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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

63RD MEETING

VOLUME II

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P R O C E E D I N G S

Statement of Conflict of Interest

DR. SMALLWOOD: Welcome to the second day's session of the 63rd meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the executive secretary. Yesterday, I read the conflict of interest statement that will apply to the proceedings of this meeting today. That meeting statement is available if anyone would like to review it.

I would also like to announce that Dr. Norig Ellison has joined the committee today. Dr. Ellison, would you raise your hand, please.

Today, the agenda will be hopefully followed as printed. At this time, I would like to turn over the proceedings of the meeting to the committee chair, Dr. Blaine Hollinger.

DR. HOLLINGER: Thank you, Dr. Smallwood.

We have three main topics today. One is an informational presentation on the blood action plan and device action plan which were mandated before to see where we are with those plans. Then we are going to talk about deferral of blood donors for risk of malaria, and finally look at the development of HTLV supplemental tests.

So, with that in mind, we will start with the first presentation. Dr. Epstein is going to tell us about

the blood action plan.

Informational Presentations

Blood Action Plan

DR. EPSTEIN: Good morning, everyone. Thank you, Blaine.

[Slide.]

The FDA has been involved with the blood action plan for about two years now and, for some of you, this may be a little bit repetitive, but, perhaps for those who haven't heard this story, it will prove enlightening.

Starting in the early 1990s, both the FDA and the blood industry came under intense scrutiny as a result of investigations into the AIDS tragedy related to blood products in the 1980s. Much of the driving force behind these investigations came from consumer organizations, particularly the hemophilia advocates but also from the press.

There were certain landmark events. These included a series of Congressional Oversight Committee hearings that were lead initially by Mr. John Dingel when the House was Democratic and then later by Mr. Christopher Shays when the leadership changed.

There was also the publication of the book And The Band Played On, by Randy Shilts, which was highly critical of governmental action, particularly, and then a series of

articles in The Philadelphia Inquirer by Gilbert Gall which drew attention to existing deviations mainly reported through FDA, establishment-inspection reports and citations on the 483 form.

Some of these events led to a request through the Congress that there should be a study on the decision-making in the 1980s and, per request to the department, Donna Shalala funded a study by the Institute of Medicine to examine the decision-making in the 1980s related to HIV in the blood supply which led to the publication of a study in July of 1995.

Additionally, at the request of the Congressional Oversight Committees, there was a series of studies requested from the General Accounting Office, or GAO, which were conducted on various aspects of decision-making in blood and there have been several reports by the Congressional Subcommittee on Government Reform and Oversight that was led by Mr. Shays.

The issues that were raised, and I am going to summarize them on a series of overheads, briefly dealt with the following areas: first, allegations of wrongdoing by industry; second, the question of poor compliance status of the blood industry and the initial focus was on the American Red Cross although later the focus shifted to the fractionaters; the question whether there had been weak

oversight and weak enforcement by FDA; the alleged failure of both industry and government to communicate the risk of blood products to consumers; the charge of poor governmental coordination and responsiveness in emergencies; and the perception of a lack of clear regulatory requirements for the blood industry.

In addition, there were a set of incidents that brought these matters to a head. And these included the bacterial contamination of Centeon's albumin which occurred, or came to light, in September 1996, a large number of product withdrawals that were related both to manufacturing problems but also to the theoretical risk of CJD which caused great fear in the public.

And then there were other specific product concerns that came to light such as an incident of hepatitis A transmission by one of the companies' Factor VIII products.

Following a series of briefing by CBER and in the wake of comprehensive report issued by the GAO in February, 1997, then Acting Commissioner Mike Friedman directed the center to identify the key issues and develop an action plan so as to focus the agency and department attention on them.

As a result, a blood action plan was developed in July, 1997 with the following global objectives: first, to restore public confidence in blood safety through

communication, through the effective correction of deficiencies and general enhancement of the blood safety; second, to bring the blood industry and all its parts into full GMP compliance; third, to streamline FDA operations in the blood area consistent with reinvention initiatives which were also ongoing mainly under Vice President Gore's Reinvention of Government Initiative; and, finally, an attempt to bring supplemental resources into the blood program to accomplish these expanded tasks.

[Slide.]

What I am showing you here is a graph that is cited from New England Journal, February '99 issue, with permission of Jim Aubichon, one of the coauthors. This shows the rather dramatic decline in the residual risk of infection with major transmissible diseases per unit of transfusion since the onset of the recognized AIDS era in blood of 1983.

What you can see is that there was essentially a three-log decrease in the risk of HIV, a two-log decrease in risk of hepatitis C, and a one-log decrease in risk of hepatitis B but that is on top of about a two-long decrease in risk that occurred with the screening of the blood supply since the early 1970s.

One might ask with these rather dramatic safety improvements, why is there an issue here?

[Slide.]

I call this current problem the blood safety credibility gap. This gap in credibility can really only be understood if one understands the implication of AIDS which I have called the shadow of AIDS. So what is the shadow of AIDS? The problem, as I understand it, is that authorities not only failed to recognize early and warn about AIDS risk from blood products in the 1980s but, at the same time, were stating that the risk was remote while, in fact, the epidemic was raging.

Then what happened is that public confidence was shaken both by the failure to protect the public from AIDS which, of course, came to light but, also, the perception that there was a belated, if you will, admission of the risk. I am not saying that any of this is wrongdoing. It is just that that is what happened.

[Slide.]

Then the question is why do those problems of credibility persist? The explanation lies in understanding a set of perceptions concerning the industry and concerning the FDA which are, in fact, the issues that we are dealing with. What were the perceptions dealing with the industry? That they denied their problems, both their manufacturing problems and the fact of emerging threats, that the industry operated secretively, that the industry did not function up

to GMP standard, that the industry maintained poor relationships with the consumer community and that the products, themselves, were of variable safety and quality.

On the governmental side, the perceptions are that government had been slow to act in any of its dimensions, whether it was establishing policy, enforcement actions, or taking precautionary measures and emergencies. We were accused of having worked inappropriately closely with the industry in establishing policies, having industry representatives voting on advisory committees, preannouncing blood inspections, et cetera.

We were accused of having a very confusing web of regulations and guidance, that our administrative procedures, particularly related to applications and the speed through which we could approve innovations was sluggish and burdensome, and that we were underutilizing available information on adverse experiences, reports that already existed either in the literature or at the CDC or through reporting mechanisms to the agency.

These issues were brought, in various ways, to the attention of the FDA through oversight activities. Who are the main overseers? The main overseers, as I have noted--we had the landmark report of the Institute of Medicine although the Institute of Medicine does not have a standing function of oversight with respect to government or the FDA,

Congressional hearings where there are, indeed, committees and subcommittees empowered with an oversight function which they liberally exercise.

The Office of the Inspector General is an arm of the Department of Health and Human Services and it conducts investigations both of activities of the agency as well as allegations of wrongdoing. And the General Accounting Office which provide reports on the model of white papers generally at the request of the Congress.

I am going to review the various recommendations of each of these bodies since 1995.

[Slide.]

First let's start with the recommendations of the Institute of Medicine in its study of July 1995. I put this first because I think that it is, in fact, the landmark event that has changed the landscape and changed the paradigm that underlies much current thinking.

The IOM recommended with regard to the Department of Health and Human Services that it should establish a blood safety director, a blood safety council, and an expert panel. The blood safety director was established by Donna Shalala in 1995 as the Assistant Secretary of Health, and I'm sure that most of you know that also with the current administration, the position of the Surgeon General and the Assistant Secretary of Health are merged into one position.

They are both currently occupied by David Satcher.

Additionally, a Safety Council was established. It is called the Blood Safety Committee. It is constituted by the Agency heads and deputies of the Public Health Service agencies, FDA, CDC and NIH as well as other components of the department. That group meets approximately quarterly to address all emerging issues pertinent to blood safety and availability.

Additionally, an expert panel was constructed. That is the PHS Advisory Committee on Blood Safety and Availability. That committee has been meeting regularly since I think it was January, 1997 and periodically makes recommendations regarding global issues of public health pertinent to blood safety and availability be they economic, social choice, legal, ethical or sort of cross-cutting public health. They have a very broad mandate to look at issues in distinction to the Blood Product Advisory Committee of the FDA which hitherto had been the only advisory group and which is really only empowered to deal with scientific questions pertinent to regulation.

So we look to this committee for scientific judgment. We look to that committee to sort of synthesize it in the global, societal sense.

The Public Health Service was specifically advised to make better use of information coming out of the CDC

Surveillance program, particularly early warnings, and to make efforts to monitor the supply and availability of blood. We have taken steps to improve the communication link between FDA and CDC, for example. We have a monthly conference call. It is a group that is called the PHS Interagency Working Group on Blood Safety and Availability. One of the key arms is liaison from the CDC and we do get routine reports on emerging issues and respond to warnings as well as coordinating our activities.

The FDA was specifically advised to rebalance the Blood Products Advisory Committee. We did this. We changed the charter in 1995 so as to permit consumer representation. Hitherto, the charter required that we have only people who were qualified based on expertise in a related science.

In addition, while we still have that criterion for membership, we have a criterion for persons who represent consumer interests but who are deemed adequately knowledgeable to discuss issues. And we have done that. That is why we have voting members who are advocates in addition to having a purely consumer representative who is nonvoting and considered a lay representative.

We were admonished and this is, perhaps, the most important thing, to implement partial solutions wherever feasible in the face of uncertainty where we thought we would do no harm. That has been called the precautionary

paradigm and it is impossible to understand the decisions that have been made regarding HIV antigen, regarding CJD, regarding the UK donor deferral, without truly grasping the significance of the precautionary paradigm as it was articulated by the IOM. That is the current mode of thinking.

Additionally, we were told to provide clearer regulation and I am going to go into some detail on a rather sweeping regulatory initiative, and to periodically review past decisions which we have been doing with the Blood Products Advisory Committee. It is one of the reasons that you are more frequently hearing informational presentations so that you know what we are up to and can think about it.

The Congress was advised to establish no-fault compensation for blood injury. That has not happened, although there have been certain bills passed, the Ricky Ray bill, for example, that have dealt with compensation for particular injuries for particular patient populations.

Physicians generally were advised to improve their discussion with patients regarding risks and therapy options. I think most treaters know that. And, lastly, the volunteer organizations were advised to be more careful about avoiding conflicts of interest

[Slide.]

What about the Shays Committee on Oversight? The

Shays Committee issued its first report in August of '96. It advised Congress to establish the department's Blood Safety Committee and the PHS Advisory Committee in law. The concern was that this was a wonderful step forward by Dr. Shalala but what happens next? Administrations are not forever but the Congress has not followed up on this.

Additionally, the Shays Committee echoed the report of the IOM and recommended that there be creation of an indemnification system for blood injury. The department was advised to disseminate more risk information and you may have noticed that there have been more public statements that the Assistant Secretary and Surgeon General have spoken out repeatedly, generally in the context of the PHS Advisory Committee on Blood Safety and Availability and taken affirmative positions on some of the complex issues in that domain.

The FDA was specifically advised to require look-back for hepatitis C. This was based on the perception that the Public Health Service in the large was not responding adequately or promptly to a perceived epidemic of hepatitis C and its sequelae of liver failure and cancer and that there was a latent epidemic, if you will, of those diseases which could, perhaps, be interdicted and that since one part of it, or about 7 percent, was due to blood transmission prior to the era of screening, that we should do something

about it through targeted look-back which we will discuss.

We were also advised that we should improve notification systems related to recalls and withdrawals, particularly of plasma derivatives, and we have an initiative in that area, that we should work to limit the size of fractionation pools. Those of you with a long memory know that we addressed that issue at multiple meetings of the BPAC and that there is now a voluntary policy within the industry to limit fractionation pool size to no more than 60,000 donors per final product including any and all secondary pooling or addition of excipients such as albumin into clotting factor. Lastly, we were advised that we should significantly strengthen our inspectional processes.

[Slide.]

The landmark recommendations of the General Accounting Office were put forward in their February, '97 report which was quite specific and came in the wake of, if you will, corrective measures that have already been put in place since 1995. They recommended that we should create regulations to require the notification of donors who are deferred as a public-health measure presumably to prevent secondary transmissions but also to prevent such donors from coming back to redonate based on educating them to their risk, that we should test all autologous donations.

This was very controversial. We had met many times with the Blood Products Advisory Committee but there was a report that came out of the AABB that was quite telling indicating that there were errors of unit release which were occurring from autologous collection--autologous donations do not have to meet donor suitability standards and this was perceived to create increased risk--as well as the concern over possible exposure of healthcare workers to positive units that might be drawn but not tested and recognizing that, in the face of human frailty, universal precautions might not always be followed.

We were asked to: require confirmatory tests on all reactive units. That, of course, has been a recommendation of the FDA going back to the 1980s but was never a requirement; to require look-back for all markers, the FDA commented that we would review which markers were pertinent. We have not fully adopted that recommendation although we accept it in spirit; to require periodic quality-assurance tests for bacterial contamination. The Centers for Disease Control is now in the process of conducting a comprehensive surveillance of bacterial contamination in platelets as a basis for future action and we have also planned another workshop on that subject; to require universal error and accident reporting, the universality here being that it is currently a requirement

for licensed blood establishments but not for the registered blood establishments which collect and process blood components and so we would be extending the requirement; to move all pertinent guidance into regulations. We are talking about taking nearly three decades of accumulated guidance and moving them into regulations, no small task; and, finally, once again, to improve our inspectional procedures.

So that is the background. That is why we put together a blood action plan.

[Slide.]

What is the blood action plan? First of all, the blood action plan consists of a set of teams that are organized around a set of issues and it is managed within the agency on the model of project management. We have a full-time project manager that tracks the activities of about sixty different working groups and the work across the agency, about 100 people.

As I said, it was developed by the FDA in July, '97. However, it requires interagency participation and, for that reason, it was necessary to gain the endorsement of the department. This plan was presented to the department in late '97 and then it was adopted on behalf of the department in March of 1998.

So, at that point, it became not just an FDA

initiative but a departmental initiative. First of all, we have a steering committee which we call a core team which meets monthly. The core team, of course, monitors and directs the activity of the working groups. Each of the issue areas, of which there are six, has a chairperson and then there are working groups in each area.

So how did we codify all this into a set of issues? We have issues related to updating the blood regulations. We have issues related to reinvention--this is really streamlining--issues related to emerging infections, insuring the compliance of the plasma fractionaters, notification and look-back initiatives and FDA responsiveness to emergencies and class I recalls.

[Slide.]

How have we done so far? The first year, which is basically reckoned from March '98 to March '99, we did a number of things. First, in terms of regulations and guidance, we published in draft form a guidance on gamma-irradiated blood and components, which is a program pilot for, if you will, deemed licensing.

This is a streamlining initiative and the main concept here is that if we publish a standard for a conventional product, that the industry shouldn't have to file a detailed application with all its operating procedures and validation data. They should be able to

simply make a showing before the agency that they are in compliance with the published standard.

We would, then, issue a license on the basis of that certification. Now, in the long term, the concept would be, then, that nothing further happens except for periodic annual inspecting. Under the pilot, however, we would still do 100 percent preapproval inspecting and use the preapproval inspection as the measure or the metric of whether they were, indeed, in compliance when they said they were whereas now we establish that both by reviewing their validation data as well as by going out and inspecting.

So the question is whether we can bypass the application filing. But that is still in draft form. It is not yet an implemented policy although if companies were to apply under the pilot, we would probably accept it on a voluntary basis.

Also, many of you, I'm sure, are aware of the change in the licensing policy for biologics whereby we have moved from a requirement for two applications, an establishment application and a product application, to a single biologics application which is harmonized with that drug application, new drug application. We would then issue a single license.

That requirement, to file the single biologics license application, is not yet a final regulation. It was

published as a proposed rule. We received comments and it needs still to be reissued as a final rule. However, the agency indicated that as it published and finalized guidance for filing out the application for different product areas, we would accept voluntary filings of a single biologics license application.

The point here is that in the area of blood and components, we have now published the final guidance for implementation on the biologics license application and are accepting voluntary submissions of the biologics license application. So we are moving forward on the streamlining initiative for application review.

[Slide.]

In the area of developing standards, we held a number of workshops. These included a workshop on blood licensing. This was a prelude to issuing the guidance. We had a workshop on donor suitability. This is part of a regulatory initiative to develop a proposed rule on donor suitability. This is to update all of the standards that have been put in place since the 1980s such as relating to infectious-disease risk factors for hepatitis and HIV.

We had a workshop on nucleic-acid testing--this was focused on hepatitis C NAT--in September of '98 and then in July of '99, we also cosponsored with CDC a workshop on tick-born illness and we have already summarized that at a

previous meeting of the Blood Products Advisory Committee.

In the area of emerging infectious diseases, we established a database of all the known significant threats to blood safety. An update of that was accomplished in April, '99, roughly the anniversary of the plan. And we provided in your packet the current updated database.

In addition, we have provided, in '98, a narrative summary of the PHS efforts to address these threats and we will be updating the narratives by September, '99. Additionally, it has been proposed that we should take inventory of all current PHS activities related to blood-safety threats and we will be developing that inventory also by September.

In the area of assuring compliance of the fractionators, as you heard yesterday from Mr. Masiello, we established something called team biologics, which is a new relationship--actually, it began in October, '96--between the field force and the center for how we approach compliance in the blood area.

To make a very long story short, what we created was a specialized cadre within the field for us to deal with biologics which includes not just blood but also vaccines and biotech therapeutic products. That cadre of about 25 people has been intensively trained in biologics law and the issues pertinent to biologics inspecting.

Additionally, they are supported by designated product specialists within the center and the product specialists go out on the inspections with them. The main change is that the lead responsibility for periodic inspecting now lies with the field instead of the center. The reason for that is that historically there has been more focus and training in the GMP area in the field whereas there was more product-specific knowledge in the center.

So, if you will, we have a bit shifted the balance toward the GMP side and therefore we have retained the premarket inspecting as the lead responsibility of the center that understands the products and the science and the lead for the postmarket inspecting on the field force which has the lead expertise in GMP.

We have already rolled out the problem for the plasma-fractionated products for the in vitro diagnostics in blood and for what we call the blood cadre which is a trained group of about 100 people who have had specialized training in blood and components.

Under this issue area, we also call for annual evaluations of effectiveness and those are being performed by the subgroup. Additionally, in the area of response to emergencies, fortunately, we have not had a class I emergency since, really, the centeon incident in '96. So we haven't been tested. But we are very mindful of the issue

of preparedness and we have had annual refresher training on emergency operations.

The most recent refresher training was just this last March. It consists of, basically, two hours of videos and discussions live with experts via pictel link. Once again, there is a quarterly performance review although there is nothing much to review quarterly when there are no incidents. But, if there are incidents, they will be reviewed on a quarterly basis.

[Slide.]

So where are we, looking ahead? In the area of regulations and guidance, we are continuing to update blood regulations and guidance and to move into guidance for implementation, the documents as the comment periods close.

I think everyone is well aware that we have a regulatory initiative on hepatitis C look-back. Let me mention that a revised guidance--as you know, the extant guidance is September, '98--that there was a PHS advisory committee met in January '99 and recommended extending the scope of the look-back to include first-generation screening since May 1990. We have, therefore, revised the guidance. We put that out on the Worldwide Web, the CBER website, yesterday morning or yesterday afternoon. You can download it off the Web and it will be expected to be published very soon in the Federal Register.

It is being published first for comment and we welcome comments. I believe we will be requesting a 60-day comment period. Let me just note that we have been working very aggressively to address the specific issues that were mentioned by the General Accounting Office such as updates on donor testing, donor notification, product standards for plasma derivatives and blood components, end-user notification in the face of withdrawals.

We will be working toward a proposed rulemaking in those areas and you will start seeing some of that in the fairly near future.

In the area of reinvention, as I said, we are in the process of finalizing the regulation on the biologics license application. We will be considering additional monograph pilots for deemed licensing in lieu of filing of applications in the blood area and we have a number of candidate proposals applicable to blood and applicable to source plasma.

We will be continuing to update the infectious disease threats to the blood supply--as I said, the last update to the database was just April '99 and you have copies that you are welcome to comment on--and, again, continuing to monitor the effectiveness.

Let me just say that there are a lot of additional areas where we expect to be developing regulations codifying

existing guidance. I have already mentioned some of these such as donor suitability. It is our current thinking that we should also address possible requirements to deal with infectious agent inactivation and removal in the manufacture of blood products, particularly derivatives, that we should probably codify labeling standards into regulations to create uniform blood labeling and, as I said earlier, extending the scope of the requirements of error and accident reporting to encompass all collectors and processors of blood and then certain of the issues related to notification in the face of recalls and withdrawals.

So that is what is on our plate. I hope that I have convinced you that the FDA has a very serious mind set addressing these issues and that they are, in fact, highly comprehensive of the concerns that have been brought to the attention of the agency by oversight bodies as well as attentive to what I call the issues of perceptions.

Opinion can vary how real or not real some of those perceptions are, but they are certainly issues, at the very least, of communication that we do need to address. So let me stop there. I am happy to entertain questions if time permits.

DR. HOLLINGER: Questions? Jay, it was an excellent summary of the blood review plan and I think something that has really been helpful to all of us sort to

understand the overview of this situation.

I might say that the transcripts of these issues are always on the website. I don't know how late they come out, how long it is between when we have a meeting and before they are published. It is not very long.

DR. EPSTEIN: Perhaps Linda can answer that. Do you know?

DR. SMALLWOOD: To my knowledge, the transcripts appear approximately 30 days after the meeting. They will be available on the website.

DR. HOLLINGER: I encourage you to maybe take a look at these again on this because it is a very good summary of where we are and what we are looking forward to. Thank you, Jay.

DR. EPSTEIN: Let me just say, by word of introduction for the next speakers, that this concept of action plans has been deemed by the agency and the center such a great success that we now have action plans in the areas of human tissue, xenotransplants and now, also, medical devices. You are about to hear about one of our newer action plans in the device area.

DR. HOLLINGER: Thank you.

With that introduction, we are going to ask Dr. Donlon, Associate Director for Medical Affairs of OCBQ to initiate the first part of this device action plan.

Device Action Plan

DR. DONLON: Thank you. And thank you, Jay, for that segue. The device action plan is the newest action plan in the center.

[Slide.]

I am going to briefly give you kind of a brief history and overview of the plan and then Dr. Lillian Yin will give you some of the nuts and bolts of where we are on some of the review and performance aspects.

As you may or may not know, the Center for Biologics is somewhat unique in the FDA in that it uses all of the regulatory authorities. It primarily uses the PHS Act to license biological products. It also uses the FD&C Act under NDAs for certain products. And it applies the Medical Device Amendments to certain devices which Dr. Yin will kind of bring to your attention.

So we do have a small component, primarily located in the Office of Blood of products which are regulated as medical devices under the Medical Device Amendments. That is basically the issue of why we needed to develop a device action plan.

The device action plan, as Jay indicated, because of the successes of our previous action plan, was initiated by Dr. Zoon and Dr. Feigal last fall. We just recently published it in April of this year. The committee members

have a copy in their folder. For those in the audience, it is available on the CBER external website under What's New for CBER. It has been posted there as of April 27.

[Slide.]

The genesis of our action plan came about, basically, last August and last fall. Under the FDA Modernization Act of 1997, there was an initiative to outreach to stakeholders. It was called the 406(b) provision in which various stakeholder meetings were held. In the meeting in August, several of the public and device manufacturers kind of raised the issue that, under the FDAMA of 1997, there were many significant changes impacting on medical device regulations.

The Center for Devices was moving fairly significantly ahead as far as developing new procedures, new policies, and, in addition, the Center for Devices previous to that had taken an initiative in what was called reengineering of medical-device reviews.

The basic question that was presented to Dr. Zoon and to our center was if the Center for Devices has all these initiatives, where is CBER as far as implementing or using these initiatives when we regulate medical devices as medical devices.

So, to address that, we basically did two things. First, we had our second public hearing in December in which

we invited very specific industry representatives and the public to voice their opinions and concerns about how we were regulating devices. Several things came up, some very predictable.

The issue of consistency; was the Center for Biologics consistently applying policies and procedures consistent with the way the Center for Devices had implemented things; harmonization between the two centers regarding those polices; the transparency of process for our centers as to how things were regulated, who was responsible, who was accountable, what the status of tracking, relative to that nature of that concern; whether or not we would facilitate reviews in a way that the Center for Devices had proposed of facilitating reviews and the availability and focus of various guidance documents; whether we were buying into some of the guidance documents that the Center for Devices was initiating and, clearly, communication not just between the two centers but also with the public and with industry.

So these were several concerns that were raised in these two meetings and, based on that, Dr. Zoon appointed Dr. Feigal and myself as co-chairs to develop a device action plan. Again, it involved several--more than several--members of the center assigned to different teams to develop that plan which eventually was finalized and signed

off in April of this year.

As I pointed out, Dr. Feigal was the initial co-chair of this when he was the Deputy Director for Medicine in the Center for Biologics. Since that time, Dr. Feigal has been appointed the Director of the Center for Devices and Radiological Health. That was not part of our device action plan, but we welcome that appointment as an indication that we can work closely with the Center for Devices in all these areas.

[Slide.]

Let me just briefly outline the issues of how we structure the device action plan and, again, we are just beginning with this so we don't really have a list of--we have some accomplishments that we can tell you about. We don't have a large list of accomplishments the way Jay indicated with the blood action plan.

[Slide.]

There are four areas that we focused on. One is the coordination between the two centers which, again, was a key concern of the stakeholders. The second was our internal review performance, ways of streamlining, facilitating that, organizing that.

The issue of compliance, inspections for devices and our working between compliance in the field, the team biologics concept that Jay discussed under the blood action

plan. Finally, our ability to outreach and inreach, basically, the communications issue, the transparency issue relative to our regulation of devices.

You have the detailed device action plan in your folder. I am just going to give you the overview of these four different teams. The Issue and Coordination Team: initially, there have been intercenter agreements between the Center for Devices and the Center for Biologics. The initial one was in 1982 that was revised in 1991.

Clearly, eight or nine years later, it is time, again, to revise that intercenter agreement based on several things, not the least of which is the advancement in technology and different devices, combination devices, different organizational structures between the two centers. So we are undertaking a joint review of that document and revision of that document. That should take several months to finalize, but we seriously need to update that to address some of the modern technical issues relative to devices and biologics.

CDRH, as I mentioned before, had initiated a few years ago reengineering efforts regarding their own process and how to establish reeingeering workgroups within the Center for Devices. We are establishing direct liaisons with that with our staff to their staff so, as they develop policy and procedures from their reengineering group that we

have an input and a knowledge of how that process is occurring and we can buy into that.

We put out, and this is one of our accomplishments, we have already published a Federal Register notice concurring with the many policies and procedures that Devices had been publishing last year. Under the FDAMA 1997 initiatives, they had a large list of action items that they were responsible for for taking the lead on as far as publishing policies and procedures.

They pretty much moved forward very rapidly on that. We were able to participate in some of those, but some of those moved beyond our ability to keep up with them. So, as an acknowledgment of our commitment to those policies and procedures, we published a Federal Register notice of concurrence basically saying that we would work within those policies and procedures as well as CDRH.

CDRH, again, is implementing a training program for the reviewer and their staff based on the FDAMA initiatives. We basically, rather than reinventing the wheel in biologics, will participate with them as they develop that again, hopefully developing a consistency of knowledge base and networking with the center.

We are developing a device web page at the center so that individuals accessing the CBER external page will find access to our device page that is under development.

That should be accomplished actually probably by the end of the summer, pretty quickly.

We do have on our web page the device action plan. We do have available on the CBER home page a list of device products that have been previously approved. We hope to have a list of our current devices that we are regulating as well as a linkage to the CDRH web page so people can jump to the CDRH web page for guidance documents.

The ongoing process here is that we are going to be participating in guidance development in preparation with CDRH in a collaborative way.

[Slide.]

Hopefully, the outcomes of these initiatives will lead to commitment, coordination, cooperation, communication and consistency, the "c" words.

[Slide.]

Another critical area that is a very significant part of the device action plan is our review performance. Dr. Yin will begin to address this in her brief presentation. Dr. Yin will have about half the time that I have because she talks twice as fast as I do.

We are currently analyzing our process, the work load and the resources we have applied to that process. This is kind of the basic strategy to define where the resources--how we can prioritize our device review, how we

can facilitate and streamline it and apply the right resources in the right way. We have limited resources. This device action plan does not buy us additional resources. We have to kind of work with what we have.

This may lead to some reorganization within the Office of Blood or the Center as far as streamlining accountabilities for these processes. This group will set review objectives and implement and manage review process.

In the center, in general, we have taken on the initiative of having a management review process for all products. Basically, this was an outgrowth of our user-fee initiative where we had certain time frames for our user fee for other products in the biologics. The devices do not come under the user fee here. That is why we don't have the user-fee resources for the devices.

Yet, we are still going to use that same management review process that we applied to the user-fee products and apply it to devices and then, basically, focus on the critical guidances that the industry will need to facilitate the review, the submissions and the review process.

Again, the outcomes, hopefully, will be defined expectations and priorities, meeting our time frames and deadlines in a priority type way, but maintaining the review quality. We don't want to sacrifice that. As you well

know, many of the devices that apply to the blood industry are very critical devices and we are not going to sacrifice quality in this process.

In the area of compliance and team biologics, again, as I said before, is addressing the issue of primarily of inspections and consistency of how we inspect our biological devices compared to how the Center for Devices inspects and the field operates.

Again, issues of policies, training, focussing specifically on an age-old question of sterility and stability of IVDs. That has always been a point of discussion and controversy. Finally, I think with the team biologics and this device action plan, we are going to get the resources focused on that to resolve that.

Again, outcome is coordination, transparent inspection process so that there is not a sense that there is a CDRH inspection of devices and a CBER inspection of devices and it is different. We want to have the sense that, if you are a device manufacturer using the Medical Device Amendments as your regulatory framework that you get consistent inspection and compliance actions, again, are consistent in the same way that we would have the same threshold and action items relative to compliance actions as follow-ups.

[Slide.]

The final team effort is the outreach-inreach. This is to maintain communications, dialogue with the public, with industry, with CDRH or other agencies that we need to be in dialogue with. In this sense, we probably anticipate having an annual CBER device open public forum where, again, people can come back, like a stakeholders meeting, and basically tell us what their concerns are and what initiative we need to be focussing on.

[Slide.]

Finally, some of the basic objectives here is harmony with CDRH for consistency, that our policies and procedures are efficient and that the communications are facilitated in all realms.

That is the overview. My colleague and now co-chair, since David Feigal left, Lillian Yin has been named co-chair of the device action plan. Those of you who don't know Lillian Yin, she is legendary in the agency. She was a division director in the Center for Devices, Office of Device Evaluation, for fifteen years. I don't know; it was a long time. She has extensive device experience and so she is very appropriate.

She is with us now. She is in the Center for Biologics as a specialist in devices and is certainly going to add to our implementation of the device action plan. And it is my privilege to show her slides.

DR. YIN: Thank you, Jerry. It is a pleasure for me to be here with you.

[Slide.]

I just joined the Center near the end of December of 1998. Before that, I was with Medical Devices and we used the acronym CDRH. I note this panel is very good. You always ask what those acronyms mean. In FDA, we are full of those. So the Center for Devices and Radiological Health is really CDRH.

And now I joined CBER. I am very, very pleased to have this opportunity because I think I know medical devices and especially FDAMA because we have been initiating those programs for all those years. Our action plan was just completed this April.

But I have the fun part. Panel chair and Dr. Epstein please stay with me for a short ten minutes or less. I usually try to time it. Normally, I will crack a fortune cookie to see what they tell me to say. But today, I don't need to. I know I have to be short and succinct so it will make life much, much easier.

I hope you all know the definition of medical devices. Okay; I took the opportunity to tear out a page to read it to you. A major distinction between drugs and devices, the definition is made in the statute of 1976. The definition of a device is recognized in the official

National Formulary or the United States Pharmacopeia or any supplement to them.

The intended use is in the diagnosis of disease or other conditions or in the cure, mitigation, treatment or prevention of disease in men or other animals or intended to affect a structure or any function of the body of man or other animals and does not--and this is the key--does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any if its principal intended purposes, because, if it met the last statement I read, it means it should be a drug or a biologic. So that is the difference.

With that, let me tell you the fun part. I always get the fun part to talk about. It is the accomplishment of what we have done since this short time, since we only had the action plan finalized in April. The majority of devices are here with us in our Office of Blood Research and Review; OBRR, CBER.

One of the members in OBRR--now, you all know what that is--helped me make this logo. We are so pleased. I am so poor at the powerpoint but she made this for me. I was so greedy, I wanted both, that one and the little square one. That is so cute.

First, our device action plan; not only are we trying to meet FDAMA, FDA Modernization Act of 1997. In this particular action plan, I am only going to focus on the accomplishments that we are doing here in OBRR. I am stationed here in OBRR. The reason is that the majority of our devices are being reviewed here in OBRR and we have sent you the list, the CBER list.

[Slide.]

There are three things that I would like to point out for this list. This list is being prepared by Len Wilson. He is a member of our Division of Blood Application in OBRR. The three major parts that I would like you to pay attention to are that we listed devices by offices. You can see the first two pages is being reviewed by OBRR.

We divided that into three divisions. The first one is the Division of Blood Applications and reviewed by the Division of Hematology and the Division of Transfusion Transmitted Devices. In the future, I am going to call these DH and DTTD and DBA. Everybody must follow with me. It took me a long time to memorize those.

This is for OBRR.

[Slide.]

The next page we have for our Office of Vaccine Research and Review and Office of Therapeutics Research and Review. You can see from the list that the majority of the

devices are being reviewed by OBRR. That is why I am going to focus my attention to the few tasks we are already working diligently so far. This is one of our accomplishments. Len Wilson did it. Dr. Donlon is going to make sure that this list will be posted, will be put on our web.

Did you notice that, under each one, we also list a contact person. We are doing all this primarily with responding to our stakeholders comment that we receive at all those meetings. So you can see that. There is another place I would like to highlight that is little noted. That is strictly for the benefit of the industry; to process applications more efficiently, sponsors may voluntarily use a submission cover sheet found at the CDRH web.

That will make the logging in of the documents much, much easier. Okay; so we have accomplished that. That is the first accomplishment.

[Slide.]

Before I leave this subject, we just published this regulatory submission in electronic format and if anyone would like to submit that in electronic format, we welcome that but please follow the government--if you don't follow the instructions, we have to redo it again--not we. All of us. So this is very good to know.

I will tell you, for the next task, I did not have

slides made. This is what we are trying to do now is to assess our review process, to see how we can streamline it. By being able to streamline it, we hope we can review our applications within the statutory required time frame. And that is one very important part of the regulation for the statute in FDAMA 1997.

So we are actively assessing our review process. Our goal is to streamline the process and our review of the submission will meet the statutory required time frame. I put it in a nut shell for you. Task 3--and that is the part. Pay attention because we will come to you for advice--we have anticipated that if we would develop reviewer and industry guidance documents, we can expect the quality of the submission to be improved and the reviewers may review a little bit faster or shorten the review time.

[Slide.]

So we have set up committees that will be developing those guidances. You have seen a lot of ours already. I am so pleased that this team voluntarily said, "I am willing to be part of it." You can see that. I am not going to quiz you but you see Robin Biswas is from DTTD. Can anyone tell me what that is? I'm bad. I think, in my past life, I must have been a teacher. That is the Division of Transfusion Transmitted Diseases.

I am not going to tell you the second one; DH. DH

stands for? Beautiful; Division of Hematology. Always remember the last one, now. Division of Blood Application. So we will be developing that.

The next thing I am going to share with you is that when we are doing that, we really need a lot of scientific know-how. Guess where we are going to find them? Right here in this panel. So be ready. When any one of us calls you, there is a good reason. I don't know about CBER panel members. In CDRH, we do pay homework for what you do for us outside the panel.

Dr. Smallwood, do we do that? Because we believe that if we have those guidance documents, both the industry and FDA, we all know what we expect in those documents so we should not receive documents that are so empty and miscollated.

[Slide.]

Let me give you a few examples that we believe would be good to have except we don't have the resources. But I am going to twist people's arms to do that. The few examples they gave us--I am not going to read it since I have to learn some of those words. Immunohematologic reagent, blending, reworking and reprocessing--we need guidance documents for those--and the product stability testing for blood-grouping reagents, anti-human globulin and reagent red cells.

[Slide.]

Examples from DH are blood collection and processing kits, anticoagulant and additive solutions used for blood collection and storage, leukoreduction filters, cell separation devices including electronics, mechanics, materials, software. Those things are very, very dear to my heart.

The last one, although not the least, is adhesives and solvents used in blood-product containers. I don't know how familiar you are with them but you will be very, very soon.

[Slide.]

Examples from DTTD; the guidance documents for INDs and PLAs--you all know PLA is product license applications--for hepatitis and retroviruse. For PMAs for retrovirus assays, for 510(k)s--I hope you are familiar with PMAs, 510(k)s and INDs. For 510(k)s for CMV, I know you all know that. Syphilis, et cetera. For 510(k)s for external controls for hepatitis, retrovirus, CMV, syphilis and other assays. Those are the examples we are giving, so we are asking for comments from you, are those the proper ones to do, to start out with, and do you have other recommendations.

So, with that, I think I am not going to prolong the talk. So let's think and let's work hard on those

documents or the new ones that you are going to recommend. So we are counting on your help and I thank you in advance.

Thank you very much.

DR. HOLLINGER: Thank you. Any questions from any of the committee members?

DR. BOYLE: Based upon discussions yesterday, what I don't understand in the action plan, there doesn't seem to be any requirement for plasma fractionaters to have an automated record system for rapid review of key quality-control measures related to product safety. If FDA did require it, as I understand it, such a system would be a medical device and then the nature of that would be regulated by FDA so that it would meet the necessary standards.

My question is, since yesterday, a lot of the discussion related to the difficulty of the time required to do reviews of key quality-control measures related to product safety which, apparently, are in large part manual records. If the FDA required that they be automated, then the FDA would also have the ability to make sure that automated system would meet the necessary standards.

So, is there any thought being given to that?

DR. DONLON: Part of that, I think, would address, like, the GMPs and the compliance ORA field inspection and that would come under that team as far as an inspection

standard or criteria. Before that occurs, though, I think we need to have a policy statement basically as to whether that would be a requirement or not as far as facilitating. My guess is that, initially, before it becomes a requirement, it would be kind of like a recommendation and this is something that would have to be transitioned into by many of the industry as far as establishing it and validating it as far as that type of record is concerned.

DR. YIN: I would also to add that we do have an expedited review process so that if any new devices like that, the company may request expedited review and we would definitely comply to that.

DR. EPSTEIN: We have requirements for keeping the records. We have requirements that they be durable, that they be maintained and that they be readily available. We have always shied away from defining the mechanism of keeping the record because that changes over time as the technologies evolve.

Whether we would review and approve those record-keeping systems as devices, I think is a little bit more tricky because, if they are strictly in-house and they are not intended for commercial use, they are actually exempt from the device requirements.

On the other hand, we could, as Dr. Donlon suggested, regard the implementation of such a presumably

electronic system as part of current GMP. So I don't think we have really thought that through from the standpoint of a regulatory requirement. I thank you for the suggestion.

DR. HOLLINGER: We had someone from industry who wanted to speak to the question on the device action plan. That is Steve Binyon from Baxter. Is Mr. Binyon here? He had asked to speak. He is not here, so I presume he is not going to speak, then.

I am convinced to work here in the FDA, you really have to like to make documents and write a lot. I am interested in all the words. My mentor used to say when you were doing these things, you say it like it is. We have words like "harmonization." I guess that means cooperation. And things like "transparency," which I guess means visibility. Then we have "inspectional practices." I think that is the same as inspections. But all these words come up.

Does anyone have any discussion anymore about these plans? I think they are very well presented. It gives us some idea of what is taking place. If not, then we will go on to the next item for discussion today. This is a very important item on the deferral of blood donors for risk of malaria.

I am going to ask Dr. Heintzelman, Deputy Director of the Division of Blood Applications, to give us an

introduction and background to the issues to be brought before this committee. I believe there is to be a vote based upon the discussion this morning.

V. Deferral of Blood Donors for Risk of Malaria

DR. HEINTZELMAN: Good morning.

[Slide.]

Today, we are here to discuss the current thinking of CBER concerning the recommendations for donor questioning regarding possible exposure the malaria. My name is Mark Heintzelman, as Dr. Hollinger said. I am with the Division of Blood Applications in the Office of Blood Research and Review, Center for Biologics Evaluation and Research.

There was an update for this topic during the December, 1998 BPAC meeting. Since that time, there has been additional discussion of the exclusionary criteria that a blood donor must meet. One area in particular that has been discussed is that concerning the risk to the blood supply for donors who have traveled to an endemic malarious area during times of broad daylight.

The sense behind this situation is that if the mosquitos that transmit the malarial parasite are not feeding during daylight hours, there may not be a need to defer the donors that travel to a malarious area during the daylight.

The Centers for Disease Control and Prevention

will present data concerning the feeding activity of female anopheles mosquitos and the risk of acquiring malaria during broad daylight. The Armed Services Blood Program Office will present a brief overview of their experience with travel restrictions in the northwestern portion of South Korea and malarial deferral.

As you listen to the presentations, please remember that there are a number of interlocking factors that contribute to the safety of blood for transfusion. Currently, there are no licensed tests to screen blood for malaria. Instead, we must rely on the donor questionnaire to determine if someone has traveled to a malarious area and been put at risk for acquiring malaria.

The value of a donor's ability to recall where they have been and when they were there is critical to the success of our policy, both current and future.

[Slide.]

This is our current policy that is in effect. I believe that I should use this as a stepping stone to talk about the draft proposed policy steps. So many of you will already be familiar with this. I am going to review it very quickly. When I go to the proposed policy, you will see that it is essentially stepping from this point and going forward. You will see these same items noted again.

So, our July 26, 1994 memo states, "Permanent

residents of nonendemic countries who travel to an area considered endemic for malaria by the Malaria Branch, CDC, U.S. Department of Health and Human Services, should not be accepted as donors of whole blood and blood components prior to one year after departure from the endemic area.

"After one year after departure, such otherwise suitable prospective donors may be accepted provided that they have been free of unexplained symptoms suggestive of malaria and regardless of whether or not they have received antimalarial chemoprophylaxis."

[Slide.]

"Two, prospective donors who have had malaria should be deferred for three years after becoming asymptomatic. Three, immigrants, refugees, citizens or residents of endemic countries should not be accepted as donors of whole blood or blood components prior to three years after departure from the area. After the three-year period, otherwise suitable prospective donors may be accepted if they have remained free of unexplained symptoms suggestive of malaria."

[Slide.]

Additionally, the memo states, "Because there are no approved tests to screen donated blood for malaria, careful questioning is essential for identifying prospective donors at risk for transmitting malaria. Blood-

establishment personnel should carefully elicit the necessary information regarding travel and disease history in order to defer those at risk."

[Slide.]

At the end of my presentation, I will review the suggested exclusionary criteria for the newest version of the malaria document. As the process now stands, we rely on a close working relationship with the Centers for Disease Control and Prevention to identify areas throughout the world where malarial risk exists. Our current guidance identifies the Yellow Books at CDCNP as being the source of information for identification of malarious areas that require exclusion from the blood supply.

This leads to some interesting observations concerning recommendations to prevent malaria in travelers and suitability of travelers to serve as blood donors. Guidance for travelers concerning the need for chemoprophylaxis to prevent malaria at times can appear to be in conflict with exclusionary criteria for blood donors.

One issue that is indirectly linked to our discussion today is the situation wherein someone travels to a low-risk area for malaria, does not receive guidance to take antimalarial drugs, but may be deferred as a blood donor as a result of our current policy. While this is a separate issue, the deferral of a potential blood donor for

a risk that was not great enough to require chemoprophylaxis does cause frustration to the deferred donor.

I don't know if we will be able to reconcile this issue, but I wanted to point it out as one factor that feeds into this situation.

[Slide.]

So the current draft document which is built from the 1994--everyone knows this is draft not from implementation in our current thinking. It is recommendations for donor questioning regarding possible exposure to malaria.

[Slide.]

The introduction states that this guidance document is a compilation of prior guidance regarding recommendations for deferral of donors for risk for malaria. In addition, the term "resident" is being defined for the purpose of malarial deferral to be a person that has resided in a malarious area for five years or longer.

These recommendations apply only to donations containing intact red blood cells or platelets. Donations used for preparing plasma, plasma components or derivatives devoid of intact red blood cells, red blood cells or platelets are excluded. This guidance document also provides the recommendations of the Food and Drug Administration for donor questioning regarding travel to

vacation resorts located in malarious areas.

[Slide.]

FDA's recommendations for deferral of blood donors at increased risk for malaria are as follows: one, permanent residents of nonendemic countries who have traveled to an area considered endemic for malaria by the malaria epidemiology section, CDCMP, should not be accepted as donors of whole blood and blood components including platelets prior to one year after departure from the endemic area.

After a year has passed since departure from the malarious area, such otherwise suitable prospective donors may be accepted provided that they have been free of unexplained symptoms suggestive of malaria and regardless of whether or not they have received antimalarial chemoprophylaxis.

[Slide.]

Two, prospective donors who have had malaria and received an appropriate treatment should be deferred for three years after becoming asymptomatic. And three, immigrants, refugees, citizens or residents for at least five years of endemic countries should not be accepted at donors of whole blood of blood components including platelets prior to three years after departure from the area. After the three-year period, otherwise suitable

prospective donors may be accepted if they have remained free of unexplained symptoms suggestive of malaria.

[Slide.]

Number four; persons that may possess a partial acquired immunity to malaria such as those that have resided in a malarious region for at least five years, immigrants, refugees, citizens or residents of endemic countries should not be accepted as donors of whole blood or blood components including platelets for a period of three years since their last visit to the malarious region.

[Slide.]

Now, five. Before I start into five, I would like to point out that many, if not all, of the blood-collection facilities are currently determining status for travel for individuals and they will ask if people have left the country in the last three years and begin a series of questions beyond that.

With that in mind, the fact that it is already there, we were trying to formalize this process a bit more in coming up with these questions. This is an area that is certainly hard to define. Many of you are aware of the problems associated with good donor questioning and getting the answers you wanted.

As we go through this process, I would encourage feedback. We are really looking for this to be a good

document and this process is very valuable to us. So, in this area, if you have comments about what you might conceive as better ways to do it, we are certainly listening very hard.

The questions that we have proposed are; "Were you born in the United States?" If the answer is yes, the donor should be asked, "In the past three years, have you been outside the United States or Canada?" or B, if the answer is no, the donor should be asked, "When did you arrive in the United States and, since your arrival, have you traveled outside the United States or Canada?"

There are many issues associated with where someone considers themselves to be a resident. We define resident, for the purposes of malarial deferral for this document, to be a five-year time stay in a specific area. An individual that may speak English as a second language really may not want to admit that they resided in an area for political reasons or any kinds of persecution reasons and may have a different feeling on this.

So this has been a very hard area for us to come up with good questions that will address these issues.

[Slide.]

If the answer to the question in A above or the second question in B above is yes, follow-up questions should be asked to determine the country or countries that

have been visited. These questions should include, for example, something along the lines of, "In the past year, have you visited any rural area including a resort in a rural area in Mexico?" The reason that we have put that there is because there are a very large number of people from the United States that travel to resorts on either the Pacific or Gulf Coast of Mexico.

I have heard numbers of upwards of 20 million a year. Not all of those are blood donors. Maybe 5 percent is the average. Maybe up to a million of them might be. So, ascertaining whether they have gone there and knowing the risk for the areas that they have visited can have a very big impact on donor availability.

If a prospective donor answers yes to this question, determine whether the rural area or resort is located in a Mexican state considered at risk for malaria by the CDCMP. If so, the donor should be deferred for a minimum of one year from the date of departure from the area. The major resort areas on the Pacific and Gulf Coast of Mexico do not have a malarial risk.

Our presentations from CDC will give you a lot of good scientific background regarding parasite areas that are endemic, activity, feeding activity, of the mosquito and such and will reaffirm that fact.

Finally, blood-collection facilities should

at

further question the prospective donor regarding exposure history to better ascertain the actual risk of exposure to malaria using the information contained in the background section of this document. If questions persist, we advise that they call the Malaria Epidemiology section at CDC for further clarification.

Of course, when more than one deferral period applies to a donor, the longest period of deferral should go into effect. That is the most conservative approach.

[Slide.]

The question that we will pose to the committee, and I hope everyone got a copy of it coming in, is, "Do the committee members support a change in the current blood-donor policy to allow for travel the areas endemic for malaria when travel exposure was limited to hours of bright daylight?"

I tell you that now so when you listen to the people in the audience, when you listen to the presentations that are coming, you will know where we are going.

DR. HOLLINGER: Thank you, Dr. Heintzelman.

The next presentation is going to be by Dr. Monica Parise, medical officer for the CDC. Oh; sorry.

DR. BUCHHOLZ: I think that what you have presented has been very interesting but, in reference to the question as it was phrased which relates to travel in bright

daylight time, it seems to me there is some very important evidence lacking or that hasn't been presented which is what do we know about mosquitos, what is bright daylight.

DR. HOLLINGER: Don, that is going to be covered, I think, very extensively here in the next--

DR. HEINTZELMAN: Yes; you are absolutely correct.

DR. BUCHHOLZ: So there are data that define and support the fact that mosquitos--which must differ from the ones at my house, because they bite me--

DR. HEINTZELMAN: You probably don't have anopheles in your house. I believe that that is the whole sense of this. Should you have further questions regarding it after this presentation and the next one, we will certainly be open to discussion. That is the point in this is to determine whether you can support the purpose of the question or not.

DR. STRONCEK: If we vote yes to this question, later on will we--there seem to be about a dozen changes there that I saw, not just this question. Maybe we will get into that later on?

DR. HOLLINGER: Yes; I think we will. Does anyone else have a question? I was going to ask one question, and I don't know if it is going to be brought up, about platelets. Is there any evidence that platelets have been associated with transmission of malaria?

DR. PARISE: There is. I wasn't going to present data on this but I will say that there is. There are published reports.

DR. BUCHHOLZ: Could someone give the committee an idea of what the magnitude of this problem is in terms of number of potential donors that fall into this category, number of donations per year that have deferred and the number of transfusion-transmitted cases of malaria?

I think we all know that this is a problem or a potential problem, but I am not sure that I, at least, have a feel for what is the size of this. Is it two cases?

DR. HEINTZELMAN: No. That number is known. I believe that Monica will be providing you with that. As far as the incidence of deferral for the individual blood donations, there are about 14 million donations a year. I don't have the number from the--maybe we will have a representative from the blood associations. Kay is shaking her head no. It would appear that they don't have the number for us today either. So the number of deferrals is an unknown at this time. Is that fair to say?

DR. FINLAYSON: John Finlayson, FDA. I don't have the number either, but if you notice, in the presentation that Ms. O'Callaghan made yesterday, you saw that for post-donation information, the major one, numero uno, for blood donors was travel to a malarious area. So it is at the top

of the list on the call-back information.

DR. ELLISON: The paper we were handed today does give us some numbers. In 1998, 1255 of the 7104 post-donation reports is 18 percent for travel to malaria-endemic regions.

DR. HOLLINGER: 18 percent of the post-donation information. That still doesn't tell us the number of pre-donation--why don't we go ahead with the presentations and then we will come back because these issues are critical issues that are brought up and they may be answered.

Presentation

DR. PARISE: Thank you for providing us with the opportunity to present some information here. I would like to say that I am going to be doing the presentation but Dr. Trent Ruebush, the Chief of Malaria Epidemiology at CDC, is also here and will also be actively participating in any discussion that is addressed to us.

[Slide.]

This morning, I am going to present technical data related to malaria to anopheline mosquito behavior and then specifically to transfusion-transmitted malaria in the United States.

[Slide.]

Malaria is a protozoan parasitic disease caused by one of four species of plasmodium which include falciparum,

vivax, malariae and ovale. It is generally transmitted by the bite of an infected female anopheline mosquito.

[Slide.]

Malaria was eradicated in the United States in the late 1940s but each year approximately 1000 to 1400 cases are reported in the United States, almost all imported infections in U.S. travelers or in foreigners. A few cases, less than ten each year, are transmitted in the United States and include about two to three cases due to either transfusion or organ transplanation, congenital transmission.

In addition, once every one to two years, we have a case or a few cases that are due to local mosquito-borne transmission in the United States. This happens very rarely in the United States because all the necessary conditions for transmission to occur here are rarely met because there has to be a contact between a mosquito vector and an infected person who had traveled and conducive climate conditions that support the development of the parasite in the mosquito and the longevity of the mosquito.

[Slide.]

Of the imported cases that occur every year, about half are in immigrants, refugee-resident category, of people who are from other countries who come to the United States and the other half occur in U.S. travelers which includes

U.S. civilians and military.

A major risk factor for the acquisition of malaria in these travelers is failure to make use of effective chemoprophylaxis. 85 percent of these cases are associated with a failure to take prophylaxis for the use of ineffective drugs.

[Slide.]

Moving on to the mosquitos, the mosquitos that transmit malaria, the anopheles, feed almost without exception between dusk and dawn, although they may feed in daylight hours in densely shaded woodland or dark interiors of houses or shelters.

This is in contrast to other species of mosquitoes such as Aedes aegypti, the mosquitos that transmit dengue, which are primarily daytime biters.

[Slide.]

The changes that occur in monitoring behavior at different times of day or night are influenced by several environmental factors which include light, which is the most important, temperature, humidity and air currents. The changes from day to night and back again to daylight conditions have a dominating influence on mosquito behavior and affect the mosquito's level of activity and responsiveness.

[Slide.]

This activity level and responsiveness underlies all the observable patterns of mosquito behavior which include host-seeking or biting, dispersion, mating, egg-laying and occupation of resting sites during daylight hours.

[Slide.]

Laboratory experiments have shown that many cyclical changes in mosquito behavior are true circadian rhythms controlled by an internal clock which is set by the transition from light to darkness at dusk. At dawn, environmental temperature and humidity are very uniform which means that mosquitos have to use predictive clues in the environment in the search to find daytime resting sites. It appears that certain combinations of overhead shade and dark background provide those clues and give the appropriate stimuli for where the mosquito will rest.

Experiments have shown that once mosquitos adopt a resting site for the day, they are reluctant to move.

[Slide.]

This slide shows the biting cycle which is shown in the red line and the peak biting times which is shown in yellow for several species of anophelines in South America, Southeast Asia, Oceania and SubSaharan Africa. It goes from 6:00 at night and goes to 6:00 in the morning.

The fact that these mosquitoes don't feed during

daylight hours is so well-accepted among entomologists that no recent studies since the 1930s even comment on daytime mosquito collections. They start work, when they are studying these mosquitos, at about 6:00 p.m.

[Slide.]

Many similarities exist between the determination of malaria risk for travelers and potential blood donors. I will say right from the beginning, the only way that we will completely prevent all cases in travelers would be for people to never travel to malarious areas.

[Slide.]

First, I will briefly discuss what we do for travelers. Our recommendations for malaria chemoprophylaxis, which are based on determination of geographical areas at risk of malaria, are based largely on information obtained from the World Health Organization. This information is updated on a regular basis every one to two years.

Several factors that can place a degree of uncertainty in these decisions are involved in deciding which areas have risk and when and are the types of information we discuss with travelers when we determine risk. Some of these include the distinction between what is urban and rural, which is especially important in the Americas and Asia because the mosquito vectors are often not

present in urban areas, the time of year of travel.

For most countries, because climate conditions can vary from year to year, the exact months when malaria is transmitted or the time of peak transmission also varies. Because we don't have detailed information in real time on these year-to-year changes in climate and malaria transmission, we generally don't vary recommendations based on season. One exception is China as the transmission there has historically been relatively constant.

The third issue is the time of day which is the dusk-to-dawn criterion which I will get into in more detail in subsequent slides. We, at CDC, have not had difficulties getting such points across to very large numbers of travelers and healthcare providers for many years. Furthermore, the evidence that we have about cases of malaria that we have at CDC as well as has been published in the literature from other countries, doesn't support that. The misunderstanding here is necessarily with the cases, but that cases occur because people don't get accurate pretravel medical advice or because they don't follow it.

[Slide.]

In our determinations for malaria chemoprophylaxis in travelers, we don't consider persons who were in a malarious area only during daylight hours and then who come back to a malarious area at night to be at risk for malaria

acquisition.

If travelers stay overnight at the resort in a malarious area such as resorts in rural areas in one of the states in Mexico that has malarial transmission that we are discussing in the proposed changes in the memo, they are at risk of malaria and must be deferred. The dusk-to-dawn criteria mainly affects the short-term traveler who spends most of his or her time in a large city or a very developed resort where there is no risk of malaria but takes a day trip to a nearby tourist site or a business site in a malarious area.

Another case scenario are Ocean Cruise travelers who are at sea at night but the boat docks during the day for persons who do sightseeing.

[Slide.]

For travelers, we aim to strike a balance between the risk of malaria and the low risk of adverse reactions to anti-malarial chemoprophylaxis drugs. In our judgement, there is more uncertainty around other issues such as urban-rural distinctions as well as time periods between the time of travel and the time of infection which I will get into shortly than around the issue that anopheline mosquitoes bit during daylight hours.

[Slide.]

Moving on to blood donors; the only way to prevent

all cases of transfusion-transmitted malaria would be to exclude any traveler who has ever been in a malarious area at any time in their life for the rest of their life. This would severely limit the size of the donor pool. Thus, instead, we aim to strike a balance between the risk of infection and the exclusion of as few uninfected donors as possible.

We have agreed upon time limits for exclusion that are set forth in the existing criteria and their scientific basis is the vast majority of cases of malaria will have been infected within these time periods.

[Slide.]

Mark has well covered the donor-exclusion criteria and the proposed change. I won't repeat these.

[Slide.]

Before I review information used to develop these criteria, I am going to briefly discuss the life cycle because there are species differences that I think are important to understand. Basically, what happens is that, in the life cycle, the mosquito injects a stage of the parasite that is called the sporozoite that is present in the salivary glands in the mosquito when it bites a person.

These forms, the sporozoites, are very short-lived in the blood. They are there for only about 30 minutes. They quickly are carried to the liver where they are taken

up by liver parenchymal cells. There they grow and undergo a development process which involves multiple divisions, evolve into a form that we call a schizont that contains thousands of little forms that will later be broken out called merazoites.

This maturation process takes, on average, 7 to 16 days and then the liver cell ruptures and these forms are released into the blood stream. Once this happens, they relatively rapidly are taken up by red blood cells and passed through several stages of development within the red blood cells.

Once this occurs, once this development occurs, that red blood cell ruptures, releases merazoites again and those parasites go into other red blood cells and the cycle repeats itself. The cycle in red blood cells takes about 48 to 72 hours depending on the malaria species.

Some of the merazoites that enter the red blood cells develop along a different pathway and develop into the sexual stage called the gametocytes. This is important because these are the ones that are infective for the mosquito and are the ones that have to be taken out for the mosquito to infect another person.

When an uninfected female anopheline bites an infected person, it takes up these forms and they undergo development in the mosquito which takes about 9 to 35 days,

depending on climate conditions and species, et cetera, and then it is ready to pass it on again.

Let me note, also, which I will get into in the next slide, a few of the species have dormant liver stages. I will talk about that.

[Slide.]

This is one of the major differences, this liver stage. The two species that don't have a persistent liver stage are P. malariae and P. falciparum. P. malariae, although it doesn't have this stage that can relapse later, it has a quality that it can remain in the blood at very low levels without causing symptoms for many years, up to decades. Case reports have been 40, 43 years. So the current donor exclusion criteria will never prevent these cases.

The other parasite that does not have a liver form is Plasmodium falciparum. Most symptomatic cases of Plasmodium falciparum come up within a few months. Persons who have lived in malaria-endemic areas who may have acquired some immunity to malaria can have parasitemia which may be asymptomatic at periods that last beyond these few months which can go up to a few years. I will present a little more data on details of those outliers in a minute. This is the species that is responsible for almost all of the deaths due to malaria.

The two species that have a dormant liver stage are Plasmodium vivax and ovale. Even without treatment, the liver stage rarely lasts longer than three years.

[Slide.]

There have been very rare cases reported in the literature and that we have noted in our U.S. National Malaria Surveillance System experience that exceed these general rules. A review of our surveillance data from 1985 to 1987 showed that, of about 7400 cases in U.S. civilians and military, information on the time between travel and onset of illness was available in about 5700 cases.

Only 2.1 percent of these arose more than one year after travel. When we consider the immigrant refugee foreigner category, there were 6200 cases which we had information about 4200. Only 7 cases--that is, 0.2 percent--arose greater than three years after travel or immigration.

Note that this one in three years that we used are the current criteria.

[Slide.]

The extreme outliers found in our U.S. surveillance system and in the medical literature are nine in 13 years, respectively, for Plasmodium falciparum, 5 in 23 years for vivax and 7 in 7 years for Plasmodium ovale.

[Slide.]

There are reasons which may be related to

immigration status, why a person may not be truthful about travel. For example, in the course of investigations of cases of alleged mosquito-borne transmission in the United States, we found that a case-patient who repeatedly denied ever having been out of the United States later admitted it. As we consider cases, both that are in the literature and in our surveillance data where there are these very long durations between travel and onset of infection, we need to consider that there could be inaccuracy in the travel history.

Many studies in human volunteers and non-human primates have shown that this parasite, Plasmodium falciparum, rarely lasts longer than a year.

[Slide.]

Concern over the three cases of transfusion-transmitted malaria that occurred during 1996 to 1998, all of which were complicated Plasmodium falciparum infections, prompted us to review all cases of transfusion-transmitted malaria reported to CDC from the years 1963 to 1968. I am briefly going to discuss this review because the epidemiology of transfusion-transmitted malaria is relevant to the decision-making process.

The objectives of this review were to describe the epidemiology and evaluate trends in incidence and to try to evaluate reasons why cases occurred and how to better

prevent them. In cases where an implicated donor was identified, donor suitability was determined using published FDA and AABB donor-exclusion criteria.

As these guidelines have changed through the years, we looked both at the donor suitability with respect to the criteria in place at the time of donation and with respect to current criteria. There was very little difference between these two analyses, so, today, I am going to focus on the current criteria.

To determine the incidence of transfusion-transmitted malaria in the U.S., the cases we used were from our surveillance data. We believe that our surveillance system is probably about 50 percent sensitive, but we tend to hear about unusual cases or cases that occur in the U.S. So we think it is very sensitive for that. And we derive number of units transfused from the medical literature.

[Slide.]

From 1963 to 1998, 91 cases of transfusion-transmitted malaria were reported in the U.S. A donor couldn't be implicated in all these cases, and there were 35 implicated donors, whose age ranged from 19 to 59 years, and 80 percent were between 21 and 40 years of age. 91 percent were male. 59 percent were foreign born and the area of acquisition of infection was most frequently SubSaharan Africa, in 45 percent of cases, followed by Southeast Asia

at

and Central and South America.

We had sufficient data to judge donor suitability for 58 of the implicated donors.

[Slide.]

36 of 58, or 62 percent, of infections would have been prevented if the current donor-exclusion criteria had been correctly applied. The screening process failed at some point; for example, the donor didn't understand the question, purposefully withheld information, or the probing process was not adequate.

Of these cases that occurred when guidelines were not followed, approximately half occurred in immigrants and half in U.S. travel.

[Slide.]

In 22 of the 58 cases, or 38 percent, the problem was that the time period from the last travel to a malarious area and the blood donation exceeded the time limits in the donor-exclusion criteria. In cases caused by P. malariae, P. falciparum and P. vivax and ovale, times ranged from 5 to 44 years, 1 to 5, and 1 to 7 years respectively.

59 percent of these cases occurred in immigrants and 41 percent in travelers. The travelers included either military or persons who had previously lived in endemic areas, now live in non-endemic areas and went back to visit. I am going to refer to these people as VFRs, visitors to

friends and relatives, because I am going to get into that in a little more detail in a minute.

So, of cases that occurred in travelers, they were either military or the VFR category. Overall, in this 35-year period, we only identified seven non P. malariae infections that occurred when the guidelines were followed.

[Slide.]

Overall, the most frequent infecting species was Plasmodium falciparum in 34 percent followed by vivax, malariae and ovale. In cases where the guidelines were not followed, P. falciparum was most frequent species and, not surprisingly, in cases where the guidelines were followed, P. malariae was the most frequent species.

We also looked at differences in implicated donors by decade to see if there were changes with time. Since 1980, there have only been three cases due to U.S. travelers. The last occurred in 1982.

[Slide.]

Questions have been raised as to whether the VFRs, the persons who visit friends and relatives, should be presumed to have retained some acquired immunity and so should be treated as immigrants and not travelers in terms of time for donor referral.

In 5 of 8 such cases, the infection arose within one year. Two cases occurred several years later that

involved Plasmodium malariae and, in only one case where the donation occurred 29 months after travel where the traveler exclusions while this three-year immigrant exclusion would have prevented the infection with Plasmodium falciparum.

This case was somewhat unusual as the donor had made several long trips since his immigration which may have contributed to retaining some acquired immunity.

[Slide.]

The bars in this graph show the number of annual cases of transfusion-transmitted malaria from 1963 to 1997. The line shows the incidence rate. We have difficulties in obtaining denominator data on units transfused in the 1975 to 1985 years, and so that data is missing. But, basically, you can see there has been no change in the incidence of malaria, transfusion-transmitted malaria, in the last decade and it has actually decreased since the early years of the investigation.

[Slide.]

The information I have presented explains our rationale for a dusk-to-dawn criteria. We believe that such an exclusion can be implemented. One may define the safe time period as the time which is after dawn and before dusk that we don't consider to have malaria risk as the time of full daylight.

Not excluding persons who have had only daylight

travel to malarious areas is very likely to impact upon the category of immigrants and will only affect you as travelers.

[Slide.]

The first step in the screening process, done as part of the probing, could be to determine how long a traveler was in a malarious area. Anyone there greater than 24 hours must be deferred as they were there overnight. So this doesn't change anything in reference to those travelers who spent that night inside a screened, air-conditioned hotel or inside a cruise ship that was docked at port. These people were overnight in a malarious area and they need to be deferred.

In considering persons who were there less than 24 hours, did they arrive after it was fully light and did they depart while it was still fully light. They must answer yes to both questions to be allowed to donate. If a traveler isn't sure or cannot remember, we do as we do in other cases of uncertainty; for example, when we can't find an area on the map, we play it conservative and we defer the donor.

Thank you.

DR. HOLLINGER: Thank you.

I think we will have the final presentation and then we will come back to questions. This presentation is by Major Groshel, Blood Program, Department of Defense.

Presentation

MAJ GROSHEL: Military duty, whether that be active duty or even reserve duty, means that a donor stands a good chance of travel to a malarial area. Donor questions on travel history and potential exposure to malarial endemic areas take up much of our donor interview time and is an emphasis of our donor training programs.

FDA recommendations for donor questioning and areas of donor travel and potential exposure to malaria must be clear, concise and as specific as possible.

When the Armed Services Blood Program instituted a restriction on donations due to travel in areas of the northwest portion of South Korea due to possible exposure to malaria, we limited restrictions to an area north of a reference river and we exempted travelers who were only in the area during daylight hours such as day-trip visitors to the demilitarized zone.

This policy not only resulted in documentation questions from our donor centers but also in other questions like how wide does a river need to be before a mosquito will not fly across it, what is considered dawn and dusk and how does a mosquito know the difference, especially on a cloudy day. What if the donor says they were only there during the daytime but they remembered getting bitten by a mosquito or what if the donor doesn't remember if they left before dusk.

These were just questions that came up in relationship to that policy. Although we don't have any specific data saying that we had any errors or recalls resulting from this policy, increases in subjectivity of donor questions increases potential risk. So we would ask that all recommendations be as clear, specific and concise as possible and expect questions that will need good supporting documentation, be very clear and specific about questions that would be expected to be included on donor cards and in follow up, be consistent with recommendations for specific follow-up questions.

The examples included in the draft guidance were very specific in wording for follow-up questions to determine if a donor had visited a rural area or a resort but did not include specific wording for follow-up questions to determine if the donor's previous country of residence was a malarial endemic area.

I think the main thing that we are asking is that the donor instructions to the donor centers be as clear and as concise and specific as possible because they are the ones that are going to have to field these questions.

Thank you.

DR. HOLLINGER: Thank you.

We are going to take a break now until 10:30 and then we will have the open public hearing and then go into

the open committee discussion. It is now 10:03. Be back at 10:30.

[Break.]

DR. HOLLINGER: We are going to have the open public hearing at this point. There are two people who have asked to speak. There may be others that want to, but the two people who have asked to speak--the first one is Dr. Mary Townsend from America's Blood Centers.

Open Public Hearing

DR. TOWNSEND: I am Dr. Mary Townsend. I am co-chair of the America's Blood Center Scientific, Medical and Technical Committee. I am Medical Director of Coffee Memorial Blood Center in Amarillo, Texas.

ABC thanks the committee for the opportunity to present our recommendations and comments on the issue of deferring donors who may be at risk for infection for malaria. For your information, ABC's not-for-profit, community-based members provide nearly half of the nation's volunteer donor blood supply. Blood-collection facilities frequently have requested clarification from FDA on requirements for evaluation of donors who have visited or lived in countries in which malarial transmission occurs.

The focal nature of malaria transmission within endemic areas, the seasonality of transmission and other intrinsic characteristics of malaria as well as the wide

spectrum of activities and their recall complicate evaluation of donors who have been in endemic areas.

The magnitude of the complexity is reflected in the high rate of errors and accidents reported to FDA as a result of post-donation information having to do with travel to malarial endemic regions. In 1998, these amounted to 1,255 of the 7,104 reports, or nearly 18 percent of all post-donation information reports.

Since prevention of transfusion-transmitted plasmodial infection is the goal of donor interrogation about travel outside of the United States, the epidemiology of transfusion malaria should be the basis of our donor screening efforts as suggested by Dr. Parise of the CDC.

[Slide.]

This table is extracted from the last four CDC malaria surveillance summaries and reflects the current epidemiology of malaria in the United States. In the years studied, only 2.6 percent of malaria diagnosed in the United States was acquired in Mexico and the Caribbean, extraordinarily popular destinations for tourists and common points of origin for immigration.

A review of the cited surveillance summary shows that none of the two to three annual cases of transfusion-associated malaria, including the three most recent cases occurring during the 1996-1998 reporting period, as reported

in the April 2, 1999 issue of MMWR, could be definitively attributed to donor infection acquired in Mexico or the Caribbean.

In fact, the three donors associated with the 1996 cases all immigrated from West Africa. Of additional interest, correct application of current FDA and AABB malaria deferral standards could and should have prevented all of the recently reported transmissions of malaria by blood components.

We attribute these failures, in part, to the increasing complexity of donor medical history. We feel that the new proposed questions regarding country of origin and subsequent travel and immigration should greatly improve the problem of donor history failures.

The adequacy of the blood supply is marginal and we believe that adequacy is a safety issue. Data from the AABB's national blood data resource center previously presented earlier this month to the Transmissible Spongiform Encephalopathies Advisory Committee suggest that demand for blood and blood components for transfusion will exceed the supply of donations from volunteer whole-blood donors in the Year 2000.

Under these circumstances, changes in malarial criteria for volunteer whole-blood donors must not result in significant increases in deferrals especially for travel to

Mexico and the Caribbean since they would not materially reduce the incidence of transfusion-transmitted malaria. This concern is rendered more acute by the TSE Advisory Committee's recent advice to FDA that certain donors with residence in the United Kingdom during the interval 1980 to 1999 be deferred due to theoretical concerns about transmission of new-variant CJD.

It is estimated that this action will result in the loss of 2.2 percent of eligible volunteer whole-blood donors. We applaud, and many facilities such as my own have already adopted, the suggested mandate by AABB for a question, "In the past three years, have you been outside the United States or Canada?" This question is unambiguous and will standardize the donor interview at blood-collection facilities.

The plan for additional and follow-up questions proposed this morning are appropriate. A precise definition of residence is greatly appreciated.

Regarding the issue raised today regarding rural versus urban resorts; we are concerned that that determination of urban versus rural resorts in Mexico, the Caribbean and elsewhere will be arbitrary absent a definitive categorization by CDC and/or FDA that can be updated as appropriate. Because of the volume of travel by donors in these two former destinations, an authoritative

list, or at least definition, for these areas would be the most important assistance in simplifying initial donor screening we can ask for.

We oppose taking from blood-collection facilities the flexibility to inquire regarding potential day versus night exposure particularly with reference to travelers to Mexico and the Caribbean. Many thousands of donors vacation in these areas and may be deferred by such a policy. The CDC has provided today for you the opinion that this is a meaningful differentiation and, in the absence of transfusion-transmitted malaria from Mexico and the Caribbean will result in donor loss with no increment in safety.

Finally, the FDA must take pains to avoid providing mixed message to traveling donors that conflict with that information that they have obtained pretravel from the CDC or from their physician relying on CDC information for malaria prevention advice. It is wrong, we think, for a donor who has been advised before traveling that that risk of malaria on a trip to a Mexican resort or a Caribbean cruise is inadequate to demand preventive medicine than to be subsequently told that he is being deferred for the theoretical risk of malaria.

Surveillance data from the CDC cited above suggests that such transmission is not occurring with a

recognizable incidence using current donor-screening techniques including discretion of medical directors to assess risk.

Before any such step is taken, its impact on donor loss, both nationally and on a regional basis, should be assessed in a survey analogous to that which was undertaken to assess the impact of new-variant CJD deferrals.

I thank you very much for your time. Are there questions?

DR. HOLLINGER: Thank you, Mary.

DR. BOYLE: Would you turn that back on for a minute? I just want to be sure I understand. Using 1995 as an example, the difference between the 32, which are malarial cases acquired in Mexico and Caribbean, and the total are ones known to be acquired outside of Mexico and Caribbean or the ones that you don't know where they were acquired?

DR. TOWNSEND: They were outside of Mexico and Caribbean. And then the two that were transfusion-transmitted were from Ghana and Nigeria.

DR. BOYLE: Thank you.

DR. HOLLINGER: Thank you.

DR. EPSTEIN: I had a question for Dr. Townsend. What is your thought, Dr. Townsend, about whether the absence of cases from Mexico or the Caribbean is due to

effective screening? It is a cart-and-horse problem. You have got screening and maybe it is more accurate for persons who, say, travel to Mexico and the Caribbean or immigrate from Mexico or the Caribbean compared with the accuracy of screening for African immigrants who travel to Africa.

DR. TOWNSEND: I think the screening has been effective. What we are looking for is some guidance in regard to differentiation between rural resorts, day and night exposure.

DR. EPSTEIN: I hear you, but I am quarreling with the observation that the risk for Mexico and Caribbean must be low because you don't see cases. That might just reflect effectiveness of screening.

DR. TOWNSEND: I wouldn't argue that.

DR. BUSCH: But I think, Jay, the issue is is there going to be a further tightening. Operationally, now, it sounds like most blood centers are not deferring people who have just had day visits out of the main resorts to these more rural regions. So if there were any consideration of further tightening, then the issue is is there any transmission of the current policy.

The second person who has asked to speak is Dr. Michael Busch who will speak on behalf of the AABB.

DR. BUSCH: My name is Mike Busch. I am at Blood Systems and University of California, San Francisco. I am

presenting on behalf of the AABB Transfusion-Transmitted Disease Committee.

The AABB is the professional society for over 9,000 individuals involved in blood banking and transfusion medicine. It represents roughly 2200 institutional members including community and Red Cross blood-collection centers, hospital blood banks, transfusion services, as they collect, distribute, transfuse blood and blood components and hematopoietic stem cells.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety of the nation's blood supply. The Association operates a wide variety of programs to meet safety priority and is proud to have played a key role in insuring the nation's blood supply is the safest it has ever been.

The AABB appreciates the opportunity to provide its comments on the topic of deferral of blood donors at risk of malaria. Malaria is a rare but potentially serious complication of blood transfusion. On average, two to three cases per year have been reported to the CDC from 1958 to 1998. Thus, three reported cases between 1996 and 1998 should not be viewed as an indication that this problem is suddenly increasing. Nevertheless, all measures currently

in place for the purpose of reducing the risk of transfusion-transmission of malaria should be examined to see if improvement is possible.

The donor interview is a critical component in determining possible malaria exposure, especially since readily available testing methods are not predictive. The AABB publishes a uniform donor history questionnaire which has been approved by the FDA. The question about travel asks, "In the past three years, have you been outside the United States or Canada?"

A yes answer then prompts more specific questions to elicit where, when and for how long. We believe this question is very straightforward and the most appropriate way to obtain this information. For donors who have been outside the U.S. in the last three years, additional questioning can determine whether the donor was an immigrant or a resident in a malaria-endemic country if FDA determines that specific deferral criteria should apply to these donors.

Adding such additional specific questions for all donors is not warranted. It will increase the amount of time answering questions which are not applicable to most donors and will add to the length of the total time required for donation. Additional questions that are not of high value in distinguishing donors at risk also take emphasis

away from the extremely important questions.

However, should the FDA decide to add questions, these questions must be practical and nonoffensive to prospective donors. It would be requested any such additional questions be field tested in selected blood-collection facilities prior to implementation in the entire country.

Such field testing would, perhaps, identify questions which are not clearly understood by prospective donors. FDA should demonstrate not only that the new questions are understood but that new questions will actually result in a more appropriate deferral than the current questions.

The major issue faced by blood-collection facilities primarily lies in the proper identification of geographic regions considered at risk for malaria. Although CDC publishes health information for international travelers, commonly known as the Yellow Book, the information is not user-friendly. AABB requests that an easy-to-locate, readily understandable and up-to-date reference be made available, perhaps on the Internet.

Blood centers also call CDC directly for information and find it very confusing when CDC advice appears to contradict the FDA advice. AABB requests that CDC and FDA harmonize their thinking so that there is an

agreement about what constitutes malaria risk.

In conclusion, AABB will be pleased to have FDA clarify its expectations in a new guidance on deferrals for malaria and urges FDA to make this guidance practical for blood centers and consistent with advice provided by CDC>

Thank you.

DR. HOLLINGER: Any questions of Dr. Busch? Mike, I want to ask you just a question about from the blood-banking circumstance. I go to Bangkok. Bangkok is considered an urban area and not of concern, Bangkok, itself. I decide to fly to Angkor Wat which has falciparum, in fact, resistant falciparum. I am there just in the day. I fly there that morning. I to the Angkor Wat. I come back that afternoon and go back to Bangkok.

That has to deal with a little bit of the question that we are going to be asked today. The same thing goes with a port. You come into a port where there is malaria in the area. You arrive there in the morning. You go out and you visit places out in the port and then you get back on your boat and the boat leaves versus the boat staying there overnight.

How does the blood-banking community now handle those two questions if I were there and I said, "Yes; I was here at these places." What would you do for me in the first instance in terms of the Angkor Wat. I didn't stay in

Angkor Wat overnight but I just went there that day and came back. How would they handle it today?

DR. BUSCH: To be honest, I am not that involved on the front-line, how the nurses actually would handle those questions. My sense would be that we are discriminating. Thailand is much more of an unknown to us so my sense would be that you would be deferred in that scenario in Thailand whereas here, probably, in the Caribbean resorts, you would not because it is a much more controlled environment.

I don't know the answer.

DR. HOLLINGER: That is the issue, basically, because Bangkok is okay but--in terms of the CDC, it is okay.

DR. TOWNSEND: This is what we do every day. Basically, in either of those cases, I think probably neither donor would be deferred. What I have done in the past, when it gets complicated, I put a phone call in to the CDC and ask them and they will tell me, this donor is at risk or is not at risk. Basically, it is based on the information that you have heard today, from a dusk-to-dawn situation.

We have similar situations when people leave the big resort and they go on a river cruise which is considered--overhanging dark trees, a little bit, high

water. So we would defer those donors but, often, it is based on a case-by-case basis and if there is a question, we consult the CDC.

DR. HOLLINGER: So, currently, what we are being asked of the questions, and I just want to be clear here, is in addition to what is being--for example, if we accept the question as it is posed about dusk-to-dawn, as it seems like it is being utilized now, then nothing different will change.

DR. TOWNSEND: That is correct.

DR. HOLLINGER: On the other hand, if we vote against that, then there will be additional factors here and those people will be viewed differently.

DR. TOWNSEND: There would be additional deferrals.

DR. HOLLINGER: Additional deferrals to those areas. Okay.

DR. NELSON: I don't think you could do that trip overnight. The airport is at Siam Reef and it is a ways, so you would probably have to stay overnight. But, at any rate--

DR. HOLLINGER: It's a good question, anyway. Actually, I did look into that. And there are planes that will get me there and get me back.

DR. NELSON: Oh; okay. But one of the questions I

had was about the 18 percent of post-donation information that led to all sorts of complex actions. I wondered what happened in that setting. Did somebody just forget? Or did they subsequently report that, oh, yeah, they stayed overnight?

Looking at those data might be--because that is really sort of what is at issue, was it a real risk or is the question too complicated now, or--I don't understand.

DR. HEINTZELMAN: I think it safe to say it is all of the above. Look back to your own experiences in the last year if you have been on a vacation. Do you remember that vacation? Do you remember where you were? Do you remember the time of day? Those are the questions that you have to be able to answer to address those post-donational callbacks that are related to malaria--I think the number on the document is 1,255--are places where the people forgot during the time of donation.

You can only wonder how many completely forgot and didn't remember a week or two later. Those are very real issues. The science for the mosquitos, the parasitology is very well understood. I don't believe there is any question about that. The implementation strategy and people's ability to recall is another part of this.

It is a very complex issue and there are differences of opinion in the blood community regarding

this. That is the reason why we bring it to your attention.

DR. HOLLINGER: Is there anybody else from the public that wishes to speak at this point before I close the public hearing and open this up for the committee.

MS. JETT: I am Betsy Jett from NIH. I just want to talk a little bit more about that implementation piece of it because that is a nightmare for us like it is for everybody else.

I would like to see CDC publish a much more detailed map than they currently provide because a lot of our donors couldn't tell you the name of the province they were in. So a better map would help. A better definition of rural versus urban would be very helpful, especially in Thailand.

The last thing is not only does the questioning take a long time, but the documentation of that interview is also very cumbersome. So I would like the policy-writing people to talk to the compliance people and kind of get together because, right now, we have to document not just that, yeah, they visited an area but we determined it was okay, we have to say where they went, all the details of the case report in our donor documentation. That is a problem for us. It is hard. It is a lot of work.

DR. HOLLINGER: Thank you. Appreciate that.

Anyone else from the audience want to say

something? If not, I am going to close the open public hearing and we will open it up for discussion.

Committee Discussion

DR. EPSTEIN: I am afraid this may add to complexity but I think one of the questions for the committee is that if you are uncomfortable about the accuracy of histories, then the recommended policies should be deferral. However, one could incorporate into that policy the concept that if one then gets more specific reliable information, one can override the deferral.

So, for example, with regard to resorts in rural areas of Mexico, it has been pointed out that all resorts are not the same and how do you define a resort. So you could have a policy that you defer donors if they went to resorts in rural areas unless the resort is identified and it is checked with CDC or it is on a CDC list that that is not a malarial risk at that resort.

Likewise, you could have a policy that you defer for exposures in malarious areas, time of day not withstanding, unless the medical director can reliably ascertain that exposure was limited to hours of bright daylight. It is really a question of where do you put the onus of checking. So I just think that we can have a little bit more complex recommendation that, on the other hand, would mitigate unnecessary deferrals, but it puts the onus

of validation on the medical director.

DR. BOYLE: Could somebody just explain to me the process--the questions now about was it during daylight, or was it urban-rural, or whatever, is that part of the standardized questionnaire people are filling out or are they follow-up questions that are being asked by nurses once they have seen the first thing on the form.

DR. FITZPATRICK: Those are follow-up questions. The initial question is, "Were you outside the United States or Canada in the past three years?" That is the only standard one. Everything else is follow up that the interviewer has to draw out of the donor.

DR. BOYLE: Is that question that is being posed to us to add this criteria to the written form or simply make sure it is a criteria that would be followed by the nurse or the person who does the follow up?

DR. HEINTZELMAN: In that regard, if you are referring to the question to the committee--

DR. BOYLE: Yes.

DR. HEINTZELMAN: If the committee was to vote in favor of that and FDA was to enact that into its policy, it would probably require a fairly extensive rewriting of that entire document so it would become incorporated into the document in the areas where it is appropriate.

Does that answer your question?

DR. BOYLE: The document being the questionnaire as opposed to the training materials.

DR. HEINTZELMAN: The document that I am referring to would be the malaria memo. I can't respond to what the individual blood banks are doing. We have to ask a representative from that area.

DR. HOLLINGER: Other questions?

DR. RUEBUSH: I am Trent Ruebush from the CDC. Perhaps I could respond to a couple of the questions or comments that were made. Someone asked about why we are not seeing more cases from Mexico and the Caribbean. Perhaps the reason that we are not seeing transfusion-induced cases from those areas is because the screening techniques are very good.

I think the real reason is there is very little malaria transmission; in the Caribbean, really only the island of Hispaniola. Haiti and the Dominican Republic have malaria. There is no malaria in any other Caribbean island and even the level of transmission in Mexico is quite, quite low. So the risk is low and I think that is the reason you are not seeing many cases.

I think it was Dr. Epstein brought up the point about, perhaps, making some slight modification. We feel very strongly at CDC that if there is ever any doubt about where a traveler is going, because we usually get involved

in that end of things in terms of prevention, or if we get a call from a blood bank, defer is there is any doubt.

But, again and again, we do get calls, and I work in a travel clinic in Atlanta where we have a lot of Coca Cola executives coming in. They are going to be traveling to Latin America or to Asia. They are going to be staying in a four-star hotel in a big city, but they are going to take a day trip to a factory in the middle of a rice field.

We feel very comfortable telling them they don't need to take malaria prophylaxis. Frankly, if a blood bank calls me, I would feel comfortable saying to them that person is okay. So I think we would feel comfortable, more comfortable, perhaps, than one side or the other with some sort of intermediary point.

Someone brought up the issue that they would like to have from CDC better maps of the malarious areas of the world. We would, too. The problem is that, in many parts of the world, the areas where malaria is really transmitted are not well-defined. Where it is transmitted this year or this season may be different next year or next season because of rains, floods, whatever.

I think we could do a better job in that, at least in some countries, come up with better maps. But many, many of our questions that we get from blood banks could be very easily answered at the blood bank if they simply had the

Yellow Book and a decent atlas because, basically, that is what we end up doing when we get a call.

They will tell us, "We have a potential donor who has traveled to a given country." We will ask, "Where?" We will pull out an atlas and then try to find the name of that city. A lot of that could be done, I think, at the blood bank. So we could, perhaps, help in providing better maps but something that would take care of, I think, 85 or 90 percent of the problems would just be a decent college-level atlas at the blood banks.

We do occasionally get questions about travel to places like Buenos Aires which they could certainly handle at the local level.

DR. PARISE: We get an average of about twelve calls a day. Some days it is six. Some days it is twenty. And that is all we do is look at our atlas. I very rarely have a difficulty with it. There are a few countries that I agree, we don't do very well, and those are Peru, Columbia and Ecuador. There may be a few other South American countries.

So I think maybe us trying to get a more detailed map of the provinces and departments in those countries would avoid confusion because it is a headache for me when I am in the middle of my lunch and I have to look for those provinces and I can't find them, either.

But, in general, a normal atlas, we answer 90 percent of these questions. We don't have anything computerized at all. We just look at the atlas and the Yellow Book.

DR. ELLISON: The suggestion was made by Dr. Epstein, I believe, that you have a list of resorts that are acceptable. Do you have such a list now?

DR. PARISE: We do have a list. We can't publicize the list with names.

DR. ELLISON: It is not a very effective list.

DR. PARISE: When we first started these discussions a couple of years ago and we got into discussions about some specific names of resorts, those resorts were on the phone with our lawyers almost immediately. I think it would be very unlikely that we are going to be able to publish names.

DR. HOLLINGER: On the other hand, if we take a cruise ship, you can look in and find out what their inspection has been with a number for any of the cruise ships around, if they have had a real safety record or the value of their score is a safe score.

DR. PARISE: I think, and there, Trent, you can comment, there are inspections of those cruise ships and CDC has information on that. We don't have that on the resorts. Really, we make this determination by looking at--no one

will agree to us going in and inspecting these resorts and collecting mosquitos.

So we really just, from Atlanta, make the best judgment we can.

DR. ELLISON: My second question has to do with the Yellow Book which I have never had occasion to use, but having just completed reading the federal income-tax guidelines, is there anything you can do to make the Yellow Book more user-friendly?

DR. PARISE: I think we would be open to a dialogue with blood centers because we are so inside of it. When I sit down with an atlas and the Yellow Book, I can answer these questions with very little difficulty. But we would be open to a dialogue with blood centers and whatever forum might be proposed to try to do that and put it on the internet. I don't think we are averse to that.

DR. CHAMBERLAND: In follow up to the question about CDC's ability to publish a list of resorts, I think Monica has indicated the difficulties that we would face doing that and that we actually, as opposed to cruise ships, don't obtain objective data.

But I would add that I would wonder if it would be possible, let's say, being in a guidance document or whatever, if perhaps CDC, FDA, could amplify a little bit of disease discussion of what constitutes an urban versus a