a cumulative period of six months or more from 1980 through 1986 be deferred. This recommendation was made after a pilot study of the effect on the blood supply and with ongoing monitoring of the blood supply.

"To date, no parallel recommendation has been made for cell and tissue donors. FDA is looking at the issue of

donor deferral based on U.K. travel and residency for cell and tissue donors. FDA will address the issue in future guidance developed through the process of notice and comment.

"FDA is soliciting data or information from the cell and tissue industry and the public in order to help us make a better informed decision on this matter. Such information could include the likelihood of transmission of variant CDJ by cells and tissues, the differences in risk among different cells and tissues.

"We know that classical CJD has been transmitted by cornea and dura mater. These tissues, as well as cells and tissues rich in leukocytes and vascularized organs may have a higher theoretical risk of variant CJD. Finally, and probably quite important, is we are soliciting data or information on the impact, on the supply, of cell and tissues that such a deferral might have."

Thank you.

DR. HOLLINGER: Thank you, Dr. Solomon.

I think we are going to move on then. Our next one is on the summary of Joint Transmissible Spongiform Encephalopathies and Vaccines and Related Biological Products Advisory Committee. Dr. Asher? You have eight minutes.

Summary of Joint Spongiform Encephalopathies and Vaccines

and Related Biological Products Advisory Committee

DR. ASHER: Good morning.

[Slide.]

I apologize for not having a slide set available to Dr. Smallwood until this morning.

[Slide.]

On July 27, the FDA Advisory Committees on Transmissible Spongiform Encephalopathies and Vaccines and Related Biological Products met jointly to consider the recent discovery by the agency that, in spite of FDA recommendations dating back to 1991 not to do so, manufacturers had used materials from cattle in BSE countries to prepare several important childhood vaccines.

The term BSE country refers to a country that has diagnosed bovine spongiform encephalopathy in a native-born cow or a country that UDSA concludes may have BSE and prohibits importation into the United States of its animals' meat, et cetera.

[Slide.]

The committee has reviewed regulatory history relevant to vaccines and then the risk associated with the various bovine-derived materials used, risks that depend on the tissues used, when and where they were obtained as well as the manufacturing process. Model risk assessments were presented by the FDA and the manufacturer.

Although the committee did not vote, they offered suggestions to CBER. The bovine-derived materials of chief concern were fetal-calf serum obtained from animals in the U.K. during years in which BSE was prevalent and used to prepare a viral vaccine and a gelatin-derivative pancreatic extract and meat broth used to prepare a bacterial vaccine. Those materials were all from moderate-risk BSE countries. The identities of the vaccines, none of which has been withdrawn from the market, have been kept confidential so far.

[Slide.]

FDA regulations require biological products to be free of extraneous microbial agents. Conscious of that in 1991, CBER first expressed concern about spongiform encephalopathies and asked manufacturers to send information on sources of bovine and ovine materials used to manufacturer biologics.

[Slide.]

In 1993, CBER revised a points-to-consider document asking that serum used in the cell culture be free of the BSE agent and sent letters to manufacturers asking them to review the document. In December of that year, FDA requested, in letters published the following year, that most bovine materials used to manufacture FDA-regulated products intended for humans not be sourced from BSE

countries and noted that the USDA maintains the list of such countries.

Following recognition of new-variant CJD in young people in the United Kingdom and France and its probable connection with exposure to the BSE agent, FDA reminded manufacturers of its previous requests and, again, noted that the BSE list is kept by the USDA.

[Slide.]

A temporary exemption from recommended BSE-free sourcing that had been extended to bovine gelatin in 1994 was rescinded for injectable and implantable products in September, 1997.

[Slide.]

Nevertheless, earlier this year, CBER learned that the four bovine-derived materials had been used in the manufacture of vaccines.

[Slide.]

The previous guidance was then repeated in a letter from the CBER Director and points that had apparently been misunderstood were clarified, particularly emphasizing that CBER had recommended BSE-free sources of bovine-derived materials at all stages of manufacture and that the USDA was to determine the BSE countries.

FDA had not previously addressed the situation in which a country, once considered BSE free, was later place

on the USDA's BSE list while products produced with the bovine materials were still in inventory.

[Slide.]

That became an issue early in 1998 after USDA included all of Europe on the BSE list. Ruminant products prohibited by the USDA include gelatin for human consumption but the prohibitions include bovine serum. In practice, however, if ruminant serum is not identified on an export manifest as a component of a product, the USDA would probably not stop its importation.

[Slide.]

Ruminant serum, itself, can be imported into the United States under USDA permit for uses unlikely to bring it into contact with animals of any kind, not just ruminants.

[Slide.]

Knowing that bovine-derived materials from BSE countries were used to manufacture vaccines, can we estimate the risk. At the moment, there are ten BSE countries listed here, ten countries known to have BSE, in chronological order. The vast majority of cases still occur in the United Kingdom where more than 750 have been registered so far this year.

Let me say, first, that there is no epidemiological evidence, and that study in the U.K.

addressed that hypothesis and it was recently published, no evidence to suggest that any vaccine has been a risk factor for new-variant CJD.

[Slide.]

Temporal and geographic risk. Although BSE has been found in U.K. cows born in the late 1970s, it is thought that 1980 marks the probable beginning of the epidemic followed soon afterwards by Ireland, France, Portugal, Switzerland and, more recently, in the Benelux countries and Denmark.

[Slide.]

BSE countries peaked in the United Kingdom at the end of 1992. It has probably peaked in Switzerland but the situation in other countries is not clear.

[Slide.]

The USDA simply considers various countries either to be BSE-free or to be unacceptable. The European Commission's Scientific Steering Committee has attempted to estimate the probable occurrence and prevalence of BSE in twenty-five countries that voluntarily submitted information.

The two countries with the highest risk are the United Kingdom and Portugal followed by the eight other countries that have found cases in native cattle. The EC also suspects that at least three other European Union

countries, Germany, Italy, France and Spain probably have cases and the USDA agrees with that.

[Slide.]

The EC classification of the United States and a number of other countries is category II--that is, provisionally free of BSE--because we imported cattle from the U.K. during early years of the outbreak, rendered some of them into meat and bone meal and instituted a ban prohibiting its feeding to ruminants only in 1997.

[Slide.]

Only a small number of countries are considered to be definitely BSE-free by the EC.

[Slide.]

As for tissue risk, thus far only neural tissues and intestinal tracts of cattle with BSE have been demonstrated to contain the infectious agent although studies are limited in number and sensitivity. Both the EC World Health Organization and the OIE, the counterpart of WHO for animal diseases, have accepted four risk categories for bovine tissues based largely on studies of other animal TSE's, especially scrapie in ruminants.

Higher-risk tissues are listed here.

[Slide.]

The materials used to prepare the vaccines, shown here bolded, are all from tissues in the two lower-risk

categories. However, as have our FDA advisory committee, the EC Steering Committee concluded that ruminant blood and, presumably, other lower-risk tissues, have a theoretical potential to transmit disease.

[Slide.]

Not only is there a risk that the tissue, itself, may sometimes carry small amounts of infectivity, there is also a risk that it may become contaminated with high-risk material during slaughter.

[Slide.]

Vaccine-manufacturing processes have a substantial potential to reduce the amount of BSE agent by should any agent be present in the final product, administration by the intramuscular route would be much more likely to result in infection than the oral route, which is thought to be the most likely route by which humans have acquired new-variant Creutzfeld-Jacov disease.

[Slide.]

FDA used a risk-assessment model proposed by PhARMA, the Pharmaceutical Trade Association, to estimate, in a general way, what the risks might be that the BSE agent could enter some stage of the vaccine production and expressed that as infectious doses of agent per number of doses of vaccines produced.

Some estimates are listed on this slide. Although

such assessments must be considered unreliable because of the uncertainties and the assumptions on which they are based, nobody disagreed that the risk seems to be very small and, in some scenarios, negligible.

[Slide.]

Considering the small theoretical risk of transmitting CDJ by BSE-implicated vaccines and the importance of the products which cannot be replaced in the short run, but not ignoring our special obligation to afford every possible protection to children, the committees offer advice that I summarize in the final eight points.

Theoretical risk of transmitting vCJD by fetal-calf serum and presumably other low-risk materials from BSE countries in vaccine seems very small but should not be ignored. Fetal-calf serum and other bovine materials from animals in BSE countries currently used to prepare working viral and bacterial seeds in cell banks should be replaced as soon as possible with serum and other bovine materials from BSE-free sources.

The risk of BSE from fetal-calf serum used to prepare master seeds is negligible and probably exceeded by the risk of deriving new master seeds, the biological properties of which cannot be accurately predicted.

[Slide.]

Bovine products obtained from any country before

1980, the probable start of the BSE outbreak in the U.K. should be of no concern. The benefit of immunizing children with the implicated vaccines outweighs the remote theoretical risk of CJD. Vaccine should not be withdrawn from the market. There should be additional public disclosure that bovine components from BSE countries were used to manufacture vaccines and that disclosure should include changes in the package insert, announcement in a journal article or a joint statement by the Department of Heath and Human Services and possibly by letters to healthcare providers.

[Slide.]

Because they do not have the same proven benefit as licensed vaccines, investigational vaccines should be considered separately and participants in clinical trials should receive all relevant information concerning theoretical risk of new-variant CJD associated with bovine-derived materials from BSE countries used to prepare investigational vaccines and that information should be included in the informed-consent document.

Thank you.

DR. HOLLINGER: Thank you, David.

Any questions? Dr. Nelson? One question.

DR. NELSON: What to tell the public is really a knotty issue. I am not sure that you can adequately inform-

-what are you going to do about it? You say that there should be public disclosure, but what are you going to say?

DR. ASHER: In the first place, the advisory committee joint meeting, itself, constituted, to my mind, a form of public disclosure. It was an open public meeting and representatives of the press were there.

I think that if the remote nature of the risk is presented along with a reminder of the high benefit of the vaccine, I would hope that the public would be prepared to accept it without panic. There are precedents for that. Recall when retroviral activity was discovered in certain cell cultures, the fact was disclosed. It was presented as a remote risk, which it is.

As in this case, there was no disease attributable to the exposure and the public accepted it without reaction. The alternative of keeping the information secret, I believe, in today's world is unacceptable.

DR. HOLLINGER: Thank you, David.

The final presentation is an update on rapid HIV test approval requirements and standards. Dr. Poffenberger?

Update on Rapid Test HIV Test Approval Requirements and Standards

DR. POFFENBERGER: Given that I have eight minutes and there were copies of the slides available to everyone on the table outside, I am going to try and trot through these

slides instead of walk through them.

[Slide.]

Switching topics for your last time before the main session starts, I am going to tell you something about FDA's requirements and standards for approval for rapid HIV test.

[Slide.]

First, I want to emphasize that these extended standards and revised requirements apply exclusively to rapid HIV tests intended for diagnosis and they do not apply to tests for blood screening.

[Slide.]

At the previous Blood Products Advisory Committee Meeting held June 15, the public-health needs for rapid tests were discussed and data for some of the tests was presented. The FDA actions to facilitate approval of rapid tests were reviewed.

Among these actions were reduction in the sample size for specificity determination and, in March of 1999, the postponement of the requirement to include Group O antigen in rapid HIV tests. FDA also made a commitment in the June meeting to revisit the sample sizes needed to demonstrate clinical sensitivity and specificity of the test.

At the end of that session, this committee

concurred with standards for approval of rapid tests that are separate and different from the standard for approval of blood-screening tests.

[Slide.]

The standard for sensitivity concurred with on June 15 is 100 percent sensitivity on the FDA HIV-1 panel; that is 11 out of 11 positives. The lower bound for the 95 percent confidence interval must be at least 98 percent for studies that include all confirmed positive serum or plasma samples from a study of positive individuals with a sample size of 1,000 and for positive samples from a high-risk population study whose sample size is at least 500.

[Slide.]

The standard for specificity concurred with on June 15 is the lower bound for the 95 percent confidence interval must be at least 98 percent for serum or plasma samples from individuals in low-risk populations in a study of 6,000 individuals.

[Slide.]

Today, we are extending those standards to apply to all sample types; that is, the 98 percent minimum acceptable performance standard for sensitivity and specificity is being extended to all sample types; venipuncture whole blood, finger-stick whole blood, oral fluid as well as for serum and plasma samples.

[Slide.]

In addition to extending the standards, we are revising the clinical-trial requirements. Since June, FDA has followed through on its commitment to revisit the trial-size requirements for rapid tests. As part of this process, we sought additional input from statisticians and met with our public-health partners at the CDC and the NIH.

The result is that the requirements which have historically been based on blood-screening intended uses are being revised to reflect the distinctly different intended uses for the rapid test; that is, for a test that will primarily be used on fresh specimens in populations with unknown HIV prevalence.

[Slide.]

The next few slides are going to show you first what the previous standard was and what the revised requirement is. HIV-1 sensitivity was previously defined in a study of 1,000 samples from individuals known to be HIV-positive. These samples could be repository and/or fresh with at least 200 samples coming from individuals with AIDS.

In the revised sensitivity-study requirement, the manufacturer may propose a trial size of sufficient power to demonstrate that the test meets the 98 percent standard. However, the FDA is requiring that a minimum of 500 fresh samples be tested for each specimen type that the

manufacturer wishes to claim.

Although 500 is the minimum acceptable number, FDA strongly recommends that 1,000 samples be tested in order to increase the chance that performance in the study will meet the 98 percent standard. AIDS samples are no longer required since the predominant use of these tests is expected to be with populations of unknown serostatus.

Samples with recent seroconverters are desirable in this study.

[Slide.]

The previous requirement for a prospective study in a high-risk population has not been changed. A study of at least 500 samples should be conducted in sites of intended use in an HIV-1 endemic population. The change is in the way that the results from this study will be used. The rapid test results with confirmed positive samples from this study will be combined with the results with the known positive samples from the sensitivity study described on the previous slide to make the determination of sensitivity.

The results with negative samples from this study will be used to report specificity of the test in high-risk populations.

[Slide.]

The requirements for specificity are being changed. Previously, 6,000 samples from a low-risk

population were required. Under the revised requirements, the manufacturers are free to propose a trial size of sufficient power to demonstrate that the test meets the 98 percent standard.

The FDA is requiring a minimum of 500 fresh samples from a low-risk population for each specimen type. The FDA is also requiring a minimum of 500 fresh samples from a high-risk population for each specimen type. Again, the FDA strongly recommends 1,000 samples be run in each population.

Please note that only a single prospective study in a high-risk population is required. As noted in the previous slide, the results from this trial will contribute to both sensitivity and to specificity determinations.

[Slide.]

In making the choice of study size, the manufacturer should consider these points, that the absolute minimum size for each study is 500 fresh samples for each sample type. The risk that the study will not meet the 98-percent standard for the lower bound of the 95 percent confidence interval increases as the sample size decreases.

This is why the FDA is recommending that 1,000 samples be tested. If the manufacturer chooses a small sample size and the study fails to meet the standard, the manufacturer should have a plan in place for conducting a

second trial or for extending the trial to an increased sample size using an appropriate p-value correction.

A valid plan for handling this failure should be in place before the initial study begins.

[Slide.]

In addition to revising the trial-size requirements, FDA is taking other action to facilitate approval of the rapid HIV tests. As was mentioned earlier, FDA announced in March of 1999, that rapid-test manufacturers would not be required to add group O antigen to their test immediately but could postpone that addition for two years.

Today, FDA is taking the further step to drop the requirement for addition of group O antigen to rapid HIV tests. Although this is not a revision, FDA is advising rapid-test manufacturers that a claim for HIV-2 detection is optional.

If manufacturers that wish to pursue an HIV-2 claim are having difficulty completing their HIV-2 prospective study, they should apply for approval for an HIV-1 claim and may amend their product to include HIV-2 when the studies are complete.

Labeling for diagnostic tests for HIV does not typically distinguish fresh and stored sample studies. Because the primary use of these tests is expected to be

with fresh samples and because data has shown there may be differences in sensitivity and specificity performance with stored versus fresh samples, the data will be listed separately in the labeling. Any study to be reported should include a minimum of 500 samples.

[Slide.]

This and the next two slides describe data requirements for rapid HIV tests that have not changed. Given the time constraint, I may just pass through those.

[Slide.]

And the next slide.

[Slide.]

One more please.

[Slide.]

The actions described today are aimed at facilitating approval of rapid tests while assuring the safety and effectiveness of those tests in the settings and with the sample types of intended use. The 98 percent standards for sensitivity and specificity apply to all rapid tests. The revised trial requirements apply to all manufacturers that have not completed their studies.

Those manufacturers with completed studies that meet previous trial requirements may be labeled differently. They would also have the option of conducting new trials that meet the revised requirements.

[Slide.]

FDA has contacted all rapid-test manufacturers with whom we had previously discussed clinical-trial plans. These revised requirements are designed to assure the safety and effectiveness of these rapid tests as they will actually be used. The requirements are meant to facilitate approval and not to delay it.

Manufacturers or sponsors with questions or concerns should contact FDA to request a teleconference or meeting. The point of contact is the Division of Blood Applications at 301 827-3524.

Thanks.

DR. HOLLINGER: Thank you, Dr. Poffenberger.

Any questions? That concludes the updates for this morning. We appreciate those updates. I wish we had, really, more time to discuss them and go through them. These are very important issues here.

III. Current Utility of Screening Blood Donors for Antibodies to Syphilis

DR. HOLLINGER: We are going to move then to the first discussion today on the screening on blood donors for antibodies to syphilis. We have eight speakers in the first part before the break. We are going to try to make sure everybody has about fifteen minutes. We are going to try to keep everybody to that. There may be some leeway if someone

has a little less and the other a little bit more, but I would like you to sort of all try to do this so we can get through this in a reasonable time. Then we will take a break and go on with our open public hearing.

I am going to turn this over to Dr. Chiang Syin.

FDA Framework

DR. SYIN: Good morning.

[Slide.]

It is my pleasure to be here presenting the FDA framework on donor screening for syphilis. Serological test for syphilis is the first test instituted for donor screening against communicable disease markers. It fulfilled an obvious need, as shown in the next slide, to protect the public health over half a century ago.

Today, we face a completely different picture in which no case of transfusion-transmitted syphilis has been reported in the U.S. in recent years. The utility of screening donors for antibody to syphilis is being raised again.

[Slide.]

This is right after World War II as the effort by the PHS to combat the syphilis problem. You could show that at that time we had close to a million cases a year of syphilis identified in the U.S. But before we get into more of the specifics of the syphilis testing, let me briefly

outline the various aspect of FDA's approach to testing.

Since you are quite aware of the FDA authority and our role in regulating blood and blood products, I will not get into the first two parts.

For the third item, for the decision-making process, as a part of the regulatory process, the FDA established standards and provided guidance, as you know. Considering approval and the recommendation of donor-screening tests depends on the sponsor's demonstration of safety, efficacy and manufacturing consistency.

Policies are developed in cooperation with other PHS agencies with public input, including BPAC. This is exactly the reason that we are here today. For the next point, our current policy on testing. Like HIV and hepatitis testing, serological test for syphilis is required by regulation since 1958.

For other tests now amended by the regulation, FDA may put forth recommendations for their use. We can also look at the perspective on the surrogate tests. Medical history is important to address conditions for which testing is not available or impractical and to address risk in the window period.

Medical, including behavior, history is used as a surrogate marker for transmissible diseases, including HIV, hepatitis, and CJD. Many consider that the continuation of

requiring syphilis testing for blood-donor screening was based solely on its unsubstantiated potential for a surrogate marker for HIV.

[Slide.]

Currently, in the U.S., serological tests for syphilis are considered as a class II device and cleared by FDA under the 510(k) mechanism. This test could be generally divided into two groups. The first one is the non-treponemal test and the second one is the treponemal test.

The two groups have distinctive characteristics that make them useful for different purposes. Non-treponemal tests detect nonspecific cardiolipin antibodies. Non-treponemal tests are useful for monitoring the progression of disease and the response for therapy. The most commonly used test today that has been used is the Venereal Disease Research Laboratory test, so-called VDRL test, and the rapid-plasma reagent, RPR test.

The problem with those tests is obviously the biological false-positives which may occur in persons with a variety of bacterial and viral diseases and those with noninfectious conditions such as autoimmune diseases. The low sensitivity of non-treponemal tests in early and late syphilis and the potential for biological false-positives may require confirmation of non-treponemal test results with

a treponemal test to establish a diagnosis of syphilis.

On the other hand, the treponemal test incorporates specifically the treponemal antigen into the system. The traditional gold standard was the Treponema pallidum immobilization test, to so-called TPI. It was replaced by the fluorescence treponemal antibody with absorption test and it was called FTA ABS, as you know.

Later on, Treponema pallidum hemoagglutination test, the TPHA, was developed. The Olympus TKPT system for automating syphilis testing cleared by FDA in 1990 is a modified microhemagglutination test. The treponemal test has a higher sensitivity, I believe, in the primary and in the late syphilis.

[Slide.]

As you can see on this slide, the treponemal test, in general, has a sensitivity of 70 percent to 99 percent. If you see only the first two items in the last column, it shows only 1 and 0 percent. That actually was not shown in the package that I sent to you. I overlooked putting this as a result of after treatment. You can see those non-treponemal tests would have difficulty to pick up previously infected syphilis patients.

Anyway, early in primary syphilis, the antibody level may be to low to detect and the test result may be nonreactive. The test cannot be used to diagnose late

syphilis, especially if treated as shown on the slide, because the titer or antibody will eventually decline to undetectable levels.

The treponemal tests have a higher sensitivity in the primary and late syphilis as I indicated earlier. Unlike non-treponemal tests, once the reactive treponemal-based antibody test will remain reactive regardless of whether the individual has been successfully treated or not. Biological false-positives are also common for this type of test, even though some studies indicated may be slightly lower than the non-treponemal-based tests.

In general, the specificity of both types of tests are comparable and neither test could detect the so-called window period infection. This is a point which you have to be careful at later discussion.

[Slide.]

This lists some of the advantages and the disadvantages of the value of the syphilis testing for donor screening. This is a table I adopted from the 1996 review written by Dr. Richard Cable on the evaluations of syphilis testing of blood donors which has been included in your package.

The disadvantage, as listed, is, as you can see, obviously there will be an extra financial cost for whoever is footing and bill and the false-positives and associated

consequences, like, obviously people understand the stigma associated with a positive result for syphilis. Also, the consequences of discarding a useful unit due to a false-positive result.

On the other hand, the testing may have value in contributing to the elimination of transfusion-transmitted syphilis, or at least preventing an introduction of this pathogen in transfusion patients.

[Slide.]

To put the FDA framework in perspective, let me briefly review our policy on syphilis testing in the historical context. Statutory requirements of syphilis testing of blood and blood products are clearly stated in Title 21 of the Code of Federal Regulations under 640.5(a) and 640.65.

Syphilis testing, at a national level, was instituted in 1938 and required by regulation in 1958. The most current memo from FDA was issued on December 21, 1991. It was the recommendation for donor deferral and product distribution.

[Slide.]

Since 1950, transfusion-transmitted syphilis was almost nonexistent in the U.S. There was only a single case reported in 1968 by NIH and, along with the fact that the low prevalence of syphilis in the general population since

the mid-50's, and other contributing factors I will touch upon in the next slide, the FDA Advisory Panel of Blood and Blood Derivatives, in 1978, recommended elimination of syphilis testing due to a lack the public-health values.

The recommendation was published in 1985 and it was accepted by PHS. But, as you recall, 1985, unfortunately, was the year that we are embroiled in the heat of the AIDS epidemic. FDA decides to withhold the proposed rule to revoke the testing requirement because of the potential surrogate value as a marker for AIDS risk.

Since then, the validity, or the surrogate value, of syphilis testing in blood donors for HIV has often been challenged.

[Slide.]

As I previously mentioned in the pros and cons of syphilis testing for donor screening, the lack of documented case of transfusion-transmitted diseases was often-- transfusion-transmitted syphilis was often cited as one of the major reasons for the elimination of syphilis testing.

These are several major factors that we could identify. The first one, obviously, is a low or lower prevalence in the U.S. population since the '50's and the practice of refrigerated blood storage. I believe this is a practice generally adopted in the '50's as well. And improved donor-selection process; this is accompanied by the

emerging of modern blood bank practices.

The other one we cannot overlook today is that maybe a uniform application of screening tests may also contributed to it. Last, but not least, transfusion recipients were often under antibiotic therapy. I believe the discovery of penicillin to cure syphilis and has been adopted since the '40's may also contribute to the lower prevalence of syphilis in the U.S. population.

Although we believe those have contributed to the disappearance of transfusion-transmitted syphilis, we have problems to pinpoint the precise nature of each factor. I hope today's presentation by other groups may shed some light on those factors.

[Slide.]

In 1995, a Consensus Development Conference on Infectious Disease Testing for Blood Transfusions was held in NIH. Elimination of syphilis testing was one of the issues under extensive discussion. However, at the end of meeting, it was concluded that the testing of donors for syphilis should continue despite little surrogate value. The major reasons cited were that many blood components, especially platelets, are stored at room temperature, conditions that will not inactivate Treponema pallidum and also because of lack of definitive laboratory data to invalidate the value of the syphilis test.

[Slide.]

The slide I downloaded from the CDC web-site, just trying to show you the low prevalence of the syphilis cases. But you have to keep in mind, this is 1990 to the current data. If you look at the 30's, and the 40's and the 50's data, you can see this is a drastic upswing at the beginning, in the 30's and the 40's.

I mentioned earlier, this is just to show you we are anticipating to see a continual decline of syphilis in the general population in the U.S.

[Slide.]

With the poor predictive value and the high false-positives from either treponemal or the non-treponemal-based tests, and the lack of a surrogate value for other infectious diseases, FDA decided to solicit public comment on whether we should eliminate the testing as part of the proposed rule, updating the requirement for testing human blood donors for evidence of infection due to communicable disease agents.

The proposed rule was published in the Federal Register in 1999.

[Slide.]

Our primary concern is to insure blood safety and an adequate blood supply. As I remember in the last BPAC meeting in June, I believe Dr. McCurdy made an interesting

comment. He said--this is probably difficult to see how we keep adding a new test, how could we ever consider dropping any tests. At this point, I think we will only expect to see more scientific data to support either the elimination or retention of donor screening for syphilis. I hope that will be the only criteria and that no other factor will be involved.

[Slide.]

As Dr. Hollinger has pointed out, we have a lot of presentations today. Following my presentation will be Dr. Markowitz of CDC. She will touch upon the background of clinical syphilis. Also, from the American Red Cross, Dr. Roger Dodd will go over the background on diagnostic testing for syphilis. He will be followed by Dr. Markowitz, again, on syphilis surveillance and blood-borne transfusion.

After her presentation, Sharyn Orton from the American Red Cross would present the American Red Cross's new data using the PCR method to evaluate the serologically confirmed positive serum to show whether any Treponema pallidum could be detected.

[Slide.]

Her presentation will be followed by Dr. Alan Williams going over the REDS study of syphilis screening as a surrogate test. We hope that his presentation will clearly show the lack of surrogates tests for other

infectious disease markers.

Dr. Markowitz will present their investigating report in the Maricopa County SDT study. CDC today will also present a proposed study to try to evaluate the syphilis testing, its value. This will be presented by Drs. Hsi Liu and Stephen Morse.

Finally, I believe Dr. Ruta is going to present a set of questions for you to evaluate. Thank you.

DR. HOLLINGER: Thank you.

We will start, then--the next presenter will be the background on clinical syphilis. Dr. Markowitz?

Background on Clinical Syphilis

DR. MARKOWITZ: Good morning.

[Slide.]

I think I can be fairly brief with this first presentation because what I would really like to do is just provide some background that will be relevant for the subsequent presentations this morning. So I am just going to highlight some of the main features but not be comprehensive. I have also snuck in a few slides on the epidemiology of syphilis in the U.S. which I think will be relevant for our discussion today.

[Slide.]

Syphilis is a sexually transmitted disease caused by T. pallidum which is a spirochete, as I am sure everyone

knows. Syphilis has a highly variable clinical course and is characterized by episodes of active clinical disease interrupted by periods of latent infection.

It is quite well known that symptoms and signs of early syphilis are often missed or confused with manifestations of other diseases.

[Slide.]

Syphilis is classified into sequential clinical stages to guide patient management and management of sexual partners and, in the case of pregnant women, to guide newborn care. However, despite their clinical and public-health utility, these stages are not precise and, in individual patients, they often overlap.

This slide shows the general time course of the different stages, and they are quite variable, that about ten to 90 days after infection, signs and symptoms of primary syphilis are manifest. These include the classic ulcer and regional lymphadenopathy.

Signs and symptoms of secondary syphilis occur between one and six months after primary syphilis. But one to three months later, the symptoms of secondary syphilis resolve and the patient enters what is considered a latent phase. About 70 percent of persons with untreated syphilis will remain latent while 30 percent will develop tertiary disease which can include cardiac and neurologic

manifestations or benign late syphilis.

[Slide.]

Just some basic features of primary syphilis. The classic manifestation, of course, is the ulcer. The classic ulcer is single, painless and appears at the site of inoculation. The location can be quite variable and the specific location and the degree of discomfort are important determinants of whether and when the ulcer is detected by the patient or the clinician. In women, the ulcers are often cervical and, as a result, often go unnoticed.

Not all the chancres have a classic appearance and they are traditionally single and painless. But they can be multiple and, as a result, can be misdiagnosed as other ulcerative SDTs. As I mentioned before, they can be painless and may be completely missed. The untreated lesions will heal spontaneously in a few weeks.

[Slide.]

Secondary syphilis is manifested by variable skin and mucous-membrane lesions and constitutional signs and symptoms. Patients will often have persistent healing chancres and the rash, which is commonly macular, can evolve to a papular, even pustular, rash and patients can have a combination of these different rashes.

It is classically present on the trunk and the rash is the most common manifestation of secondary syphilis.

Other manifestations are generalized lymphadenopathy, headache, fever, condyloma. Of note, and of importance for this discussion, is that some patients with secondary syphilis will not report any systemic illness at all at the time when they are diagnosed.

[Slide.]

After primary and secondary stages, most patients, for a variable period of time, will become completely asymptomatic. In this stage, the only evidence of infection is serologic. This is considered the latent syphilis.

About 25 percent of patients with latent syphilis will develop relapses to the secondary stage, demonstrating the very characteristic waxing and waning part of syphilis. Latent syphilis is somewhat arbitrarily divided into two stages; early, latent and late-latent. In light of the data indicating that about 25 percent of patients will develop relapses into secondary syphilis, and that most of these relapses occur within the first year of latency, latent syphilis of less than one year duration is considered by CDC as early-latent. These patients are considered potentially infectious.

Patients who have latent syphilis of more than one year duration are considered late-latent and are deemed relatively noninfectious. However, as I will mention a little bit later, congenital syphilis does occur with late-

latent disease and transfusion-transmitted cases have also been reported.

[Slide.]

Just briefly, to review these stages from the pathogenesis point of view, after sexual exposure, T. pallidum invades the body through the mucous membranes and it attaches to the host cell and it begins to multiply. Within hours, the organisms appear in the regional nymph nodes and disseminate to multiple organs and tissues.

The chancre develops at the site of inoculation and is considered to be teaming, and is teaming, with treponemes. Secondary syphilis is considered the disseminated stage with treponemes throughout the body and the condyloma is also teaming with treponemes.

In the latent stage, treponemes are in the spleen and lymph nodes and intermittently seed the blood stream. As shown in the slide, the latent stage can revert to the secondary stage.

[Slide.]

This just reviews the stages, primary, secondary, latent divided into early and late, and then the tertiary which I am not going to really touch on for this presentation this morning.

[Slide.]

Just a few words about congenital syphilis. I

think it is relevant for our discussion. It is one of the major causes of morbidity and mortality from syphilis. It does demonstrate blood-borne transmission. Congenital syphilis can result in several outcomes which I have listed on the slide and the risk of maternal-fetal transmission changes with stage of disease.

However, a vertical transmission can occur at any stage. The risk is highest in primary and secondary disease where vertical transmission has been reported about 70 to 100 percent of pregnancies. In about 40 percent of early-latent, there is transmission and in about 20 percent of late-latent.

[Slide.]

Just very briefly, I think most people know this, but penicillin is the treatment of choice for syphilis. There are different regimens for the different stages but it is very effective. There is no resistance to penicillin that has been reported for syphilis. There are alternatives, also, available for people with penicillin allergy.

[Slide.]

I am not going to go into this because I see that both the presenter before me and after me will go over the diagnostic tests. So I think I will just skip over this.

[Slide.]

I am also not going to go over this to save time,

but I wanted to point out that we do have a variety of case definitions for surveillance at CDC and they have used both clinical criteria and the laboratory criteria that are going to be discussed this morning. Both probable confirmed cases for each of the stages have been developed.

[Slide.]

I am not going to go over this, either. This is for the early-latent clarification.

[Slide.]

I do want to touch on some epidemiology very briefly again. This slide shows the number of cases from 1941 to 1998 reported to CDC. We normally follow primary and secondary cases because these represent incident cases in the time period which is being studied.

This slide shows primary and secondary in the yellow, early latent in the red and then total cases in the blue line. As you can see, we have decreased to very low rates in the U.S. In 1998, which is the last year for which we have really completed our data, we have 6,993. It is slightly less in 1999.

You can see that syphilis in the U.S. declined dramatically in the '50's with the widespread use of penicillin in U.S. programs that were implemented. There was an epidemic in the 1990's. That was a nationwide epidemic and since that time, rates have decreased really

throughout the country. Last year, because of these really remarkably low rates, the Public Health Service announced a national syphilis elimination goal. The goal is decrease syphilis to a rate below 0.4 per 100,000 by the Year 2005 and also to have 90 percent of the counties in the U.S. free of syphilis.

So that initiative is one-year old now and the goal is, again, 2005.

[Slide.]

This shows the rates by gender in the U.S. The rates have been greater in men than in women, but the difference between the genders is narrowing. Both of the rates are below the Year 2000 objective which is the dotted line. The overall rate in the U.S. is 2.6 per 100,000.

[Slide.]

This slide just shows the age-specific rates for men and women showing that the rate for women in highest in 20 to 24-year-old women with a rate of 6.1 per 100,000 and, for men, it is slightly older; it is the 30 to 39-year-old age group has the highest rate for men of 6 per 100,000.

[Slide.]

Despite the overall decline in syphilis, it remains an important problem in the South and it affects predominantly African-Americans with the rates of about 20 to 30 times higher in African-Americans than non-African-

Americans.

This slide shows the rates around the country. We had 40 states that were below the 2000 objective which is in yellow. You can see that all of the high-rate states are in the South. There were five states that had rates greater 8 per 100,000 and seven states with rates 4 to 6 per 100,000 in all these except Arizona and Maryland, I think, are in the South.

[Slide.]

The geographic focus is even more striking if you look at the county map. 78 percent of the over 3,000 counties in the U.S. reported no cases of syphilis in 1998. There were only 310 counties that reported rates above the 2000 objective. Another way to look at this is the counties in red, here. There are 28 counties that reported half of all cases in 1998 so it really is quite a focal disease now in the U.S.

[Slide.]

I think I am going to skip this. It might be touched later but this is just to mention that there is--I think most people know an association between syphilis and HIV. Just briefly, I will mention this. There was a review of 30 studies that look at the prevalence of HIV in syphilis patients. These were 30 outbreaks that were investigated.

In male syphilis patients, the mean HIV prevalence

was 27.5 percent. In women, the median HIV prevalence was 12 percent. So these diseases often travel together and, even this year, we have several outbreaks of syphilis among HIV-infected persons.

[Slide.]

This is my last slide, just to say that even though syphilis is a very focal disease, we do have outbreaks and now the outbreaks will become more sporadic and, perhaps, more unpredictable in different cities. In 2000, these are four of our largest outbreaks and, by no means, the only outbreaks. There is an outbreak in Miami with 81 primary and secondary cases. Los Angeles, which is having a large outbreak of syphilis among HIV-infected men, 112 cases. Indianapolis, this is mainly heterosexually transmitted in Indianapolis, 228 cases. In Detroit, 163 cases.

So it still is a disease which we are seeing outbreaks in the U.S.

That's all I have.

DR. HOLLINGER: Thank you. The outbreak in Indianapolis didn't occur after the Bobby Knight firing, did it?

Any questions of Dr. Markowitz in general? Just one question; does everyone that is infected with syphilis develop clinical symptoms? That is one question. The other

question is at what stage or stages is the blood considered to be infectious for transmission? If it is going to be covered by somebody, I can deal with it later. But, if not, could you answer that?

DR. MARKOWITZ: I would say that probably not everyone does develop--well, the issue is do they develop symptoms or do they recognize symptoms. I think some people don't recognize symptoms so they are picked up and they report never having symptoms.

So, in that situation, the primary stage can be totally missed. People may not report any symptoms and they can be picked up only on the basis of the serologic tests. So that does happen.

When the blood is infectious, I tried to illustrate that. Maybe I wasn't so clear on my pathogenesis slide. The feeling is that in primary and secondary, certainly, the patients are bacteremic and, in latent syphilis, early-latent syphilis, there is intermittent seeding of the blood stream so there would be bacteremia during early-latent.

My understanding of the old literature is that it is in late-latent as well, because there are cases of congenital syphilis that occur in late-latent and because there are some transfusion-transmitted cases that have occurred in those stages. So I think the risk decreases.

And I think the data from congenital syphilis would illustrate this best.

DR. HOLLINGER: Questions? If not, we will move on. Thank you, Dr. Markowitz. The next presenter, Roger Dodd, is going to talk on--oh; I'm sorry. I did promise Dr. Schmidt that he could show two slides. But you don't get fifteen minutes, Paul.

DR. SCHMIDT: Part of this is a going-away gift to Blaine. He can say, "I was at a committee in Washington and they showed slides of patients," or at least parts of patients.

[Slide.]

This patient is the case that you keep hearing referred to which is the last case of transfusion-associated transmitted syphilis in the United States. This was a patient we had in 1966 at the Clinical Center of NIH who had a lymphoma. Among other treatments, he had 25 units of very fresh platelets, all negative by the VDRL and, several months later, he came back to the clinic like this.

He was well treated, but we were able to retest all but three of those donors. All the ones retested were still VDRL-negative. We were not able to retest three of the donors.

[Slide.]

This next slide, there was classic secondary

syphilis. The old literature describes it as this way and commonly seen on the extremities. I had never seen a case before or, obviously, since. We mentioned in our report we ought to be seeing more of these with the introduction of fresh platelet transfusion, but we haven't seen them. Of course, in my thinking, it was always that post-transfusion syphilis was a disease of direct transfusion, direct donor-to-patient transfusion.

Also combined with the fact that in that era which was pre-World-War II, we did not have penicillin. So this died out pretty rapidly after World War II.

But, anyway, thank you for the opportunity to show a patient.

DR. HOLLINGER: Paul, just one question. You said the VDRL was negative in this case.

DR. SCHMIDT: I'm sorry; in all the donors, and negative in the patient when admitted to the hospital but strongly positive in the other tests as well when he was retested at this stage.

DR. HOLLINGER: But it was never proven that any of the other donors were positive; is that right?

DR. SCHMIDT: That's correct, but there were three who avoided us and--

DR. HOLLINGER: David?

DR. STRONCEK: I have kind of an obscure question.

Do you know anything--if we are given more apheresis platelets now and if a donor was infected, would the bacteria be more or less concentrated in apheresis platelets than in peripheral blood?

DR. SCHMIDT: I hope we are going to talk about the studies to find out why platelets don't transmit. The number of platelets given is enormous. I do have a copy here of the first NIH minimum requirements for whole blood which are 1945. In there, it says, "The random selection of donors should yield only one bleeding containing viable S. pallidum in approximately 9,000 bleedings."

So you can make the calculations at the much greater frequency of it in donors at that time, but still, with all the platelets we are giving, we should be seeing it.

DR. HOLLINGER: Thank you, Paul.

Roger? Dr. Dodd on diagnostic testing for syphilis.

Background on Diagnostic Testing for Syphilis

DR. DODD: Thank you very much, Blaine.

[Slide.]

I would like to follow Mike Busch's lead and offer my tribute and thanks for your service as chairman of this committee. I would like to point out that I have known Blaine for many, many years and his hair turned white long

before he joined the committee.

[Slide.]

My job, really, is to try and guide you through the morass of the diagnostic tests for syphilis and to indicate how they are used in the transfusion environment or the blood-screening environment. I think my primary message is that you really have to kind of dissociate the two components; that is, you have to not think exclusively about the diagnostic data that you have heard to date because this is all founded on some clinical expectation that there is going to be a disease and checking out that expectation vis a vis screening where you really have no other information at all about the individuals who are tested.

[Slide.]

I wanted to make three key points before proceeding. The first one I have already made and this is a commonality for all aspects of blood-donor screening, that screening asymptomatic populations is very different in context from performing diagnostic tests.

Secondly, and this is a message you have already heard, in this particular case, syphilis, the sensitivity, the clinical sensitivity of any test varies with the phase of disease and the nature of the test, itself. Finally, I shouldn't need to remind this audience, but the positive predictive value of any test--that is, the proportion of

reactive results that turn out to be true positive--is inversely proportional to the prevalence of infection in the population.

So, if you have a very low prevalence of infection, you may have a--did I get this right way around? If you have a low prevalence, in any case, you will have a very low predictive value, positive predictive value.

[Slide.]

You have just heard about the key phases of syphilis, clinical syphilis, primary, secondary, latent and late and/or tertiary disease. We would also point out that we need to have in our minds what happens after successful treatment. That may not be the right place to put it in this particular sequence. And I would also comment that clearly there is a pre-seroconversion phase that we do not know a great deal about but we might want to recognize that there is some potential for infectivity before what is classically termed the primary syphilis.

[Slide.]

As you have already heard, and I am going to choose to look at these in three different categories, there are really different categories of tests, diagnostic tests, for syphilis. The non-treponemal tests are, in fact, tests for antibodies that react with a relatively non-specific antigen.

In the early days of syphilis work, there were attempts to develop a syphilis antigen from which to develop tests and these were developed by various treatments of organs from infected individuals. These tests worked and it wasn't until much later that it was determined that the antigens which were putatively syphilis antigens actually came from the organs, themselves.

Quite a lot of effort was put towards developing a standardized cardiolipin antigen which is not a treponemal antigen although some believe that the agent, itself, really may be some of these sorts of antigens. Typically, and I am not trying to be exhaustive here, the tests that fall now into this category are VDRL and RPR, which you already heard about.

Treponemal tests, really there are two sets of these. The first is some way of directly observing the organism, itself, the spirochete, and this is done on exudates from lesions and does not really relate to our discussion right now.

But conventionally there are really three techniques that are in use right now. The first is the fluorescent treponemal antibody test so you are really doing a standard fluorescence assay. The ABS refers to an absorption step which removes a number of the antibodies to nonpathogenic treponemes before the test is undertaken.

And there are a number of agglutination tests, red-cell and now even particle agglutination tests in which particles are coated with treponemal antigens and are used to detect antibodies. There is at least one EIA test which is also designed to detect antibodies to treponemal antigens.

You will hear a little bit later what is really an investigational test at this time, nucleic-acid testing, either for treponemal DNA and/or for RNA. I will only mention that briefly as I go through the rest of this presentation.

[Slide.]

This is a chart that I stole from a very nice review by Sandra Larsen dealing with diagnostic testing for syphilis. I think quite a lot of points can be made from this graph. Here you see the various phases of disease, primary, secondary and the late stages of disease. Late in this case actually starting on this graph at ten years and going out to 40 years.

The first thing is that both treponemal and non-treponemal tests come up relatively rapidly at the early phases of primary disease. As I pointed out, we really don't know what is happening here but I suspect that there might be some potential for dissemination of the organism although that is not really relevant to the rest of the

discussion, I think, other than what you will hear from blood banking organizations.

I think the key thing to recognize here is that, on this chart, are two treponemal tests, a microhemagglutination and the fluorescent treponemal antibody test. Both of these come up, although at slightly different periods, and are maintained throughout the disease, itself, or throughout the course of syphilis.

On the other hand, here RPR or non-treponemal test drops off over the years. But I would point out again, on this diagnostic chart, that it never really--the sensitivity of this test never really drops to zero in terms of untreated disease.

[Slide.]

So just commenting, again, briefly on the non-treponemal tests, I have already discussed the fact that they detect antibodies to a nonspecific antigen. The specificity of the non-treponemal tests is considered to be 100 percent in secondary disease; that is, 100 percent of cases will be detected by non-treponemal tests. But subsequently there is a decline in both the levels of antibody and the proportion of individuals who react and this decline is very marked with treatment.

If you look at the specificity of these non-treponemal tests, they are quoted as 97 to 99 percent. That

means that in a nonsyphilitic population, you might expect 1 to 3 percent of all tests to be false positive. Not very impressive.

[Slide.]

This, again, from Larsen's paper, represents the changes in titers of results from non-treponemal tests attendant on treatment with penicillin. You can see the titers drop very rapidly into essentially undetectable levels within three months of initiation of treatment. So this is a key component of the non-treponemal test site.

[Slide.]

Treponemal tests, as I discussed, detect antibodies directly. The sensitivity of the treponemal tests is quoted as 100 percent in secondary and latent, so the point here is that the treponemal tests remain high throughout the course of disease. So the decline with disease is not so apparent and reactivity is maintained after treatment.

Although the treponemal tests generally have higher levels of specificity, it is not 100 percent so you will still get false-positives and these will represent a fairly high proportion of all reactives in, for example, a donor population.

[Slide.]

I don't think that we need to spend much time on

what is sensitivity, what is specificity and what is predictive value other than to point out that predictive value will vary with prevalence. These are inherent characteristics of the test, itself.

[Slide.]

Having said all that, here are some data taken primarily from the Larsen paper and also from one of the manufacturer's product inserts. The points to be made on this particular chart which represents diagnostic performance is that in primary syphilis, none of the tests is 100 percent sensitive. In fact, all of them are in the 83, 84, 85 percent range.

So even in primary syphilis, the sorts of tests that are used for screening or diagnosis may not always be reactive. Secondary syphilis, however, when, in many cases, the individual is symptomatic, these tests are all 100 percent sensitive so it should pick all of those up. The other point is that the non-treponemal test listed here drops but only to about 73 percent in late or post-latent syphilis whereas the two treponemal tests maintain their levels throughout this disease.

[Slide.]

Let's see how this pans out in the blood-center environment. This represents primarily the American Red Cross algorithm for syphilis screening of donors. Other

major blood organizations have rather similar algorithms. We screen each donation by an agglutination test, the PK-TP test which runs on an automated blood typing machine and reactive samples are repeated in duplicate.

The repeatedly reactive samples are then further tested for confirmation by FT-ABS fluorescent treponemal antibody ABS or, in some cases, by treponemal enzyme immunoassay test. Certainly, in our case, from this group, the positive and minimally reactive samples are further evaluated by a non-treponemal test, RPR. This is used for counseling only and the concept is that the an RPR reactive is more likely to represent active disease.

[Slide.]

This represents 22 months worth of data from the American Red Cross system. So this is the number of repeatedly reactive donors that turned up in our testing on a monthly basis round about 800 with a peak when we moved from a PK 7100 to a PK 7200 system generating, if you like, a new population of what must be false-positive results because the FTA ABS confirmed and the RPR rates did not vary very significantly here although I think you can see a little peak here.

[Slide.]

If we look at that in terms of numbers, those data averaged out on a monthly basis so our system collects about

500,000 units each month. Amongst those, almost 900, or 0.18 percent are repeatedly reactive by the screening test, the treponemal screening test.

Of those, 424, or only 43 percent, are actually confirmed by FTA ABS representing 0.08 percent of our donor population or our donations, to be more accurate. As you will hear later, if you take these kinds of samples that are PK-positive, FDA-positive, or PK-reactive, FDA-positive, and you do PCR on them, whether for DNA or RNA, Sharyn Orton found that none of them had detectable levels of treponemal nucleic acids and the 95 percent confidence interval of that observation would not exclude the possibility that some 3 percent of this group could potentially be at least circulating detectable RNA or DNA.

Within this whole group, only 23 percent are actually RPR-reactive. You will remember from the diagnostic category, you would not expect to find this at any stage. You would expect all of these to be true-positives and probably 60 or 70 percent of them should be RPR-positive if you didn't have treated individuals in this group.

[Slide.]

This is not really critical, but these are bulk data. What I really wanted to point out is that we categorize the fluorescent antibody testing into two groups,

minimally reactive which represents 9 percent of the total here tested and, of those, only 6 percent are RPR-reactive, leaving one to wonder if there isn't some form of false-positivity for both markers.

Of the 9,300 or so that were confirmed as greater than plus, 29.4 percent were RPR-reactive, again a very low number and, again, overall, a similar figure, 24.5 percent of FTA ABS reactives were RPR-reactive.

[Slide.]

So I don't want to draw any strong conclusions from this. My comments about these kinds of observations would be first of all that in a pre-screened donor population--that is, many of them have been tested time and time again, the positive predictive value of the PK test is less than 50 percent for antibody. We don't know what it is for disease but, clearly in terms of its relationship to detectable nucleic acid, it is much lower than 50 percent.

The frequency of reactive test results among PK-TP reactives, so you take these screening-reactive individuals and you confirm them is actually inconsistent with the diagnostic model, so this is the real message; don't equate diagnostic models with screening models.

I think that a small to zero proportion of STS confirmed positives have evidence of active TP infection in studies to date.

Thank you very much.

DR. HOLLINGER: Thank you.

Questions? Carmelita?

DR. TUAZON: Later on, the PCR, are the 97 RPR reactive?

DR. DODD: Dr. Sharyn Orton will be discussing that along the way.

DR. HOLLINGER: Thank you.

Ken?

DR. NELSON: Of these that are repeatedly reactive, you then counsel or have histories on the donors. How many of those have had a history of syphilis in the past that was treated?

DR. DODD: I don't know if Sharyn is going to show this data, but when we get down to this confirmed group, on the basis of case-control evaluations, and correct me if I am wrong, Sharyn, about 50 percent of them report having a past history of syphilis, in many cases treated syphilis.

So, certainly, we are picking up some individuals with a history of prior syphilis. I heard your question and I don't know the answer to how that distributes by RPR but, perhaps, Dr. Orton can comment on that.

DR. NELSON: And those that don't have a history, then they are referred for medical evaluation, I guess?

DR. DODD: They are notified and the results are

interpreted to the best of our ability and they are advised to seek medical support. But this is generally a hands-off process rather than a personal interaction.

DR. HOLLINGER: Roger, you seem to suggest that the difference between the RPR-reactives and the FDA-positives, that 22 percent versus 43 percent, is either because of post-treatment of latent syphilis? Is that the assumption?

DR. DODD: I think the simplest explanation in my mind is that if you accept that the FDA's really, truly confirm, then the majority of them must represent treated or are long past infection.

DR. HOLLINGER: Thank you, Roger.

Dr. Markowitz now is going to return and talk about syphilis surveillance and bloodborne transmission.

Syphilis Surveillance and Bloodborne Transmission

DR. MARKOWITZ: Thank you.

[Slide.]

I don't know what the real correct title of this talk should be. It has had different titles. But actually the main thing I am going to talk about is something that we tried to address at CDC and that is whether or not persons with infectious syphilis, primary or secondary primarily, will actually go to donate blood, will they not be sick enough, will they not be picked up at the time of intended

donation.

So that was the main purpose of our analysis of surveillance data. Then we did find that those cases of primary and secondary syphilis do go to donate blood. So, after that, we tried to obtain some estimates of the potential of transfusion-transmitted syphilis. So I will walk you through both of these exercises.

[Slide.]

The main question that we attempted to answer was do persons with infectious syphilis donate blood and, if so, how many, approximately, each year donate blood. That was the main initiating objective of this exercise.

In order to review this, what I am going to do is first briefly provide an overview of syphilis surveillance in the U.S. so people can understand how we obtain these data. Then I will give some information on reported cases that we did identify from donor screening that were reported to CDD and, finally, I will present some estimates that we made on the potential of transfusion-associated cases that might occur in the absence of screening.

[Slide.]

Syphilis, I think as most people know, is a reportable disease in the U.S. and reporting to health departments occurs through various routes. I have tried to represent this schematically on the slide.

First of all, a symptomatic person can present to a clinician and be diagnosed with syphilis and then be directly reported to the health department. Also, both symptomatic and asymptomatic persons could have serologic screening either as a diagnostic test or because they are ill or just for routine screening.

Those serologies are directly reported to the health department, so the health department can obtain both a case report and a serologic report. Once a serology or a case is reported to the health department, further evaluation occurs. The first thing that happens is that serology and there is checked in a registry that is actually kept in all health departments. This allows the health department to determine which serologies may be follow-up titers on previously diagnosed and treated cases.

These cases are not investigated further. Health departments with a very high case load actually have other criteria for which they use for making decisions on investigation or noninvestigation of cases. If it is indicated, after checking in the central registry, the follow up is initiated by the health department and a team of investigators would go out and investigate the cases, or I should say the person.

The persons are interviewed, examined or their medical records are reviewed and the case definitions that

CDC uses for surveillance are applied. At that point, the disease-investigation person either makes a decision that it is not a case, in which case, it is not reported, or it is a case that is reported to CDC.

Since this is often a population that is very hard to follow up, in many states, there is a sizable proportion of persons with positive serologic tests for syphilis that cannot be located and are lost to follow up and, therefore, cannot be reported or evaluated. So only cases that actually have a full evaluation get reported to CDC.

[Slide.]

The syphilis reporting system has changed in the past decade as state and local health departments have moved towards electronic reporting for all communicable diseases. NETS, which is the National Electronic Communication System for surveillance, was first implemented by CDC and state health departments in 1992.

This has allowed collection of data that was not previously available on cases. Relevant for our discussion is that source of report is one of the fields that is collected electronically now. So if a patient comes in and was reported by a private physician, it is private physician. If it is the STD clinic, STD clinic. And if it is a blood bank, it will say blood bank on there.

Now, the previous system, which has been in place

for a long time, is the STD morbidity report system. This will be eventually replaced by the electronic system, NETS. It collects hard-copy data as aggregate data from all 50 states.

Detailed information is not available on all of these cases. Since 1992, each year more states have sent data electronically and, in the Year 2000, all but a very few states are now reporting electronically.

[Slide.]

To estimate the donation-identified cases of early syphilis, and for this exercise, we just looked at primary, secondary and early-latent from 1995 to 1998, we used the source of report field in the NETS data that was coded as blood bank.

In order to estimate the number of cases that occurred in the whole country, we had to make an adjustment because not all states were using NETS in 1995 to 1998. So we adjusted the NETS data using all the data that reported from the STDMR system by multiplying by an estimation factor. This was simply dividing the STDMR cases by the NETS cases.

Then we multiplied the number of NETS cases that had been identified as having blood bank as their source by this estimation factor to come up with a projected total cases for the U.S.

[Slide.]

This slide shows the data that we came up with using this. First of all, you will note that the estimation factor decreases between '95 and '98 because more states were reporting electronically. So we didn't have to make as large of an adjustment in the later years.

We also made separate adjustments for primary, secondary and early-latent. In this column is the total cases reported in the U.S. and these are the numbers that were reported to NETS and then our estimation factor.

This is the number of cases that had blood bank as their source of report. So, overall, in these four years, we had 67 primary and secondary cases that had blood bank as their source of report. And then, using our estimates, that turned out to be 142 cases during that four-year period that had blood bank as their source of report.

For early-latent, there were an actual 261 cases through our electronic reporting system who had blood bank as their source and that projected up to 785 estimated cases that would have had blood bank as their source. Now, there are problems with all this but I am just walking you through to show you how we try to get these estimates.

So then a total of primary, secondary and early latent, we had 927 estimated cases during the four-year period that were reported through the blood-banking system.

These are people, then, that were detected, had a positive serology by the blood bank and they were referred--they were investigated by the health department and the health department made a determination that, in fact, yes, they were primary, secondary and early latent based on a review of clinical records and interviewing the patient.

[Slide.]

One major limitation of the NETS data that came up actually when we were doing this analysis is the fact that the NETS data doesn't really distinguish between a blood bank and a plasma center so that they would both be coded as blood banks.

When we actually first saw these data, we were surprised, ourselves. So what we did is we went back and we called the STD program directors of four states that accounted for the majority of donation-identified cases in 1998. This is a year-and-a-half later when we did this because this is all occurring in the last year in response to our discussions with FDA.

So this was not a real-time interview of these STD program directors. But just to let you know, one director said almost all the identified cases were from plasma centers. One STD program director said they were all from blood banks. In two other states, they said they were from both and the proportion from blood banks was only slightly

less than the proportion from plasma centers.

I didn't bring this data but most of these, the four states that reported the majority of the cases identified through blood banks or plasma centers were all in the South in areas that we know are high-incidence states.

[Slide.]

Just to put this in perspective, and if anyone got an earlier slide, there was an error that I have corrected but I just wanted to show you the proportion of blood-donation-identified cases in relationship to all of our reported cases and they actually account for a very small percent.

So, during these four years, there were over 43,000 primary and secondary cases. Only 0.3 percent were identified through the blood-donation system There were over 76,000 early-latent cases and 1 percent were identified through this--they had source of report of the blood-bank system.

[Slide.]

The next thing we tried to do was to estimate the number of donors who would be potentially infectious. To do this, we made a variety of assumptions. In this slide, I have shown the assumptions we used to find out how many infectious donors would result from these primary and secondary cases.

So the first assumption was that all primary and secondary cases were bacteremic at the time of donation. The second assumption was that early-latent cases, 5 percent of them, would be bacteremic. We could pick different numbers and I am mainly walking you through so you could see our thought process that we used.

So, therefore, we had 102 primary and secondary cases divided by 4 to get the yearly number times 100 percent is 36 of those, 36 primary and secondary per year, would be bacteremic at the time of donation. For early-latent, 785 divided by 4 times 0.0510, so we came up with possibly 46 donors per year would be bacteremic at the time of donation.

[Slide.]

The next part of this I even had more difficulty I think getting some real data. I have had some discussions with a variety of people at the American Red Cross and the FDA after we made our initial assumptions, and I will present two different ways we looked at this.

The more we thought about this, we realized we didn't have a lot of good data to estimate the risk posed by these 46 bacteremic donors. The reasons for that are the following, and I am sure other people here will come up with other reasons.

First of all, we didn't really know what we should