other than just simply saying, you know, here is a strategy. Are we right?

MR. BABLAK: This is a difficult subject obviously, and what the companies have agreed to do here is to develop an enhanced GMP review of the critical viral inactivation procedures for their particular products because each product is different by manufacturer.

Each manufacturer has to then develop their own check sheets, their own information for those products that are separate. Now, the companies have licenses from the FDA for all of these, and in those licenses are contained certain parameters for each of these, and those are what will be in the check sheets, those will be what are checked against and verified before the product is released.

So, it has to be done by each individual manufacturer. The policy of doing this type of general review is what everyone has agreed to do in general. The specifics of it have to be done on a company by company basis, and then have to be verified by the FDA because those are company-specific issues.

DR. HOLLINGER: Dr. Kleinman.

DR. KLEINMAN: A point of clarification. Obviously, products now go through a CGMP review of some type before they are released, I assume, and you are talking about enhancing that. I am not quite sure how enhancing

that review fulfills the goals of interdicting window period units that may have been introduced based on getting history.

In other words, you are already doing all these--I thought you were already doing CGMP reviews, already doing viral inactivation steps and documenting those. So, I mean it sounds like a good strategy to enhance those, but I really don't understand the specifics of what is changing.

MR. BABLAK: Two things. One, the specifics of what is changing would be the training of the individuals doing those reviews. So, currently, in many instances, the individuals would do those reviews, do what would be considered a typical GMP review, which is this says this, is that what was there.

So, if it says 23, did I get 23, not understanding what 23 means. So, there will be additional training to understand that 23 is really important, and 23.1 doesn't do it. So, that is part of what this is.

Additionally, then, there will be further documentation that that review has been done for those critical viral inactivation procedures. Obviously, it is already done. There will be additional work that has been accomplished that is written down that accompanies each batch record as it is released.

So, there is just some additional documentation,

but really what is the important thing is the training of the individuals doing that review.

DR. HOLLINGER: Does that imply, Mr. Bablak, that it wasn't done this way before?

MR. BABLAK: What it is implies that this is an enhancement. What was done before is a GMP review, which as I said, really talks about did you get 23 when it says 23 without an understanding of what 23 means.

So, this is bringing up the knowledge of the reviewers and plus documenting that yes, this additional review was done, these have been done, and it is accompanied with each product lot.

DR. HOLLINGER: Mr. Dubin.

MR. DUBIN: I think Dr. Stroncek said it directly. I mean we feel like how many you need to get with the program to license the test. I think, Jason, there is a couple of things. I think the industry on some choices has got to make some hard decisions about where they are going to be more cooperative with each other.

I think John has echoed something that we scratch our head about regularly because we have a number of software writers on our board of directors who are pretty computer agile, and everybody has been amazed at the lack of standardization.

I want to underline what John was saying. You are

sitting at a screen, you have got a data field, and you can't get to the next data field if you don't enter it, because it won't take you there.

It seems to me that that is something that would be pretty easy to agree on, it would make your life easier. It would certainly make FDA's life easier when they need information or need to look back, whatever the issue is.

I think what we have learned with HCV is poor recordkeeping causes us all a lot of pain including the companies that make up IPPIA, I mean let's face it. So, at what point do we get to the point where we all agree, competition aside, there is a basic degree of standardization that serves ultimately the interests of your companies, your component companies, as well as the FDA and the government, as well as the consumers.

This seems to be one of those issues that we can all get behind and say everybody wins, everybody benefits if we move on, and we live in such a technologically advanced society, yet we can't come up with a standardized system of reporting and data information, sometimes it boggles the mind from our perspective.

We have got most of our work on computer and standardized, it's so easy. I think you guys can't have it both ways. You can't get up and say we are going to do this as an industry, but these parts of it we are going to resist

because we are individual companies.

I just want to underline what was said down here, which is you have got to get with the program and you have got to make some choices.

MR. BABLAK: If I could respond, I think it is not clear maybe what I am trying to day. I think all the companies are agreeing to do virtually the same things. What the difference is, each company, first of all, has different processes, they have different parameters for those processes that have been validated, so those are different, and one company can't use information from another company because they don't have that particular process either validated or it's not run at their facility.

So, that is why it is important that each individual company has to come up with their own individual check sheets and individual SOPs against those check sheets because they are different processes. One company, you can't take it and run it at another company because it's completely different.

MR. DUBIN: Understood.

MR. BABLAK: That is all I am trying to say. I think the general idea of having documentation and records, I think they are all going to end up looking pretty similar. It is just the data that goes in, is what is different.

MR. DUBIN: Don't disagree.

DR. HOLLINGER: Dr. Buchholz.

DR. BUCHHOLZ: I was just going to echo that same statement. I think every manufacturer goes in with a different process. If these processes were all the same, it would be most surprising. There are differences in probably virtually any aspect of these fractionation procedures.

It is sort of like if you have a problem with your brakes, well, you say you get your brakes fixed, but, you know, does it make a difference if you have a Toyota or you have a Lincoln Continental, and I think the point that Jason made is a very real one in terms of no manufacturing process is identical among manufacturers, and thus there has to be individual variation.

But I think the message comes through very clearly that this is something that everyone wants to do and will lead to the desired result.

DR. HOLLINGER: Dr. Epstein.

DR. EPSTEIN: I think we shouldn't lose perspective here. We have made significant progress in the dialogue over post-donation information and that the Advisory Committee has endorsed a principle put forward by the FDA that either in the case of inadvertent pooling of test-positive units or in the case of risk factors, that the end products can be released provided that GMP was followed in manufacturing.

Basically, we are saying that given the current state of the art, manufacturing procedures that deal with hepatitis B, hepatitis C, and HIV are indeed adequate, and that is the key insight here, and therefore the whole debate shifts to ensuring the adequacy of GMP.

What we are really talking about here is whether there are measures that can be taken, such that a quarantine and a retrospective review of GMP issues can be obviated. I think that this is a very delicate issue because the underlying problem is that there have been GMP deficiencies revealed regarding procedures at many of the fractionaters, so there is a judgment call here what constitutes adequacy of this up-front review.

I would be the first to say that if there has been careful scrutiny of deviations in manufacturing, and they have been resolved with the conclusion of no potential safety impact with respect to inactivation of the viruses in question, that it's a safe product, but the issue is whether such determinations have been made adequately.

One of the buried questions here is, well, when would it be appropriate for FDA to take a second look at the batch record, you know, when would it be appropriate to challenge the conclusion of whatever group of, quote, unquote, "experts" reviewed the batch record in the first place.

I think that these are difficult questions and we are not going to come to closure on them today, but I just wanted to try to clarify where the issue is, and again, just for the sake of clarity, we seem to have a consensus and indeed recommendation with strong majority votes that we need not be concerned about these identified case of post-donation information even in the face of positive test results, let alone risk factors, when GMP has been complied with for the manufacturing procedures that are in place today with the current scientific state of the art. That is important.

Therefore, this whole debate is what constitutes adequate GMP oversight. I think that there will be a lot more that needs to be said about that. Certainly, the FDA is interested in industry proposals that suggest progress. You know, we are going to take these proposals very seriously, but the judgment call is whether these are adequate up-front or they aren't because one could have argued, and it has just been argued, well, isn't this what you have been doing all along.

Yes, the answer is that is what should have been happening all along, and yet in instances of post-donation information potentially affecting the safety of the derivative, we have repeatedly found that manufacturing deviations were not adequately addressed.

For example, there might have been a temperature excursion in the viral inactivation step to a temperature outside of the bounds of the validation data for the manufacturing process, and it went unrecognized at the time the product was distributed.

If we can be sure that such things no longer happen, you know, prospectively, and to some extent retrospectively, I think we could say we are there, but that is the question.

DR. HOLLINGER: Dr. Tabor, do you want to have any response at this point?

DR. TABOR: I just want to emphasize what Dr. Epstein said. We showed in a series of BPAC presentations in 1997 that the manufacturing procedures and the inactivation procedures in place at present are adequate to remove or inactivate any virus that could be present in the pool.

It all boils down to whether the inactivation and removal procedures are being done adequately. I am glad Mr. Dubin is here today because in those meetings, he brought up at least on one occasion the issue of the importance of ensuring that the GMPs are followed, so that those procedures that can inactivate the viruses will do so.

I think the IPPIA should be commended for their proactive stance. This is I think the second really major

proactive program that they have brought forth in the last year and a half or so or two years, and I think it is certainly worth us taking a good look at a detailed outline of their program.

I think one of the problems we are going to have to deal with is once their program is in place, how long would it take FDA to verify that the program works, and that might take a series of inspections that would take quite a bit of time, but those are problems that we will deal with the future, and we would certainly like to take a good look at the details of your program.

DR. HOLLINGER: Thank you, Ed.

We are going to take a break now. It is about 10:48, so we will break until 11:15. We will reconvene here at 11:15.

[Recess.]

DR. HOLLINGER: The next topic actually is a real critical topic on Strategies for Increasing the Blood Supply. It is really informational, but it is such an important issue since more and more donors are being lost either indefinitely or for a short period of time.

So, these concerns hopefully will be dealt with a little bit about what strategies can be used for increasing the blood supply. This is going to be discussed today by Mary Gustafson.

I. Strategies for Increasing the Blood Supply - Informational

Introduction and Background

Mary Gustafson

CPT GUSTAFSON: Thank you.

[Slide.]

If you will recall in the updates, Dr. Nightingale reported to you on the last meeting of the PHS Advisory Committee on Blood Safety and Availability, and this committee continues to be concerned with the availability of blood derivative and blood components.

As a refresher, at their April meeting, Ms. Marian Sullivan from the National Blood Data Resource Center reported the results of a survey that was conducted last year using data from 1997, which indicated that blood collections have decreased and blood utilization has gone up since the last survey, the previous survey in 1994, and also extrapolating the data, she showed that if there were no changes in blood collection policies, recruitment practices, or in blood utilization, that the lines would intersect in the year 2000 and that the blood usage would outstrip the supply.

You also heard from Dr. Mary Beth Jacobs from our office that we have issued guidance recommending that blood establishments defer donors who have traveled in or resided

in the United Kingdom during a six-month cumulative period between 1980 through 1996.

Dr. David Satcher, who is the Assistant Secretary for Health, and the Surgeon General, and who also serves as the National Blood Safety Director, recognized that the decision to defer the donors would impact a blood supply that may, in fact, be in a crisis.

Recognizing that the decision to defer donors who had traveled to the U.K. would impact the blood supply, Dr. Satcher requested that the Interagency Working Group on Blood Safety and Availability prepare a report on strategies to monitor and increase the U.S. blood supply.

An ad hoc subgroup comprised of representatives from the FDA, the Centers for Disease Control and Prevention, the National Institutes of Health, the National Heart, Lung, and Blood Institute, the Department of Defense, and selected members from the Blood Products Advisory Committee were asked to develop these strategies.

[Slide.]

The members of this committee are shown, and from the BPAC and also from the CDC, we have Mary Chamberland, John Boyle, and Marion Koerper.

The group of health officials recognized that the expertise, experience, and insight to solve these problems actually lies with the blood industry itself. Therefore,

representatives of the blood industry were invited on a one-time basis to provide input and comment, and those persons are shown on the next slide.

[Slide.]

The subgroup recognized that there are a variety of problems that contribute to the blood shortages, and the group also recognized that not all problems can be readily solved, but we have identified some strategies for approaching solutions that can be achieved on a short-term basis and some on a longer term basis that would require the cooperation between government and industry.

In the interest of time, I will go directly to these recommendations. There are five of them.

[Slide.]

The first is to monitor the blood supply. The group recognized that reliable, timely data on national and regional blood supply, collection vis-a-vis blood usage, transfusion, are unavailable. Although periodic retrospective surveys have documented collection and usage trends for specific time periods and seasonal variability is well known, there are not reliable national instruments for anticipating shortages with sufficient lead time to accomplish increased donor recruitment or deliberate redistribution of existing supplies.

In the past, this effort has not been funded

adequately by the private sector. The group feels it is essential that both industry and the PHS have timely access to data to facilitate planning.

With this goal, it recommended that under interagency guidance, an appropriate agency within PHS should arrange for ongoing proactive monitoring of the nation's blood supply. The resulting information would be used by government and blood centers to forecast or rapidly identify shortages and implement timely remedies.

In the short term, it seems most reasonable for the PHS to support the current ongoing monitoring efforts at the National Blood Data Resource Center. Ms. Marian Sullivan advised the group that it is feasible to set up an information system which would provide up-to-date blood supply information on a routine basis if NBDRC resources could be expanded or externally funded.

The group had suggested that funding be provided initially to support monthly surveys of a representative sample of U.S. blood centers and transfusion services because longer intervals, going to two or three months, would not be sufficient to respond to shortages and may not reflect short-term variability supply, such as seasonal variability or impact of the new donor deferral recommendations.

The National Heart, Lung, and Blood Institute is

in the process of contracting with the National Blood Data Resource Center to conduct monthly surveys starting with blood collection facilities and later including transfusion facilities.

While the group viewed support of the ongoing effort as the most expeditious approach, it also concluded that the appropriate long-term strategy would be the use of competitive contracting under the direction of PHS to ensure adequate monitoring of blood supply availability and use.

[Slide.]

The second recommendation was to encourage more donations by eligible donors. It has been estimated that nearly half of the population over 17 has donated blood at least once, however, only 5 percent of that population donates blood in a given year.

Among active donors, the average number of donations per year has been consistent at 1.5. These data indicate that the number of eligible donors in the United States is adequate to meet the country's blood needs. The problem of shortages can be solved by encouraging current donors to give blood more frequently and to recruit more eligible donors into the current donor pool.

A 15 percent increase in the average number of donations per donor per year would increase the national blood supply by 10 percent.

One way to do that would be to get many donors who donate only once or twice a year to give one more time. Beyond that, it is important to encourage a lifetime habit of donating by donors who have given only once or twice.

One way to encourage donations is to publicize the need for donors. Any publicity campaign should focus on both the retention and increased participation of established repeat donors, as well as the recruitment of lapsed and first-time donors.

An appropriate short-term strategy would be an industry-developed, broad-based national media campaign to encourage volunteer blood donation. Where appropriate and strategic, the PHS can encourage such a campaign by the industry. For example, public service announcements by high-ranking department officials who would be readily recognized by the public could be provided, and Dr. Satcher announced at the PHS Advisory Committee that he would be willing to participate in such an effort.

In addition, an organized effort should be made to identify successful recruitment models. Various research activities can be supported by PHS agencies to determine why one or two time donors have not continued to donate and to see what measures, such as incentives or recognition programs or increased convenience, would encourage more frequent donations by current donors who give an average of

only 1.5 times per year.

A long-term strategy would be to address the education of children to foster the civic responsibility to be blood donors. Public education starting in elementary schools should be useful in developing positive attitudes towards donation.

[Slide.]

The third recommendation is to improve donor relations as part of recruitment and retention. The blood supply is dependent upon the volunteerism of Americans. Strategies that can be undertaken on a long-term basis should address customer service improvement.

There are competitive pressures to volunteer for many charitable causes, and Americans demand better customer service now than in the past. Information from an earlier era indicated that few donors, maybe only 2 to 3 percent, are lost because of a bad experience at the time of donation. However, those studies are over 20 years old. Much has changed in donor interactions with increased donor deferral criteria and increased competition among blood centers for the same donors.

There is a need to determine if current donor practices are effective in encouraging and retaining blood donors, recognizing the need to avoid undue incentives to donate.

The issue of donor relations is mostly in the purview of local blood centers, but there may be more similarities than differences from one region to another. The task group identified areas in which the government can play a role. In the absence of current published studies, the PHS may co-sponsor with industry a public workshop for identifying best practices for donor recruitment and retention.

In addition to sharing best practices, the public workshop should address the need and study design of instruments to evaluate donor interactions since much available donor behavioral information is anecdotal.

Longer term projects that can be undertaken nationally include simplifying the donor questionnaire and/or designing a simplified questionnaire for repeat donors.

Dr. Davey, at the April PHS Advisory Committee, and others, have reported that donors find the current questionnaire extensive, intrusive, and tedious for repeat donors. The task group felt that the responsibility for this project should be shared within the PHS agencies.

Another longer term project is the development of the computer-assisted donor history questionnaire. The NHLBI is currently supporting a study that is presently in the clinical trial phase. Once developed, the FDA can

encourage its use by accepting the instrument and study data for use by blood centers.

[Slide.]

The next recommendation is to remove restrictions to safe donation. Some healthy donors are restricted from donation for transfusion by existing government or blood center policies. The PHS should investigate whether all current deferrals are necessary to protect the public health.

In terms of hemochromatosis, the PHS should move proactively to determine whether hemochromatosis patients can donate as normal donors. The patient group is very active and would like to be able to donate. Medical data support that hemochromatosis patients are not less safe because of their disease, however, there are questions about the voluntary nature of their donations because people with hemochromatosis require phlebotomy as therapy.

The obligate need for phlebotomy introduces an incentive to donate blood for transfusion because most patients are charged for the therapeutic removal of blood. The concern is that a financial incentive to donate at no cost rather than be phlebotomized therapeutically might cause the donor to be less truthful about acknowledging risk behaviors. Removing patient costs for therapeutic phlebotomy would alleviate that concern.

The working group recommended that DHHS identify and remove barriers to providing reimbursement support for all therapeutic phlebotomies.

I will take a moment to tell you what has been done in the area of donations by the hemochromatosis patient.

[Slide.]

At the April PHS Advisory Committee, the committee made this recommendation to the Department of Health and Human Services, that the Department should create policies that eliminate incentives to seek donation for purposes of phlebotomy, and that the Department should create policies that eliminate barriers to using this resource.

[Slide.]

Following the meeting in July, Dr. Shalala, the Secretary of DHHS, sent a letter to Dr. Kaplan, the Chair of the PHS Advisory Committee on Blood Safety and Availability in which she concurred with the recommendation and said that she was directing Health Care Financing Administration and the FDA to identify strategies to implement the recommendation.

Further, Dr. Satcher sent memoranda to Health Care Financing Administration and FDA with the action item, identify strategies to implement the Advisory Committee recommendation.

[Slide.]

On August 10th, Dr. Jane Henney, who is the Commissioner of FDA, responded to Dr. Satcher with strategies that were developed by the Center for Biologics Evaluation and Research and the Office of Blood.

[Slide.]

Those strategies include consider on a case-by-case basis exemptions under Title 21, Code of Federal Regulations, 640-120, which is our exemption clause, exemptions from existing regulations when phlebotomy is performed at no cost to the phlebotomy.

These are regulations that require the label to state the disease that required the phlebotomy and also the regulation that limits the frequency of whole blood collection under normal circumstances to once every eight weeks.

[Slide.]

We included the request that there be conditions for the exemption, and those conditions are that we would expect the blood center to submit to us safety data, and these are data that would be collected on donors anyway, on viral marker rates, seroconversion rates, post-donation reports, and any donor recipient adverse events.

It was pointed out at the PHS Advisory Committee that we may not get data that we would be able to evaluate

in a meaningful way, and the truth is that the blood supply is safe. The risk is so low that collecting this type of data on the number of persons may not give us data, however, it is a change, and if we don't look and we don't specifically collect the data and look at it nationwide, we won't have any information at all.

[Slide.]

Additionally, we in the FDA had said that we would review any funding plan proposed by our sister organization, Health Care Financing Administration, to determine the adequacy in removing the financial incentive.

We understand more now maybe than we did even a month ago in terms of the Health Care Financing Administration and their limitations. They are limited by their statutory authority and also in their scope of jurisdiction.

HCFA is responsible for implementation of Medicare entirely and it cooperates with the States in the implementation of the Medicaid program. There are still a vast number of persons who will not fit into these programs including persons insured by private insurance providers and, unfortunately, persons who are not insured in this country.

So, for the foreseeable future, the responsibility of removing financial incentives appears to fall on any

blood center wishing to collect blood from donors with hemochromatosis. So, as we will have a case-by-base determination of requests to remove or to exempt the regulations, each blood center will have to do an evaluation also in terms of the advantages to them to entering these donors into their donor pool.

[Slide.]

Additionally, most blood centers and blood collecting facilities are accredited by the American Association of Blood Bank, and the AABB has the standard still that prohibits use of blood from therapeutic collections.

[Slide.]

After having a program of case-by-case evaluation and exemption from current regulation, and after financial incentives are removed with favorable outcomes of surveillance data, FDA will propose revisions to regulations.

If you could go back about six slides to the Remove Restrictions, if you can't find it, that's okay. It just lists our other, more longer term strategies or our other strategies, and that is to review the donor deferral policies in terms of the history of male-to-male sex.

We have had workshops, we have had BPAC discussions on this issue, and we need to move forward in

making a decision on whether this should be a lifetime deferral or whether there is some other deferral time that will be adequate from a safety standpoint.

Another longer term strategy would be to look at donors who are hepatitis B core antibody positive to see whether these donors could be reentered into the donor pool. It has been suggested that the hepatitis B core antibody testing offered only a limited benefit and about 0.5 to 1.5 percent of the donors exhibit reactivity, however, data are not available which specifically address the safety of eliminating the test.

Also, there are no figures which indicate the number or percent of donors who are eliminated solely because of their HBc antibody reactivity especially after readjustment of the cutoff for the test to improve its specificity, and the task group recommends further studies in this area.

[Slide.]

Our final strategy was to address the economic issues facing the blood industry. Throughout all of the discussions of the task group and with the industry participants, concerns were repeatedly expressed about the economic distress of the blood industry.

Reimbursement practices and competitive pressures of health care today make it difficult for blood banks to

recover the cost of new innovations even when such measures are required.

These economic limitations are a strong disincentive for change. The task group recognizes that the economic issues associated with changes of the blood industry need to be addressed. They were addressed, as Dr. Nightingale told you, at the August meeting of the PHS Advisory Committee on Blood Safety and Availability, and as he also said, there are continuing actions beyond the scope of this committee and also beyond the scope and jurisdiction of the Food and Drug Administration.

In conclusion, the success of any national effort to affect the blood donor supply will depend on improving the bond between the blood industry, the blood donor community, and the Federal Government.

Effective leadership by government and cooperation of the blood industry are needed to ensure that the American public can depend on a safe and readily available source of blood therapies.

Thank you.

DR. HOLLINGER: Thank you, Captain Gustafson.

Dr. Boyle.

DR. BOYLE: Just one point of clarification. The task group has laid out strategies, short term and long term, for trying to improve the blood supply. Given the

fact that this is brought about by estimates that that demand will exceed supply by next year, we have not said that any of these short-term strategies will alleviate that shortage next year, isn't that correct, we are taking a position on what are the best strategies, not that we are actually not going to have a blood shortage next year?

CPT GUSTAFSON: That's right, and I think that is limitations of the report. I think it is also limitations of the study, that it was based on a couple of points from 1994 and 1997, retrospective data, and mainly the projections were made showing if there were no changes, and we know that the blood community over the years has been very reactive to changes in terms of recruiting donors and alleviating problems.

DR. HOLLINGER: Dr. Buchholz.

DR. BUCHHOLZ: Mary, I certainly applaud the efforts in this area, and I think collection of data is always very admirable, but I am a little puzzled by the committee's recommendations with respect to hemochromatosis.

It looked to me like there was a certain extent of data collection for the purpose of data collection. I mean there is obviously some issues of is this a safe procedure for the donor.

Well, in this case, the donor is a patient who would require this therapy, and whatever events happen,

presumably, would happen to that donor on the basis of a therapeutic procedure being performed whether that blood was thrown out or used for transfusion.

The second thing is it looked like there was a lot of data that I assume is in some way incremental to the routine collection of that same data on infectious disease and so forth, and I am not sure, I am a little confused as to what the purpose of that is.

I mean are we saying that we don't have faith in our infectious disease testing, because I think that probably is not the reason, and if we did have faith in that testing, why are we doing this incremental data collection for this particular group of patients. I may have missed something here along the line.

CPT GUSTAFSON: I think the data collection is done anyway, and what we would be asking as a postmarketing surveillance or making an exemption from our regulations, and we are making the exemption, quite frankly, not on prospective data, but on the findings. We have had presentations that the disease state itself does not cause any safety concerns, however, we have over time been concerned about undue incentive to donate and the fact that there is a financial incentive in this case.

I think we are not aware of any long-term studies being published on the patients or donors although I think

there are places who have collected the data.

So, it would be a request from us to stratify the data on these donors separate from just the regular donor population and provide it to us to have a national surveillance effort because we don't really know the numbers from data that have been published.

Transfusion in June had a couple of articles that indicated that there may be a big jump in the donor population, but there has been other reports that, in fact, there may not be a huge number of donors that would be entered into the system.

So, in order to provide a surveillance activity in the absence of long-term studies, we would like to see this type of data.

DR. BUCHHOLZ: Just a second question that I was a little surprised you didn't mention relative to some of the newer techniques in blood collection that involve automation, for example, platelet collection with the various several blood cell separators out there that, in fact, can get a therapeutic dose of platelets from a single donor, and now there are beginning to be on the market instruments that will allow for two units of red cells or a unit of red cells and two units of plasma, that sort of thing.

I am a little surprised the committee did not take

a more proactive stance against some of these applications, which I think can have a tremendous impact on alleviating the supply problem. Certainly, if you are looking for a 15 percent incidence of return donors, implementation of two units at once would sound very attractive.

DR. HOLLINGER: Also, on the issue about hemochromatosis, as well, the incentive actually for patients with hemochromatosis to donate is because of their health. Personally, I don't think it would matter whether it is being paid for or not being paid for. The issue is to prevent them from developing cirrhosis.

So, they are going to go in for their iron removal on a regular basis at least until the iron is removed, and then they can't, like anyone else, once that iron is removed, donate any more frequently. It is going to result in the same problems they had before, that is, in terms of developing anemia and other things.

So, up until that point, though, they could donate on a weekly basis for a year or two or more, as long as if they have very high concentration or iron in their blood. But I don't think it is the incentive for whether it is going to be paid or not, to me would be an issue.

Dr. Mitchell.

DR. MITCHELL: I guess I understand that the reason for collecting the data would be to see if that group

is at higher risk of other risk factors that might impact the safety of the blood because of their incentive to donate for health reasons and also for financial reasons. So, I think it is very important to collect the data on that if they are at higher risk than average.

DR. HOLLINGER: One clear thing is, again, back in the hemochromatosis, because a lot of the patients with hepatitis C, who have iron overload as either an aspect of their disease or not, because the iron makes a difference, a lot of them are sent to the blood bank for therapeutic phlebotomies, so obviously, one does have to make a conclusion of whether you really have hereditary hemochromatosis versus somebody with iron overload, which is a lot different.

Dr. Nelson.

DR. NELSON: It seems to me that you might remove the incentive if the policy was changed that all hemochromatosis patients, despite whether or not the blood was used for transfusion, the financial burden was removed, so I would not link the cost as to whether or not if a person had hepatitis C or HIV and the blood was tossed out, they still didn't have to pay for this.

It seems to me that that would probably obviate the financial incentive. Is that not what was being considered?

CPT GUSTAFSON: Yes, that is where we are going is to eliminate the charges for the therapeutic bleeds, and it would more or less level the playing field, and not give an incentive to maybe perhaps not give totally truthful information during the donor history part of the donor screening.

DR. HOLLINGER: We have two other people who have asked to speak. Are there any other questions for Captain Gustafson at this point? We can come back in the committee.

Yes, go ahead, Mr. Dubin.

MR. DUBIN: Did the committee at all consider--and I know, John, you were part of the process--but did the committee consider at length using--there is a lot of us who are essentially grass-roots organizations, and we engage the society at a level that is different than government and different than the industry, and we have kind of always proposed that there is something there that government and industry need to take a look at, because I think a lot of organizations could do a lot of good towards education at the community level, in high schools, in grammar schools.

I spoke to my daughter's classes, my youngest, twice on blood donating, and I guarantee some of them are regular donators now. I think that is something that we could really bring a number of organizations in beyond the ones you see in this room. There are lots of them, and it

has got to get to that level. It has got to get down into small communities where people are living and we can play quite a role in that, I think.

CPT GUSTAFSON: That is a good point, and, yes, we did have discussions, but as we would move forward on the implementation of some of the longer term strategies, particularly the childhood education, that you would need to have to have a strong bond between the community group, the blood industry, and the government in order to move forward.

DR. HOLLINGER: We have two other groups that have asked to speak on this issue in the open public hearing.

Is Dr. Peter Tomasulo here? We weren't sure if he was going to be here. If not, then, the next person who has asked to speak is Susan Parkinson, the Deputy Director of America's Blood Centers.

Open Public Hearing

Susan Parkinson

MS. PARKINSON: I am Susan Parkinson from America's Blood Centers. For those of you who don't know, America's Blood Centers is the consortium of not-for-profit community blood centers that provide about half of the nation's blood supply.

ABC is pleased to be here today to have the opportunity to comment very briefly on the recommendations of the Public Health Service report commissioned by Dr.

Satcher for strategies to increase the blood supply.

I would like to take just a few moments to make some specific suggestions that we feel may help the FDA and the PHS Interagency Task Force to be most effective in assuring an adequate blood supply in the future.

[Slide.]

ABC supports the first recommendation of the PHS Task Force and specifically supports the planned NHLBI studies on donor recruitment, motivation, and screening. There is no doubt that better understanding of our donor base would increase our chances of recruiting more donors, more often.

We encourage the FDA, however, through the Interagency Task Force, to seek broad input from local and regional blood centers into the study designs. These studies will be more effective when local blood centers have had the opportunity to participate in their development.

[Slide.]

ABC also supports Recommendations 2 and 3, encouraging more donations by eligible donors and improving donor relations to facilitate recruitment.

ABC is specifically interested in encouraging the development of a broad-based national media campaign to increase donation. This media campaign should include donor recruitment materials that can be adapted to all regions and

ethnic groups across the country.

In addition, we are enthusiastic about the PHS offer to find high profile public figures to make public service announcements for the donor awareness initiative and would welcome the opportunity to be involved in the discussion and selection when and where appropriate.

In addition, we encourage top HHS officials to be publicly supportive of existing donor recruitment campaigns like the cooperative effort of all blood organizations during National Volunteer Blood Donor Month in January and National Donor Day in February. HHS assistance in promoting and recruiting public figures for public service announcements for these existing efforts would be greatly welcomed.

To assure that the tools of a public education campaign will be effective in rural and urban areas, as well as on the national level, we urge PHS to establish a donor recruitment advisory panel made up of donor recruitment and communication professionals from the local blood center level. ABC and the other blood organizations have many talented individuals ready and willing to be of assistance.

To that point, ABC encourages the PHS to establish a biannual round table where industry professionals, public health officials, and donor groups, like civic and corporate leaders, meet to discuss ways in which they can work

together to help blood donation easier and more accessible.

We are very encouraged to note that the Office of Blood Diseases and Resources of the NHLBI under the direction of Dr. Barbara Alving have initiated support for these and other possible initiatives under NHLBI's umbrella. This effort already has the endorsement of ABC and others. NHLBI may well serve as the most logical agency to help implement Points 2 and 3 of the recommendations.

[Slide.]

Finally, ABC also strongly encourages the removal restrictions of safe donation and encourages the reevaluation of current deferrals to assure that they contribute to the safety of the blood supply without unnecessarily impacting the adequacy of that supply.

We remain particularly concerned with the new variant CJD deferral, and again ask FDA to outline what will trigger a reevaluation of this deferral. Additionally, we request that FDA reevaluate the continued usefulness of the hepatitis B core antibody test, which defers many safe donors each year with little or no return on safety, thanks to the availability of new technology.

If, after careful analysis, FDA still deems these deferrals appropriate, we request that the agency help develop specific instructions and literature for all blood centers to distribute to affected donors.

In closing, ABC thanks the committee for the opportunity to present our views on ways in which PHS could assist in donor recruitment. We look forward to an industrywide, public and private sector cooperative effort to help achieve a safe and adequate blood supply for future patients.

We ask that BPAC publicly encourage FDA and PHS to implement these specific recommendations.

Thank you.

DR. HOLLINGER: Thank you.

DR. BOYLE: One question. Studies of donor recruitment and retention are sort of basic market research.

MS. PARKINSON: Yes.

DR. BOYLE: You are enthusiastic about government doing it, and government normally doesn't do market research, and it is being done because of the absence of it.

The question is why hasn't ABC and other blood organizations been doing this kind of thing, seeing the decline of donors over these years?

MS. PARKINSON: Actually, we have, and I think independently, all the blood agencies have been doing it, and even within our own organization, independently, blood centers have been doing market research, but what we would really like is a combined effort where all the blood agencies, with the help of government, it lends credibility

to a major marketing effort.

DR. HOLLINGER: Mr. Dubin.

MR. DUBIN: If you have been doing it, there is nothing here.

MS. PARKINSON: I think that we have regional results, and that is really the initiative. If this is going to be a national blood crisis, we have regional information and nothing that really lends itself to a national solution.

DR. BOYLE: Does this mean that you are willing to pool that information with government rather than having government sort of start from scratch to do it?

MS. PARKINSON: Oh, definitely. I think that the experts of the blood banking industry should be the ones that help develop this program, but again we need the backing and support of government to really make it a national effective effort.

DR. HOLLINGER: Go ahead. I was going to say before we do, I want to see if there is anyone else during this open public hearing, allow them to give some comments first, and then we can come back with the committee.

Dr. Kleinman.

Steven H. Kleinman, M.D.

DR. KLEINMAN: Steve Kleinman. I just wanted to make a comment about donor recruitment and blood centers'

interest in it.

You know, it is not a new interest at all. I mean it is what blood centers have done for years, and having worked in Los Angeles for a number of years where it was very difficult, I mean we spent massive efforts in trying to recruit donors.

Basically, it is a difficult thing to do, and you can study it as much as you want, and I hope another set of experts will be better at it, but I think it is difficult, given the donation process, given the operational limitations, and sometimes it is logistics, it takes time for people to donate blood, it is not a pleasant experience. Blood centers in the past have not made it convenient for donors. That is one thing that can be improved for sure.

But it doesn't take rocket science, I think, to understand there are certain basic things you can do to increase recruitment, and there is a certain basic resistance to giving blood that many people have.

I mean I think it is great there are these initiatives going on, and I agree there should be better education, but I don't think this has happened in an absence of the industry trying to recruit more donors.

Now, maybe the new creative ideas aren't there.

MS. PARKINSON: I would like to comment on that briefly. I absolutely agree with you, and I think what this

new initiative, about the PHS initiative could do is lend credibility to a national campaign.

From a PR perspective, it is very difficult to constantly go back to the donor base and say please give more blood, and a new program just gives us a better hook to go back to the media, and this is a good time to plug the National Blood Data Resource Center data, which has given us great media coverage which brings in donors.

DR. KLEINMAN: If I could say one more thing. This idea of educating people when they are young to become blood donors has floated around since I started in blood banking. I mean I heard it 15 to 20 years ago, but it has never really been done effectively, so maybe there is the room for a national program to try to provide some impetus for these educational efforts to happen more.

DR. HOLLINGER: Is there anyone else from the public that wishes to make a comment at this point?

[No response.]

DR. HOLLINGER: If not, you may want to make some comments after you hear this, but Dr. McCurdy.

DR. McCURDY: Some of us are old enough to remember historical things. Back in the late 1980s and early 1990s, the National Heart, Lung, and Blood Institute had a national blood resources education program, which was doing all these things or trying to do all these things with

advice from the blood banking community that were discussed today. What is different now? What would make that effective? It was discontinued because the blood banking community thought that it was not being effective in recruiting donors.

DR. HOLLINGER: Any comments? Celso, you look like you want to get up and say something. Dr. Bianco.

DR. BIANCO: It is a very good question, what is different now. What is different now, Paul, is that the world has changed. We have been telling everybody that blood is not safe. There is a tremendous amount of fear. There is a tremendous lack of trust in the entire system, and that has discouraged people from the act of donating blood as one of their community activities.

Also, there are many more competing interests from the internet, to multimedia, to all those things, and so when you try to convince a group of young people to participate in the donation process, you are competing against many other interests that you didn't have before.

Before, the communities were more stable, there were more links, it was easier to do it. The demands today are kind of different. We have to be much more sophisticated. I think that this program, as I see it, its birth now, and the interaction.

If the United States recognized a blood donation

is a public health issue, I think that we are going to be much more successful in that.

DR. HOLLINGER: Corey, the last comment.

MR. DUBIN: Two things. I agree, Celso, there is a trust factor, and some things could be done about that. For us, the hepatitis C lookback was one thing that could have gotten a lot of good press and maybe still can.

The second thing, it doesn't help that you guys are all competing out there, and like there is a hostile takeover in Santa Barbara, the blood bank, and it is front page news in the local paper every day, and it doesn't really go over well with the local citizenry that this blood bank we have all known for years, and has been pretty good, is now being hostilely taken over by some giant.

So, I think there has to again be some sense of what the priorities are, and then you have got Red Cross trying to take over everybody. On this issue, maybe we could like separate you guys from the ring, call a time out in the battle, and say we have got a problem.

I know sometimes it sounds extremely naive, but I am looking at it, sitting in my living room in a little town called Goleta, reading about this hostile takeover, and all my friends are going what the heck is going on, can we trust these people, it's all about money. The wrong images were being presented in that story. Even if that wasn't what was

happening, that was what was being presented.

I think we have consistently felt like the consumer groups like us have not been tapped enough, there is a lot of us out there, and I think, as naive as this may sound, we have got to make blood donating good citizenship, and you have got to go back to the kids to start that. You have got to go back to the kids, and I think we can help that others can help that, but I also think we need the Congress and the administration to get involved in a much greater way.

I have been sitting at this table five years, and I have never seen the Congress and the administration get involved at the level we believe is necessary to make this a national priority.

Maybe it is going to take all of us approaching the administration and the Congress together with one voice, but I think there are some things we can do.

DR. BIANCO: I agree with you entirely, Corey, and I think that I want to use a word here. I think in recent times, because of managed care competition, but people try to transform blood into a commodity. Blood is not a commodity. Blood is the gift of life.

DR. HOLLINGER: Dr. Stroncek.

DR. STRONCEK: I would just like to support the proposal put forth by Mary Gustafson. As the discussion has

shown, this is a very complicated issue. In some hands, blood centers do and must act like private competing groups. On the other hand, they have a very important public service role, so it is a very difficult situation.

Concerning the blood shortage, if you look at the numbers, we don't need twice as much blood, we only need a small increase. So, if you talk about having public appeals, you might double your donors one day, but you don't need that many, and you turn people away. So, it is very tricky to give the right messages so you get a sustained, steady increase that is going to be sustained over the years rather than just a one-time increase in donors and give the donor a wrong message and turn them away with an appeal.

DR. HOLLINGER: Thanks, David.

DR. BOYLE: Just one observation about Corey's comment about getting the President and the Congress involved. If we run out of blood as projected next year in the middle of a presidential campaign, one of whose participants may have been the head of the American Red Cross, I think we will get a lot of political attention.

DR. HOLLINGER: We are going to move on to the next topic for this morning. It's on Nucleic Acid Testing of Blood Donors for Human Parvovirus B-19.

We will start with an introduction and background by Dr. Lynch.

II. Nucleic Acid Testing of Blood Donors for Parvovirus B-19

Introduction and Background

Thomas Lynch, Ph.D.

DR. LYNCH: The topic now is the implementation of nucleic acid testing or some other laboratory control assay for human parvovirus B-19.

[Slide.]

After this brief introduction, Dr. Neal Young from the National Heart, Lung, and Blood Institute will give some background on the medical and scientific state of knowledge, and then I will come back and pose the regulatory question really, which has to do with the framework in which FDA will regulate and assure the consistency and effectiveness of this testing.

I should note, in addition to Dr. Young, Dr. Kevin Brown, also from the Heart, Lung, and Blood Institute, is also with us, and he is an internationally recognized expert in this field in his own right.

[Slide.]

B-19, as you know, is a small, non-enveloped, very tough virus that is very common in the community. It is readily spread by casual contacts, as well as through some transfusions and transfusions of manufactured products.

Notably, it is very resistant to methods of

inactivation commonly used in manufacturing plasma derivatives including heat and solvent detergent.

[Slide.]

When a normal individual is infected, the course of the active infection runs over a very brief period, vigorous immune response follows early viremic phase, which results in the neutralization and clearance of the virus, and confers life-long immunity on an immune competent individual.

During the active infection, symptoms, where they exist, tend to be relatively mild. Probably the most common is a subclinical anemia that one can pick up only by doing testing of the patient.

However, there are at least three at-risk groups that have been identified in which B-19 infection has significant clinical consequences, those being patients suffering from an underlying hemolytic anemia, in which case an infection can push them into an aplastic crisis; pregnant women, especially those infected during the second trimester where there is a greater risk of fetal loss through a condition called hydrops fetalis, and finally, patients who have some sort of immune deficiency or suppression in which case a B-19 infection can become chronic and develop into a chronic and significant anemia, as well.

[Slide.]

Among blood donors, well, first of all, there is no screening presently done for blood or plasma donations in the U.S. There is no licensed test to perform such screening, but we know that about half of the donors are seropositive for B-19.

Now, it is important to bear in mind that that does not indicate that half of the donors are infectious. That just indicates a past history of infection, and the vast majority of seropositive donors are, in fact, simply immune.

It is also important to bear in mind that the antibodies contributed by those donors end up in products such as IGIV, and although B-19 is not a formal indication for the use of IGIV, it is widely used with reported great success in treating chronic B-19 infections.

Of more concern are donors who have active viremia and the numbers are rather soft here. For all viremic donors, the estimate I have up here, 1 in 3,000 to 1 in 5,000, may be an underestimate in some cases, a very high number, nonetheless, and perhaps 20 to 30 percent of those donors have very high titers of B-19 virus in their plasma.

Viremia can reach prodigious proportions, up to 10^{14} genome equivalence per mL, although that doesn't necessarily directly translate into virus particles, it's an estimate, very high concentration. Of course, most donors

would be asymptomatic at the time they made the donation of blood or plasma.

[Slide.]

Regardless of these numbers, or in spite of them, transmission by blood components, such as red cells or fresh frozen plasma, is thought to be an extremely rare event. Transmission would require a viremic donor prior to or shortly after seroconversion, i.e, before all the virus was neutralized, and the transfusion of a unit contributed by such a donor into a seronegative recipient.

Now, it must also be admitted that it is possible that transmission of B-19 by transfusion of blood components is more frequent than we appreciate, and is simply unrecognized because the disease is asymptomatic and not noticed.

The situation is a little bit different for the manufactured products. At first, I should point out that we have no confirmed reports that the immune globulin products or albumins have transmitted B-19, although there are case reports that have been published from time to time about this.

There is, however, significant transmission by some, perhaps many, of the plasma-derived clotting factors that are used to treat hemophilia, specifically, Factors VIII and IX. This has been demonstrated in a variety of

clinical trials, as well as the epidemiology of seroprevalence among hemophiliacs compared to the general population.

[Slide.]

Now, the manufacturing procedures for these products, at least in some cases has been validated to clear a certain level of parvovirus, but this capacity is equally clearly not sufficient to render these products non-infectious in all cases.

Among the various alternatives that one could contemplate to address or mitigate this risk, screening of the incoming plasma appears to be the most practical and easiest to implement in a short period of time.

Antibody screening is inappropriate because it doesn't pick up your infectious donors, and it would eliminated a valuable characteristics of IGIV, but antigen or nucleic acid testing are possibilities. Nucleic acid testing, we assume at the moment is more sensitive.

There has been interest in introducing this testing, and because of decisions that the FDA made with regard to nucleic acid testing for hepatitis C or HIV, the question has been raised whether clinical trials to demonstrate the clinical effectiveness of these tests need to be demonstrated prior to implementing NAT for B-19.

Now, the focus of the question today is on plasma

for further manufacturing. There is two reasons for that. One is for a variety of technical and logistical considerations, it is more practical to implement NAT testing for plasma for further manufacturing than, I think, for whole blood donations.

If the need arises, we can always revisit the subject of whole blood donations at a later date.

Secondly, the most significant risk posed by parvovirus is related to the use of manufactured products rather than transfusable components, so for both practical considerations of effectiveness, we should focus the discussion today on plasma for further manufacture.

Without any further delay, I would like to turn the microphone over to Dr. Young.

Presentation

Neal S. Young, M.D.

DR. YOUNG: Well, Tom Lynch has given you an indication of a far more grand talk than I had the intention of delivering, which I am sure is going to be a relief to you. My intention is really to be brief and not to present a 45-minute or 50-minute overview of everything we know about B-19, which is considerable, but rather, in 15 or so slides, to focus the discussion at least on my part on the parameters. I am using that word literally in terms of the boundaries of what we think of as the spectrum for B-19

parvovirus disease and the risks associated with the transmission in blood products.

[Slide.]

Tom provided really a wonderful overview both in the written material and in what he just discussed. What I will try to emphasize is really complementary to what you have already heard.

These are the diseases, at least the last iteration of the diseases that I think can be reliably, more or less reliably related to parvovirus infection. You have heard about some of these already, and I just want to reiterate.

Fifth disease is obviously a very common childhood exanthem, which we now know is due to acute parvovirus infection, but just as Tom indicated, probably most parvovirus infection is, in fact, asymptomatic and patients never know that they are infected, they just seroconvert.

Parvovirus infection in the normal adult produces more commonly an arthritis or arthropathy, which can in fact be a frank joint inflammation that can mimic true rheumatoid arthritis, but is self-limited, although it may be self-limited within weeks or months and even up to a year of significant symptoms. So, there is no known joint destruction or long-term sequela.

Transient aplastic crisis, of course, the reason

that hematologists are interested in this syndrome, that is again an acute infection occurring in the individual who has underlying hemolysis, not necessarily a frank hemolytic anemia because the hemolysis can be compensated, so classically, for example, a patient with hereditary spherocytosis and a normal hemoglobin can present first to medical attention after parvovirus infection due to the acute exacerbation of their anemia.

Then, there is the pure red cell aplasia which occurs in individuals who are immunodeficient, and this is the only syndrome that we are really confident represents chronic parvovirus infection in which B-19 really is there for months or even years, and it occurs in situations of congenital immunodeficiency, patients who are undergoing cytotoxic chemotherapy for cancer or for autoimmune disease, and in particular, in patients who have HIV infection, and this is one way of patients presenting, in fact, with HIV. They appear to have pure red cell aplasia.

Hydrops fetalis, I will spare you the actual pictures later on. It is a terrible consequence for the pregnant woman, mid-trimester infection transmitted in the uterus to the fetus, and the baby is born dead.

We described from our laboratory, in a Lancet paper a few years ago, the sequela of mid-trimester infection in several infants who were born with congenital

infection that mimics either pure red cell aplasia, that has been considered constitutional, diamond black fan anemia, or other congenital anemias.

I mention paroxysmal hemoglobinuria because I think that this is probably in children likely to be due to B-19 infection although our evidence--and it has never been published--is it is weak mainly because of the absence of sufficient serum samples. I knew I would be talking with a lot of blood bankers, and I always hope to get some more PCH samples from them.

[Slide.]

I don't have on this slide, but the Japanese have presented fairly compelling data that some hemophagocytic syndrome, which is a pancytopenia that commonly occurs after herpesvirus infection, is also a sequela of B-19 infection, and I think that that is fairly well established.

[Slide.]

One of the points I want to make in this 15 minutes or so is that there a lot of things that we understand about B-19 parvovirus. In fact, it is one of the best understood and remarkably well understood given the relatively brief period of time with which we have been familiar with it, but we don't know everything.

Let me start with the things that we do know quite confidently. This is from normal volunteer studies that

were done in England back in the 1980s. These experiments were done by intranasal inoculation of individuals by Professor Tyrell and his associates.

They get the virus in the nose here and develop a viremia about a week later, which is quite profound, as Tom indicated, and that is followed as expected by an IgM and then a specific IgG response.

The viremia produces a rather nonspecific viral illness, which is probably what a lot of people experience, but never know that it is due to parvovirus - fever, chills, headaches, joint and muscle pain.

It is at the time that the antibody is made and immune complexes are formed that classic fifth disease occurs, and these individuals that got a lot of virus, they got both the rash and the joint symptoms.

What happens in the bone marrow is occurring actually in the period of viremia, and they completely stop red cell production. They don't actually develop anemia, and I think that this is actually not probably a symptom or even a sign in most patients, although reticular cytopenia almost certainly occurs even in normal individuals.

There also are effects on platelets and neutrophils that we don't understand very well.

The specific effect--and I am not going to talk about the basic biology, interesting as that is, probably

much to your relief, but we know that this virus is highly specific for erythroid precursors of the human bone marrow because of its cellular receptor, which was identified by my colleague, Kevin Brown, a few years ago being erythrocyte p-antigen, and that is the way that the virus enters the cell and accounts for its erythroid specificity in large part.

[Slide.]

So, we can come up with nice models of the known B-19 parvovirus infections and how they occur, so I have told you that the virus infects erythroid progenitor cells in the bone marrow.

This is, in fact, the only cell that has been reliably identified as being the target in humans. It is really quite strange in that respect although we assume that the virus gets in through the nasopharynx and probably propagates at some point there. There is no evidence that those sorts of epithelial cells in fact can support viral propagation.

A lot of antibody is made and certainly the overwhelming evidence is that it is the humoral immune response that accounts for clearance of the virus and life-long immunity. It has been very difficult to document a cellular immune components, it's this immune complex formation probably with antibody excess that results in the symptoms of fifth disease in children and in adults.

In patients, for example, a sickle cell patient or a hereditary spherocytosis patient, they also mount a perfectly appropriate antibody response. They very rarely, if ever, develop this sort of immune complex of symptoms. Even Caucasian patients with hereditary spherocytosis have not, with very rare exception, been reported to develop these sorts of symptoms, and instead they develop a purely hematologic disease due to this temporary cessation of red cell production, obviously an increased demand for red cells producing profound anemia.

In chronic infection it is the failure to mount an antibody response that results in this long-standing destruction of the erythroid compartment in the bone marrow, and that can be interrupted, as you have heard, by commercial immunoglobulin preparations, which are a very rich source of B-19 antibody from the normal population.

This disease does not look like a virologic syndrome. There is no fever, there is no rash associated. It absolutely resembles the hematologic syndrome of pure red cell aplasia.

In the fetus, infection probably, primarily in the liver, which is the site of red cell production in mid-trimester, as well as the bone marrow, and perhaps also the heart, because the heart also shares the cellular receptor. The fetal heart has p-antigen on it, produces hydrops

fetalis, which is congestive heart failure and anemia.

Then, in a mechanism that we don't understand, infants that are rescued by transfusion after in-utero infection, can go on to the syndrome of congenital anemia, which is not cured by antibody.

[Slide.]

Now, that is what we know, and this is more, although it is a published and presumably peer-reviewed paper, this is more in the arena of what we don't know. So, this is a paper appeared a year ago in the proceedings of the National Academy of Science, and it is certainly not a title that suggests any doubt on the part of the authors.

I will read it for the people in the back. It is "Human Parvovirus B-19 is a causative agent for rheumatoid arthritis."

Now, this paper, we and others have attempted to confirm what appeared to be very compelling data in this paper, quite unsuccessfully, and I would also add that there were dozens of papers that have been published before this manuscript appeared in print that also suggested that rheumatoid arthritis, the rheumatoid arthritis that we see in rheumatology clinics with joint destruction in older people, in fact, was not related to B-19 parvovirus infection.

But I raise it because this and other syndromes do

have their proponents, and although my own bias is that the types of diseases that are caused by parvovirus are, in general, self-limited, when they are not, occur in very distinctive populations, and, in general, are not major public health problems, I think that the FDA and the blood community is going to have to face these sorts of publications. As I think everyone who participates in the medical literature game, knows it is very difficult to remove papers like this from the public and even the scientific consciousness once they appear.

[Slide.]

Now, there are a lot of problems with the study of or determining the spectrum of parvovirus disease, and I want to just touch on those because I think they are going to remain uncertainties for some years to come.

The title of this slide is actually incorrect. It is the seroprevalence, of course, that increases with age, and Tom referred to this, but obviously very young infants who inherit antibody or have antibody from their mothers, but over the course of life, you can see the steady increase by perhaps 10 percent every three to five years, a steady increase in the number of individuals at every age who are antibody positive, have IgG and have therefore been exposed and are now immune to the virus.

So, again, as Tom mentioned, simply finding IgG

antibody is not evidence of infectivity. It simply means the patient has seen the virus sometime in the past. It is a very common infection with or without symptoms.

[Slide.]

The second point is that the method to detect, the method now commonly used to detect acute infection, which is PCR gene amplification for B-19 genomes, is also fraught with problems, not just the technical problems, of the significance of a positive assay. I will put in parentheses "especially in the significance of a positive assay" when you are dealing with a virus that has an extraordinarily stable, small genome, virtually difficult to eradicate from a laboratory once you have contamination.

So, this is really a bear. The best laboratories have the greatest trouble, I think, actually doing B-19 PCR because they tend to have the most B-19 around as it is the source of study material for other experiments.

This is from the CDC and it actually understates the problem of the detection by PCR B-19 DNA in normal individuals who have seen this virus, have a clinical diagnosis of parvovirus.

It understates it because of this line drawn here, and you can appreciate, although this slide only goes out to two months, and that is the extent of the study, there are plenty of individuals out several months, and we now know

six months, even a year or more, who may remain B-19 PCR positive after an infection that they have obviously cleared, and we don't really know what the source of that virus is, but it obviously isn't the problem to the patient. Of course, we have no idea whether this is truly infectious material.

[Slide.]

The second area of persistence even in normal individuals is within the viscera, and there are now two published papers, a paper by Gunter Siegl has actually appeared in print since I made this slide, that have looked at tissue.

Of course, these are very important studies of normal tissue, very important studies in terms of now examining claims of B-19 as a disease agent especially with biopsy material. There is a wonderful paper published by Soderland and her colleagues in Finland. It seemed very likely that juvenile rheumatoid arthritis might be a B-19 parvovirus infection, a clinical history of a viral syndrome before the child develops joint pains.

We know that the arthritis can be a sequela of parvovirus infection. So, Soderland looked at a lot of kids in Finland with juvenile rheumatoid arthritis, and I am sure she was very happy when she detected about a third of them being positive by PCR.

Then, of course, she made a terrible error. She went and looked for controls, and the controls she got were Finnish Army personnel who were undergoing arthroscopic procedures because they had trauma to their knees, and when she did this, half of those individuals are positives. There goes the hypothesis that B-19 is responsible for juvenile rheumatoid arthritis, but note that a very large proportion of these joints were positive by B-19 testing.

In the marrow, Siegl detected B-19 in about 20 percent of normal marrow donors in Switzerland, and in Kevin and my studies, we are interested in the relationship between B-19 and hepatitis, we think that somewhere between 10 and 20 percent of livers, now, they are not normal livers, but livers that you obtain for other indications, will also contain virus, and my guess is that the virus is harbored in a rather innocuous fashion, in reticuloendothelial cells in these organs, but it complicates the determination of etiology.

[Slide.]

From the clinical point of view, establishing a disease relationship also is quite difficult. Some of this is historical and some of it looks forward.

This is from Terry Chorba's publication in the Journal of Infectious Disease. Terry was at the CDC at that time, and he was sent to Cleveland, lived in a hotel room

there for six months, because there was a documented seemingly B-19 parvovirus causing dozens of cases of transient aplastic crisis in sickle cell clinics throughout the Cleveland Cuyahoga County area.

Now, obviously, that has gone on periodically for many years, and have not been recognized as being due to B-19, that is understandable, but at the same time, Terry was able to document the major epidemic of erythema infectiosum or fifth disease in the pediatric population.

The point of this is not that this is a very elegant study, it was a very important study to CDC, but obviously, for many years, these two diseases had existed concurrently, had gone through the hematologic clinics and the patients with sickle cell disease, at the same time they went through the normal population, and nobody saw the relationship even though it must have occurred many times previously.

[Slide.]

Here is an individual patient's bone marrow. This is one of our cases. This is a young man who was referred to the clinical center at the NIH with chronic anemia. He had had this pure red cell aplasia for 10 years. His older brother had died of pure red cell aplasia.

Now, from a hematologist's point of view, this is a bone marrow that is consistent with that diagnosis, and we

have all sorts of hand waving, we knew about the etiology of pure red cell aplasia, and it was only because we had individuals in our laboratory who were growing this virus and recognized these very giant erythroid precursor cells, so-called giant pronormoblasts, as what they saw in their laboratory cultures that we even bothered to do B-19 testing.

He, of course, was the first patient who was documented as having pure red cell aplasia as a result of B-19 parvovirus infection.

[Slide.]

So, we found a million genome copies in his blood, which, as Tom indicated, is not a particularly high number, but in data that I won't show you, although it is in the original publication, we were able to document that his spleen, which had been removed some years earlier, also contained parvovirus, and his deceased brother's spleen also contained parvovirus.

This young man was treated with immunoglobulin and had a remarkable response, one of the nicest experiences I have ever had in clinical medicine, his profound reticulocytosis, and return of his hemoglobin to normal, which is where it has been subsequently.

So, this is a disease that appeared to be solely a common pure red cell aplasia, something we have seen, can't

explain, that obviously had a very good explanation.

[Slide.]

A third example is from Kevin's study, a very unfortunate child who died in Washington, D.C. after a year, a year from birth, just at one year of age, with a congenital anemia, very clear history of mid-trimester transmission of virus from the mother to the infant, and this child had been repeatedly negative by serologic testing in our hands and elsewhere.

When the child died, the serum continued to be negative, here by PCR testing, but you can appreciate this profound signal in the bone marrow and elsewhere.

So, here is another example of the subtlety of parvovirus infection without circulating virus, fatal outcome, but plenty of virus in the bone marrow producing this terrible picture.

[Slide.]

That is all having to do with a known virus and the difficulty of nailing down a syndrome, and I wanted to just, on Kevin Brown's suggestion, provoke you with the opposite, which is the possibility of there being other viruses out there that resemble B-19.

[Slide.]

This is from Kevin's data. Kevin has been very interested in some of the monkey parvoviruses, and we now

know that there is a fairly large family of erythroviruses that share this property of B-19 of infecting erythroid progenitor cells and producing profound anemia in the right clinical circumstance.

There are actually some viruses missing. There are at least two macaque viruses and a cynomolgus monkey virus that are similar, but not identical to B-19. I will mention parenthetically also that we now have a good animal model for B-19 infection as a result of Kevin's studies.

But the point of this is that there probably are other human viruses other than B-19 that may produce similar syndromes, and recently, French investigators--they published it just last month in one of the microbiology journals--have described a virus they call V-9, which varies by something like 15 percent in an otherwise generally well conserved region of B-19.

That is much greater than the sort of differences that people have identified, which are just a percent or two in B-19 strains, so-called strains. There are really no strains, but V-9 appears to be sufficiently different, produce transient aplastic crisis, may account for some of the PCR-negative cases of transient aplastic crisis because its genome will be not be detected by most of the conventional PCR primers.

[Slide.]

This is from Kevin's data. It is not a particularly great slide, but it is really meant to show you that this is a positive direct DNA hybridization dot blot in a patient with HIV infection, pure red cell aplasia, who was repeatedly negative by PCR testing at an outside institution, as well as in Kevin's laboratory.

Here, the patient is showing a very obvious signal even at small amounts of DNA, so that we would suspect that this patient probably has this variant erythrovirus infection, something like V-9.

[Slide.]

Now, I want to finish in the last couple of slides by indicating that there is hope, although it may not be very useful for your deliberations today, but Sachiko Kajijaka laboratory some years ago produced--you can't see it at the bottom, it's not crucial--these are insect cells that are lighting up with antibody to B-19 capsid proteins.

[Slide.]

Sachiko produced in this baculovirus system the viral capsid proteins. They have the nice property of self-assembling into empty capsids. Here is the major capsid protein only, here is the major and minor capsid protein together, so they look like viral capsids, but they don't have any DNA in them, so they are empty capsids.

When these are injected into animals, if you have

the VP-1, if you have the minor capsid protein as a component of this capsid, in fact, the more minor capsid protein you have, the better, then, you can produce very nice neutralizing antibody titers as shown up here.

They are quite comparable titers to what are seen in individuals in the convalescent phase of infection. So, this has been the basis for the development of a vaccine, and we now know that with the right adjuvant--these are now data from rhesus monkeys that were inoculated here at NIH--with the right adjuvants, unfortunately alum, very unfortunately, alum didn't turn out to be the right adjuvant, and with VP-1 present, we can get very high neutralizing antibody titer shown here.

This slide is not meant for detailed analysis. The point really is that we have a good vaccine reagent and now with adequate non-alum adjuvants, and this will be in human volunteer trials and I think also in patients with sickle cell disease, probably within--certainly in normal humans this year, and in patients with sickle cell disease, I hope within a year or two, and this should be a safe and effective vaccine for the human virus.

Thank you for your attention.

DR. HOLLINGER: Thank you, Dr. Young.

Dr. Lynch.

FDA Perspective and Questions for the Committee

Thomas Lynch, Ph.D.

DR. LYNCH: Thank you, Dr. Young, Mr. Chairman.

[Slide.]

To return to where I left you, the regulatory question was created by the context in which hepatitis C, HIV, and hepatitis B NAT testing is being introduced, which includes the pursuit of clinical effectiveness evidence in clinical trials performed under INDs before appropriate license applications and approvals are forthcoming.

The question here is whether the rationale for imposing that requirement for the "more significant viruses" on testing for B-19 applies. I should briefly note that the rationale really traces back to whether there is a need to establish the clinical sensitivity and specificity of the test, whether there are clinical consequences to individuals of the results of a positive test or, for that matter, a negative test, and whether or not informed consent issues, ethical issues are raised by performing an investigational test on materials derived from real human beings.

These issues arise only in the context of a test that is performed as a laboratory control, whether by the manufacturer or by a contract laboratory. A test that is designed to be marketed as a kit is a medical device, and if it is used to screen blood donations or plasma donations, it is subject to licensing under the PHS Act in the normal

course.

So, we are talking about tests that are performed in someone's laboratory to control the quality of raw materials coming into a facility.

[Slide.]

Now, our premises for considering the value of NAT testing is that it would almost assuredly reduce the viral burden of manufacturing pools, and as one reduces the contamination of these manufacturing pools with the virus, the amount of virus should be significantly reduced in the products manufactured from that plasma.

That, we feel, would directly address a risk associated with certain manufactured products, such as the clotting factors.

[Slide.]

Other issues to consider, well, the technology is really at the point where large-scale testing can only be done on minipools, that is, numbers of individual units, aliquots of individual units that are mixed together in order to form an aggregate sample, which is then tested.

Plasma for further manufacturing is really where the practical point of implementation lies, but we are still stuck with sort of a precedent that the agency set in determining that in nucleic acid testing for hepatitis C, HIV, and hepatitis B, should be considered as donor

screening, and could not be implemented simply as an in-process control. That gave rise to the need to perform clinical trials.

Now, I should elaborate on what I mean by those two terms.

[Slide.]

An in-process control is a test that controls the quality of materials during manufacturing and requires as a component of licensing and good manufacturing practices, that the test be validated thoroughly as an analytical test. That includes verifying sensitivity, specificity, and reproducibility among many other requirements.

However, one need not establish any clinical correlates between the outcome of the test and the result in any individual patient or subject, and that is true provided that one is not making decisions about patient care or donor management, and basing those decisions on the outcome of unproven tests, and there are no claims that the testing enhances the actual safety of a product to the users of that product.

Now, an in-process control, since it doesn't have a clinical trial component associated with it, has a lower regulatory burden, and inherently can be implemented much faster.

We have analyzed this issue and believe that an

in-process control test and the regulatory requirements associated with that testing is appropriate for B-19, and that is clear when you consider why a donor screening test is considered to be so, and that is based on basically the severity of the disease that is being screened for, which warrants the identification and notification of the affected individuals - the donor who gave the positive donation and the recipient of any implicated products.

Now, this notification and presumed followup, clinical followup, may have significant implications for those individuals, and therefore, the effectiveness of the test ought to be demonstrated, and that effectiveness is demonstrated through clinical trials under IND. That is how we got where we are for hepatitis C, for example.

[Slide.]

The validation of these two types of assays can be more clearly understood by considering this slide. A donor screening test requires the evaluation of the performance of the assay in both preclinical and clinical settings, whereas, an in-process control would require the preclinical validation side of this slide, but not necessarily clinical trials.

Now, the requirements of preclinical validation are quite high. Specificity and analytical specificity, sensitivity and analytical sensitivity are all requirements

of the validation package, and this really establishes to a great degree of assurance what the performance characteristics of the test are. In addition, the precision, reproducibility, and proficiency of the labs performing the test also has to be satisfied.

Now, these standards, as I said, provide a high degree of assurance that the test is performing as anticipated.

[Slide.]

Let's go back and consider the rationale of deciding that NAT for hepatitis B or HCV was donor screening, and that rationale can be divided up into basically three areas - those related to the donor, those related to potential recipients, and those related to disposition of products.

With respect to the donor, it was felt that the individual donor of a positive unit should be identified and notified, and there are several reasons for thinking this. First, was the desire to defer the donor from making further donations or at least until his clinical condition could be determined, to afford a donor of a positive unit to seek treatment where such was available, and to take appropriate precautionary measures to avoid secondary infections.

With respect to the recipients of an implicated product, such as a lookback unit or a component made from

the same donation, it was important to identify and notify those individuals in order that they may seek testing and clarify their clinical status, and if they were, in fact, infected, to seek treatment and avoid further spread of the disease.

Now, finally, both the donor and the recipient have an inherent right to know about the potential of being infected with any of these diseases, and I think I need not elaborate on that.

Finally, there are product related criteria. Obviously, the positive unit is to be interdicted. That is the whole point of doing the test. You also would want to quarantine or retrieve other components that were derived from the same donation. Obviously, if the plasma is positive, you would like to avoid transfusing the red cells if you can.

Finally, a lookback, retrieving prior donations is also a component of these studies to minimize the possibility of window units even with enhanced testing being transfused or used in manufacturing.

Now, the justification for those decisions trace back directly to the characteristics of these three viruses. First, they are all responsible for severe diseases in many, if not most, of the cases. That raises the need to notify the implicated individuals.

Secondly, there is a possibility of a long window period in all cases, and that creates the need to look back and retrieve prior donations.

Third, there is a high possibility or certainty of chronic infection, and that creates the need to defer the donor permanently.

So, all of the decision-making regarding the regulatory framework for NAT testing for hepatitis B, hepatitis C, and HIV can all be traced to these basic characteristics of the viruses and the needs of the individuals that are implicated by the testing.

Comparing these characteristics to B-19, one has to realize that in most cases--and Dr. Young has pointed out some important exceptions to this--but in most cases, the severity of disease is much, much less than for the hepatitis viruses or HIV.

There is virtually no window period since viremia follows very quickly after exposure, and seroconversion very soon after that. Finally, the occurrence of chronic infections as opposed to depots the virus in other tissues, chronic infections almost never occur in the general populations although certainly are a risk for immune-compromised individuals.

[Slide.]

Let's take the criteria for reaching a decision

that a particular test should be considered donor screening, step by step, and see how the decision points shake out for both classes of viruses.

In the first instance, these criteria relate to the donors, and one would not want to defer a B-19 positive donor, certainly not permanently, whereas, that is certainly an objective to testing for the other viruses.

Treatment is not usually indicated if the presence of the disease is recognized at all for B-19 unless the individual is among the high risk groups that Dr. Young mentioned.

Avoidance of secondary infections is critical for these viruses, hepatitis C, for example, or HIV, where there are certain high risk behaviors that could be modified to avoid those secondary infections. However, B-19 is readily spread by casual contacts, that there are really not a whole lot of precautions that can be taken that are effective.

There is certainly a right to know in both cases. This is personal information regarding an individual, but arguably, an individual would have a greater interest in finding out about a clinically serious infection than they would about an infection such as parvovirus B-19.

[Slide.]

With regard to the recipient of a potentially implicated product--and by that I mean a component that was

donated at the same the test-positive unit was donated, or perhaps does not really apply here, a lookback unit--the interest in such an individual seeking out testing to clarify its clinical status, I think is low because of the very unlikely chance that the infection, if it occurred, would be clinically significant, and the possibility of seeking treatment or avoiding secondary infections are just the same as they are for the donor, a very low level of importance.

Again, there is a right to know, but I question whether the interest is quite the same in both settings.

[Slide.]

Third, related to the products that are made from these donations--and I am really talking about the units, the units that are donated--you, of course, want to interject the positive unit. Again, that is the purpose for doing the test.

One would also wish to quarantine and destroy the unit wherever that is possible, a unit that was derived from the same donation. If the plasma, for instance, is infectious, it is likely that the red cells would have a high risk of transmitting, as well.

In the context of testing, however, PCR testing, if that is what is to be implemented, a recovered plasma unit might complete testing long after the expiration of

other components collected at the same time. So, it is unclear what the ability to retrieve related units would be.

Finally, because of the very short duration of the disease, and really the absence of any window period, we think that lookback is inapplicable in the context of B-19.

[Slide.]

So, in conclusion, careful consideration of the public health interests that drove a decision that hepatitis C, HIV, or hepatitis B, nucleic acid testing should be validated by clinical trials under IND do not mandate the same sort of regulatory framework for B-19 testing.

Specifically, there is not a compelling argument that a single individual unit and an individual donor be identified or notified. That means that the clinical effectiveness of the NAT to predict infection in the donor is also not compelled, and we can therefore validate the effectiveness of the testing in eliminating contamination of the plasma used for manufacturing by validating it in a preclinical setting to establish the sensitivity, specificity, and overall reliability, let's say, of the test.

FDA has more than sufficient regulatory authority under its licensing mechanisms to ensure the ongoing quality of these tests.

[Slide.]

We expect that reducing a regulatory burden that we think does not contribute to the quality of the plasma that is undergoing the testing could expedite implementation of parvovirus testing more generally.

However, it seems reasonable that where it is possible, and where B-19 testing is performed on recovered plasma used for further manufacturing, untransfused components of the same donation should, wherever possible, be retrieved.

That again will depend on the schedule of the testing and reporting back of the results to the center doing the collecting.

As I said at the onset, we would like to defer the more general question regarding nucleic acid testing of whole blood donations to a later date if we need to bring it back at all.

[Slide.]

So, the question that we pose for the committee, I know I have provided a lot of background information, and I apologize for that, but it is a difficult question: Does the committee agree that pending a policy on screening of whole blood donations, the Food and Drug Administration need not require studies to validate the clinical effectiveness of NAT for B-19 under IND for plasma for further manufacturing?

Thank you, and I will take any questions.

DR. HOLLINGER: Yes, Paul.

DR. McCURDY: A question that has been bothering me for some time is that if this is essentially a self-limited infection with long-term immunity, why is viremia so frequent in blood donors, healthy blood donors?

DR. LYNCH: Well, I think the infection rate is probably quite high, I would guess somewhere on the order of 1 to 2 percent per year, but maybe some of our experts could clarify that. So, if you assume a period of a week peak viremia, and a longer level where there is low residual levels in the plasma detectable by techniques, such as nucleic acid testing, a substantial portion of the donors would be expected to be positive.

During community outbreaks, Paul, the numbers can go much higher than the 1 in 3,000 figure that I gave. You might be up pushing close to 1 percent.

DR. HOLLINGER: Dr. Stroncek.

DR. STRONCEK: A couple things. One, I think that while it's nice to theoretically think you can separate the whole blood donations from testing plasma for fractionation, I don't think, practically speaking, that is going to work. I think, if it starts, it is quickly going to move into whole blood donations.

Second, this is not an antibody test, this is

viremia, and some of the levels are pretty high. I would feel uncomfortable not notifying donors. We see that for the most case, these infections are not problematic, but in some cases they can be. A pure red cell aplasia is a serious disease. It's not hepatitis, it's not AIDS, but it is, nonetheless, a serious disease.

Third, I didn't quite understand one of the slides because you are proposing that you are not testing down to the individual donor, yet, then, you are advocating to withdraw the components made from individual units.

Well, if you are testing a pool, and not figuring out which unit is possible in the pool, that implies you have to withdraw from your inventory all the products made from, all the components made from all the donors in that pool.

DR. LYNCH: Let me try to take those in order. We are not in a position to make a recommendation regarding testing because there is no licensed test to recommend. The initiative is coming from the industry initially, who wishes to implement this test and needs to know what the regulatory requirements will be to do so.

I can't predict what the blood banking and whole blood collection segments will do in the future. I think there may well be interest there and may well be justification for implementing the test. That remains to be

seen, but it is not necessarily compelled, I think, by plasma testing.

The second point that you raised about the seriousness of certain diseases, like pure red cell aplasia, is certainly well taken. I think, if I am not mistaken, the severe clinical consequences are most often seen in individuals who would not be expected to be donating blood in the first place, so the donors that you wish to notify would not be at particular risk for these serious sequelae of an infection.

Third, with respect to retrieving components without necessarily--and I say necessarily because an individual sponsor may choose to do so--without necessarily tracing back to a single unit, that is feasible if one traces the positive reaction back to a small number of units greater than 1, and then discards all of the components that may be in-date associated with all of those collections.

Although that sounds a little byzantine, in fact, there may be some efficiencies there, and a manufacturer may choose to do exactly that.

DR. HOLLINGER: We are going to break for lunch. It's 1 o'clock. We will be back here at 2 o'clock to begin.

[Whereupon, at 1:00 p.m., the proceedings were recessed, to be resumed at 2:00 p.m.]

AFTERNOON PROCEEDINGS

[2:25 p.m.]

DR. SMALLWOOD: We have a number of people who have requested to speak, and if you are not here, we will move on to the next person, but we will try to get everyone who has requested to speak.

Dr. Hollinger.

DR. HOLLINGER: Thank you. We are really sorry for the delay. The restaurant had a problem, but anyway we are sorry.

We are going to continue the discussion about nucleic acid testing of parvovirus B-19, and we have had four individuals speaking with different groups on this topic. The first will be David Kennedy from the American Red Cross.

Open Public Hearing

David Kennedy, ARC

MR. KENNEDY: As Dr. Hollinger said, my name is Dave Kennedy and I am the Manager of Medical Affairs of the American Red Cross Plasma Services. I want to thank the committee for this opportunity to address you on the issue of PCR testing of human parvovirus B-19.

The American Red Cross serves as the distributor of Plas + SD, that is pooled plasma solvent detergent treated, and is the provider of input plasma for its

manufacture. As a condition of licensure, a letter was issued by the Food and Drug Administration on May the 6th, 1998, indicating that VITEX, VI Technologies, Inc., the manufacturer of Plas + SD, was to undertake and complete clinical studies regarding the risk of transmitting non-enveloped viruses through the use of Plas + SD.

In December of 1998, the first subjects were enrolled in a Phase IV clinical study to determine the infectious disease risk for hepatitis A and parvovirus B-19 by the infusion of Plas + SD.

On March 26th, 1999, a report was submitted by VITEX to the FDA as the first clinical safety report of the Phase IV study. The report provided clinical and serological data in healthy volunteer subjects who had been infused with one unit, that is 200 ml, of Plas + standard.

The initial serological data from the study showed two subjects who had seroconverted to parvovirus B-19 with a rise in IgM levels within 10 days of infusion. Subsequent testing three months later showed an increase in parvovirus B-19 IgG levels. Neither of these subjects exhibited clinical symptoms consistent with B-19 infection during this three-month interval.

PCR testing of all lots of Plas + SD involved in this Phase IV study was performed and revealed the presence of various levels of parvovirus B-19 DNA. In relating the

parvovirus B-19 DNA levels in the product to those subjects who seroconverted, it was found that all the seropositive recipients had received "high titer" lots. The high titer lots contained parvovirus B-19 DNA levels ranging from $10^{7.5}$ to $10^{8.5}$ genomic equivalents per 0.667 ml of plasma.

None of the recipients of the other lots had seroconverted at the 7- to 10-day time point, and none of the recipients for whom data were available at the three-month time point seroconverted. These seven other lots contained parvovirus B-19 DNA levels of between $10^{0.5}$ and $10^{3.5}$ genomic equivalents per 0.667 ml of plasma.

On September 2, 1999, VITEX submitted the latest monthly clinical safety update on the study, Phase IV Protocol, Postmarketing Pharmacovigilance of SD Plasma.

Of the recipients of the other 8 "low titer" lots, none of the 46 are seropositive at the 7- to 10-day time point, and none of the 30 subjects who have data at the three-month time point have seroconverted.

From this preliminary data, it appeared that subjects who received lots of Plas + SD with parvovirus B-19 DNA titers of $10^{3.5}$ or less did not seroconvert. On this basis, and with the concurrence of the Food and Drug Administration, the decision was made to test all lots manufactured to date for parvovirus B-19 DNA by PCR and eliminate from distribution all lots with titers greater

than 3.5.

Data from the VITEX testing program to date suggest that approximately 1 in every 800 blood donors is positive by PCR for parvovirus B-19 DNA. In order to minimize loss of fully manufactured product, and as part of the ongoing commitment to safety by the American Red Cross and VITEX, the decision was made to test our input plasma for parvovirus B-19.

VITEX implemented minipool testing of input plasma for parvovirus B-19 by PCR in May of this year. Units are tested in batches of approximately 20 units. This is called a primary pool.

Five sets of primary pools of 20 units make up a minipool. A complete pool is formed when sufficient minipools, representing a maximum pool size of 2,500 units, have been PCR tested. The minipool of 100 units is tested first, and if it nonreactive, all 100 units are released for pooling.

If the minipool is reactive, each of the 5 primary pools making up the reactive minipool are tested individually. All primary pools in any minipool that tests reactive are removed prior to the start of pooling.

Resolution stops at the primary pool level, since there is no currently approved methodology for obtaining a second sample. Therefore, an individual donor unit will not

be identified. After all units from non-conforming primary pools are removed from the warehouse, VITEX Quality Assurance Department releases the lot for manufacturing.

The FDA has evaluated PCR testing strategies that have been implemented by VITEX. On June 28, 1999, Dr. Epstein, of the FDA, informed VITEX that the FDA had approved the company's request to supplement the product license application for pooled plasma, solvent detergent treated for implementation of PCR testing for hepatitis A virus on the final container product.

National Genetics Institute performs HAV and human parvovirus final container product PCR testing for VITEX. A human parvovirus B-19 labeling claim for PCR testing was submitted to the agency on August 25, 1999, and we await FDA approval.

The American Red Cross and VITEX maintain the highest commitment to product safety and recommend that PCR testing of input plasma for parvovirus B-19 DNA continue in the manner described. Because this is clearly raw material qualification as opposed to donor screening, testing should proceed without filing an Investigational New Drug application.

In addition, since testing of the input plasma is performed long after most components derived from the whole blood donation would have been transfused, and long after

any clinical benefit of donor notification would have passed, the value of recipient or donor identification and notification of positive test results is moot.

Thanks to the quick and collaborative efforts of VITEX, the American Red Cross, and the Food and Drug Administration, we were able to quickly put into place a product and plasma screening system that improves safety.

In this case, implementing plasma and product screening under an IND would only have slowed the process and added no benefit.

Thank you for the opportunity to address this committee.

DR. HOLLINGER: Thank you.

Steve Kleinman for the AABB.

Steven H. Kleinman, M.D.

DR. KLEINMAN: Frequent transmission of parvovirus B-19 infection by transfusion of Factor VIII concentrates prior to the widespread use of viral inactivation technology has been well documented by the detection of parvovirus B-19 antibody in recipients. Such transmission has continued even after the introduction of virally inactivated concentrates. This is due to the relative resistance of parvovirus B-19 to viral inactivation and to the high level of viremia in acutely infected persons.

Despite relatively high transmission rates to

recipients of pooled plasma products, very few adverse clinical outcomes have been reported in patients with hemophilia. A 1999 review article cites only three cases of erythema infectiosum and one case of hypoplastic anemia.

Since 1994, when two significant articles appeared in the journal Transfusion, there has been a heightened concern in the blood banking community about transmission of B-19 by transfusion of single donor blood components. Despite this increased concern, only three cases of clinical disease associated with B-19 transmission by blood component transfusion have been reported in North America and Europe.

In each of these cases, the recipient developed anemia. One case was successfully treated by IVIG, one case spontaneously resolved, and one case did not report follow-up data.

The level of significant clinical disease from transfusion transmitted B-19 is lower than that reported for malaria, babesiosis, and Chagas disease. There have not been any systematic controlled studies to indicate the extent of B-19 transmission and clinical disease development in recipients of blood components.

Nucleic acid testing technology to perform B-19 screening in pools currently exists. Using such techniques, parvovirus B-19 viremia rates in blood donor populations have been reported to range from 0.03 percent to 0.6 percent

with a 1 percent prevalence--that is 1 in 1,000--in a recently published study of Pittsburgh.

From studies of patients with hemophilia and from recent clinical trials of SD plasma, it has been well established that pooled plasma products greatly amplify the risk for parvovirus B-19 transmission to recipients.

As we have heard, NAT of pooled plasma samples for B-19 has been recently adopted for manufacture of SD plasma, and to my knowledge, is in use by some manufacturers of plasma derivatives.

One question to consider is whether such screening should be extended to donors of whole blood components. The AABB believes that the issue of whole blood donor screening for B-19 nucleic acid should be considered on its own merits and should not be dictated as a consequence of policies adopted for screening of recovered of source plasma that will enter further manufacture.

One mechanism to maintain the distinction between screening of pooled plasma products and whole blood donor screening is to perform B-19 nucleic acid testing on minipools of plasma intended for further manufacture. This would serve as an in-process manufacturing control and would accomplish the aim of interdicting B-19 viremic plasma units prior to manufacture without resulting in identification of the individual donor.

Under this mechanism, B-19 testing in the plasma sector would not be regarded as a donor screening test and hence, the precedent for applying such a screening test to whole blood donations would not be established in the absence of a direct policy decision to do so.

Adopting the in-process control mechanism is justified for the following additional reasons:

B-19 infection in a blood donor is of no consequence to the donor's health and secondary transmission of the infectious agent does not occur by preventable parenteral routes. Therefore, donor notification is not needed and would most likely result in a high degree of donor confusion and/or anxiety with no benefit to the donor. This contrasts starkly with the situation in HIV or HCV infection where donor identification and notification is necessary for both individual and public health reasons.

Safety for recipients of blood components would not be significantly enhanced by identifying and deferring the individual viremic donor since B-19 infections fail to cause clinical disease and spontaneous resolve in almost all cases.

In addition, donors are no longer infectious after a short period of time. Given that B-19 infection transmitted by transfusion of blood components has only rarely caused clinically significant disease, the AABB

believes that B-19 nucleic acid screening of whole blood donors is not indicated at this time.

The aim of assuring further safety of pooled plasma products can be achieved by performing B-19 screening as an in-process manufacturing step. The AABB believes that further work is needed to more clearly define the magnitude of transfusion transmitted B-19 infection prior to initiating a routine donor screening program.

The NAT screening programs adopted for HIV and HCV should not be used as models for B-19.

The issue of increasing recipient safety by application of costly new tests is one that will continue to be faced by the Federal Government and by the transfusion medicine community. Numerous agents have been shown to be infrequently transmitted by transfusion and to rarely cause significant clinical disease.

The AABB believes that it is not an effective use of health care dollars to perform screening tests for all such agents. Benefits to be gained by addition of new tests must be weighed against the downsides of unnecessary donor deferral and donor loss, confusing and alarming notification messages to donors with positive screening test results, and the complicated logistical issues arising from new test implementation.

Thank you.

DR. HOLLINGER: The next speaker is Celso Bianco for America's Blood centers.

Celso Bianco, M.D.

DR. BIANCO: Good afternoon. I want to thank FDA and the Blood Products Advisory Committee to comment on the issue of screening for parvovirus B-19. This statement was prepared before we heard Dr. Lynch, and I must say that we agree 99.8 percent of his statement.

The only thing that we are concerned is that we don't feel that you should have broken his leg in order to obtain his statement.

ABC is a consortium of 73 not-for-profit, community-based blood centers that collects over half of the blood from volunteer blood donors.

We understand the desire of manufacturers of pooled plasma products that have been virally inactivated by the solvent detergent process to screen for the presence of high titers of parvovirus B-19. This non-enveloped virus is not inactivated by this procedure, and we are aware of the recent recall of solvent detergent treated plasma by American Red Cross and VITEX following the seroconversion of research subjects in Phase IV studies.

We support the efforts being made to prevent the transmission of B-19 by virally inactivated plasma derivatives, however, we request that issues related to

screening of blood donors be considered very carefully and in the context of the clinical significance of parvovirus B-19.

I am essentially repeating what many speakers previously said, that a large proportion of the normal population has been exposed to the virus. The prevalence of antibodies ranges from 30 to 70 percent in some studies.

The infection has limited clinical significance in the general population.

Cases of hydrops fetalis or erythroid aplasia are extremely rare and their relationship with blood transfusion is anecdotal.

The prevalence of antibodies to B-19 is high among recipients of clotting factors, but several cohort studies, such as the one carried out by Margaret Ragni and published in 1996, have shown no detectable B-19 viral activity or associated long-term clinical or hematological sequelae in these patients.

Thus, we see value in screening of plasmas used for further manufacture because of the pooling of a large number of units. The majority of plasma pools are positive for B-19 DNA. Viral titers can be extremely high, overwhelming antibodies present in the pool.

We do not see clinical value ins the screening of the general blood donor population or products dispensed as

single units, particularly in a regulated fashion. We have a very good historical parallel with cytomegalovirus, CMV. After several studies and a long clinical experience, we initiated screening of a limited number of units for use in premature infants of low weight of seronegative mothers and in seronegative transplant recipients.

If studies show that a similar approach is valuable, blood centers will not hesitate to create systems to provide for specific patient needs. We already provide CMV negative units for neonatal wards or rare red blood cells for sensitized patients.

Parvovirus B-19 is an issue of medical practice and should not be the subject of regulatory control.

Thank you.

DR. HOLLINGER: The final speaker is Dr. Thomas Weimer from Centeon.

Thomas Weimer, M.D.

DR. WEIMER: I would like to thank the committee for giving us the opportunity to present some B-19 NAT screening data, which were obtained in our laboratories, and talking about introduction of B-19 NAT screening, that means addition of a new target to an already existing NAT screening system.

Please allow me to update a committee about Centeon's experience in NAT testing.

[Slide.]

Centeon's current NAT program is the screening of minipools for hepatitis B virus, hepatitis C virus, and HIV-1. It was implemented in the U.S. under IND in April of last year. To date, we have screened by PCR over 3.6 million donations worldwide.

We have identified and removed from further manufacturing 530 HBV, HCV, or HIV-1 PCR reactive donations, and this minipool screening has resulted in over 1,000 PCR-negative manufacturing pools. We do that screening on the pool as a regular quality control test.

[Slide.]

As was mentioned in the previous talks, B-19 differs from HBV, HCV, and HIV, and it is a self-limiting infection with few clinical consequences.

It may reach very high titers, it is pretty resistant to physical-chemical methods for viral inactivation. It is highly prevalent, and there are certain indications or risk groups, like pregnant women and immunocompromised patients where a B-19-free plasma product would be desirable.

[Slide.]

B-19 is not a reportable disease, short acute and self-limited illness. At the time the PCR result becomes available, infection is already resolving or resolved due to

immune response.

Plasma donors are neither pregnant nor immunocompromised, so an IND linked clinical study would not provide any clinical benefit. This is the reason why Centeon would support the idea of running B-19 NAT screening as an in-process test.

[Slide.]

Our initial screening for B-19 was to obtain data on the prevalence of the virus, and we screened about 53,000 donations using sensitive PCR method. We found that about 1 in 830 donations, donations, not donors, were PCR reactive.

Most of them contained low B-19 levels, less than 10^5 genomes per mL. Those numbers are soft because we do not have an international standard yet. This is an in-house standard and they are not comparable to other numbers you will hear and have heard.

About 1 out of 10,000 donations contained high titers, greater than 10^6, and the range was between 10^6 and 10^{12} genomes per mL.

Due to this high observed prevalence, B-19 NAT screening targets the removal of high titer donations, and its detection and removal of such donations from further manufacturing will prohibit 9 logs or more of virus from entering manufacturing.

[Slide.]

Our B-19 PCR screening system was designed to detect and remove B-19 positive donations with titers of greater than 10^6 genomes per mL. It can be integrated into the current minipool testing procedures.

It will result in a reduction of the potential B-19 load of fractionation pool to below 10^5 genomes per mL with an emphasis on donation removal rather than donor deferral.

[Slide.]

We made a pilot study where we screened with this high titer approach over 170,000 donations. We identified among them 15 high titer donations, and they were removed from production, and the result with regard to the fractionation pools which resulted out of that, you see on that graph.

The first 30 were pools, manufacturing pools which we made from B-19 non-tested plasma, and the green ones were made from plasma which had been pre-screened by the B-19 high titer screening.

What you see is that overall the B-19 titer is low and that we removed peak virus titers as you can see here.

[Slide.]

In conclusion, by the high titer screening process, we will remove plasma units with high levels of B-19 from manufacturing, which will decrease significantly the

virus load of fractionation pools, and it complements our current virus removal steps in production.

The process is almost ready for implementation and will be submitted to FDA for review by the end of this year.

Thank you.

DR. HOLLINGER: Thank you.

Is there anyone else that would like to speak to this? Yes, Mr. Bablak.

Jason Bablak

MR. BABLAK: Good afternoon. I am Jason Bablak with IPPIA and I am going to summarize my statement that was passed out to you since a lot of this has been said over and over again.

First, I would like to start off and say that IPPIA supports the development of regulatory policies that encourage incremental increases in product safety. In the specific case of parvovirus testing, no regular screening for the presence of this virus is currently conducted.

We support the FDA position stated today that NAT testing for parvovirus can provide an additional safety measure when implemented as a properly validated in-process control test used to identify and remove certain units from further processing.

Consistent with this policy, we believe that if a regulatory policy is formulated, it should allow firms to

pursue this objective.

At present, our members are investigating the development of a voluntary industry standard to address parvovirus. We hope to be able to implement such a standard by the end of the year 2000, and while we are not completely finalized with the details of this, we envision that NAT testing will be involved, and you just heard from one of our members on the work that they have been doing.

Regarding the implementation of testing for parvovirus, we agree with the FDA that the screen should target donations, not donors. The use of a parvovirus assay method as an in-process control test for donations is a rational strategy for all the reasons you have heard earlier.

I will just summarize them. Basically, there is no public health concern to defer the donor from making further donations. There is no medical justification to identify and notify plasma donors reactive for parvovirus, and since the products that we make include IVIG, which requires anti-parvovirus antibodies to maintain their efficacy, our pool require donors who have been exposed and cleared this virus.

We believe that the use of NAT screening as a properly validated in-process control test provides an additional safety measure without requiring unnecessary

lengthy and costly clinical trials and that can be implemented in a timely and cost-efficient manner.

The parvovirus in-process control test will still require rigorous validation and documentation which must be reviewed and approved by the FDA.

We look forward to working with the agency and other regulatory bodies worldwide to develop a strategy to address issues related to this virus including NAT testing where appropriate.

Thank you.

DR. HOLLINGER: Thank you.

Anyone else from the public that would like to speak to this issue?

[No response.]

DR. HOLLINGER: I am going to close the official public hearing and we will open it up for committee discussion on this topic.

Committee Discussion and Recommendations

DR. MACIK: Some of my questions are about perhaps some of the science of this. If we know that roughly 50 percent of people are antibody positive, and you are now taking a pool of plasma which some people are viremic, and mixing that, the unit of a viremic, with all those antibodies, is that why maybe it takes a very high titer?

When you do the PCR on a pool, you are going to

find the DNA, but in some of these cases, is the DNA already neutralized, already bound to antibodies that with infusion, may promote the clearance?

I don't know enough about the science for that, but that might be part of the reason why you are not seeing infections. We have two infections high titer because you are basically, by making a pool, you are mixing viremia with antibodies and coming out kind of neutral towards the end.

The other question I would have from a clinical standpoint would be just how common. Dr. Stroncek had asked the question before, you know, pure red cell aplasia is a bad disease, how frequently do you want to see that.

I don't know this even being a hematologist. I know that pure red cell aplasia is extremely rare whether it is due to parvovirus or anything else, and is there a number to be associated with otherwise normal, not a hemolytic anemia patient who has gotten parvovirus-induced pure red cell aplasia? Do you know a number?

DR. YOUNG: Pretty close to zero.

DR. MACIK: So, a zero number.

DR. YOUNG: In answer to your first question, I think that you are absolutely correct, the anticipation, the expectation has always been that the antibody that is present in pooled plasma should neutralize any virus that was there, but the VITEX experience suggested that that, in