Blood Products Advisory Committee.

The American Red Cross collects more than 6 million units of blood from volunteers each year in the United States. The donated blood is also fractionated into plasma derivatives. I am Don Fipps, Vice President, Quality Assurance Blood and Plasma Operations in Biomedical Headquarters, and I am responsible for the quality of blood and plasma distributed by the American Red Cross.

The American Red Cross agrees that there should be standards for recovered plasma. We recommend that the FDA use the standards of whole blood collections for that of recovered plasma. We believe that these standards can and should be different from that of source plasma.

Source plasma and recovered plasma are collected from two different sources of donors using different collection and frequency standards. As these processes are different, so should the standards associated with the resulting products to ensure a safe material for further manufacturing into licensed plasma derived products.

We believe the current high standards for whole blood collection, testing, and processing results in very safe transfusionable blood and

blood products. Recovered plasma benefits from these high levels of safety requirements. The product comes from a volunteer donor as frequently as once every 56 days.

The donor is qualified through a health history and mini-exam. Within the ARC, the confidential unit exclusion is also used as an additional check on the motive of the donor. Safety testing currently includes testing for HIV-1 by both nucleic acid testing and antibody HIV-2 antibody, hepatitis C by both nucleic acid testing and antibody.

Only whole blood donors are also tested for antibody to hepatitis B core, the antigen to hepatitis B and for other retroviruses, HTLV-I and II antibody. Additionally, all whole blood donors are also currently tested at each donation for syphilis and unexpected red cell antibody.

We believe that the current processes used in the industry to attract, medically screen donors, and using very sensitive tests makes recovered plasma a very safe product. Accepting donations from volunteers provides a level of assurance that donors will not provide anything other than accurate answers to the health history

questions.

As stewards of the gracious donation of volunteer whole blood from our donors, we use the plasma recovered from manufacturing to make critical and life-saving plasma-derived products. The American Red Cross currently manufactures recovered plasma through contracts with Baxter BioScience and ZLB Bioplasma, AG, into albumin, immune globulin and antihemophilic factor.

Specifications for starting materials among all the manufacturers of plasma derivatives are highly variable nationally and worldwide. For example, recovered plasma, the Red Cross processes with Baxter BioScience follows a specification in which only plasma frozen within 24 hours after collection may be used, whereas, ZLB Bioplasma, AG, has a different specification that allows for plasma to be frozen greater than 24 hours but less than 120 hours after collection.

The Red Cross supplies intermediate products, Fraction IV-1 paste, to Bayer, and again we have detailed and extensive requirements for that starting material, as well.

Storage temperatures for recovered plasma are also varied in that, for plasma from which

antihemophilic factor will be produced, the storage temperatures must be maintained at minus 20 degrees or colder versus a specification as warm as minus 5 degrees Centigrade when plasma is intended for albumin and immune globulin.

Temperature variations also occur between what is expected in the U.S. at minus 18 degrees, and what is accepted in Europe at minus 20 degrees. The age of the recovered plasma used by the manufacturer is set by the specifications for the product being manufactured by the manufacturer.

Through existing standards of whole blood collection, testing and processing, and specifications from plasma derivative manufacturers, which are different between each manufacturer and product, we believe that there is no need for further regulatory guidance at this time.

If action is deemed necessary, the American Red Cross proposes that recovered plasma use, as an appropriate standard, that of whole blood collections.

I would like to thank the FDA for the opportunity to present our statement to the Blood Products Advisory Committee. The American Red

Cross is willing to work with the government and industry on recovered plasma.

I would like to thank you for allowing me to do this today. There are a couple of issues that I would like to define for the American Red Cross. The American Red Cross does have a national donor deferral registry where we collect all of our deferred donors in, however, that is not shared with other blood agencies in the United States or with PPTA at this time.

Also, there was a question about concurrent plasma. When the American Red Cross implements concurrent plasma collections in our system, we estimate that we will collect an additional 50,000 units annually from that.

So, those are a couple of questions that I would like to clarify. That is the end of my statement.

DR. NELSON: Thank you.

DR. HOLLINGER: Not necessarily a question here, but this is always very confusing to me, and I guess for the record, I will bring it up.

That is, we have organizations that are seemingly speaking for each other, but then we see different questions raised. The AABB apparently

supposedly speaks, initially, gave the impression that it was speaking for the American Red Cross and America's Blood Centers. Then, we see America's Blood Centers have an issue they talk about, and the American Red Cross then has an issue, which is different from what we just heard from the AABB.

I think this is very confusing. We see it almost every meeting that comes here. I think that is confusing to have those different viewpoints when one seems to be speaking for the same organization.

I understand the American Red Cross is part of the AABB, is that correct?

MR. FIPPS: That is correct.

DR. HOLLINGER: America's Blood Centers are, too, and then at the same time, you have different proposals basically. You don't feel that there should be any new regulations, whereas, that is not what I heard from the other presentations.

MR. FIPPS: Well, we just represent a portion of the AABB, so we don't represent a majority vote in that organization. We agree with a lot of what Kay stated in her statement about the need to make other plasma products available for us to turn into recovered plasma for further

manufacturing. We don't disagree with that one in the least.

We agree with their quality standards and their regulations as far as the AABB goes. The position of the Red Cross at this time is we don't--because we sell our recovered plasma to these manufacturers, we didn't think that their particularly additional regulatory guidance needs to come out now. We will continue to work with industry to develop, on a voluntary basis, the standards, and we are working with them on that. But I appreciate your statement.

DR. FITZGERALD: Don, I just had one. From the time of making the recovered plasma until you ship it to the manufacturer, do you have any idea how long it is in storage at your facility before you ship it?

MR. FIPPS: Well, in our storage it is not very long. It could be within one of our regions for a couple of days, and then we ship it through a third party, to Baxter, within a week. Primarily, that is most of our products.

The stuff going to Europe takes longer because it has to be containerized before it is sent overseas on a ship to Switzerland.

DR. FITZGERALD: But less than a month?

MR. FIPPS: It could extend longer than that. I don't think I have an average off the top of my head how long that is. It is not a year, but it is usually within six months.

DR. FITZGERALD: In the second paragraph, you say, "We recommend FDA use the standards of the whole blood collections," but then you say you don't want more regulation.

Are you saying that if you do have regulation, you would like it to be--

MR. FIPPS: Absolutely. We think it is sufficient at this time. If the decision is that regulations are needed, then, we propose that of whole blood be used for recovered plasma instead of overlaying source plasma requirements for that of recovered plasma, because there are different sources of material and different frequencies.

So, that is our position on that.

DR. CHAMBERLAND: I guess I have to admit to a certain level of confusion, as well, on a different issue, and I am not sure it you are perhaps the right person to address it.

What you have outlined here, the various agreements that you have with these various

manufacturers, there is a lot of variability, and I guess my understanding with that, FDA has regulatory requirements related to processing for the source plasma industry.

Not to use this in a negative term, but in point of fact and reality, do those represent a certain kind of a minimum level of standards, and then the source plasma folks, with their agreements with various manufacturers, do they have to do something different depending on what the ultimate product is going to be? Is this heterogeneity present in the source plasma industry, as well?

DR. WHITAKER: Would you repeat your question, please?

DR. CHAMBERLAND: I was just noting with interest that the Red Cross outlines, they have variable requirements related to various processing steps, time to be frozen, et cetera, depending on the individual agreement with the manufacturer and I guess the ultimate product at the end, and I was curious, in the source plasma industry, do you face these requirements, as well.

I guess I had maybe an oversimplified view that the current FDA requirements for source plasma were kind of uniform, and it didn't matter based on

the plasma-derived product at the end, that they weren't different.

This suggests that there is actually a lot of different requirements and that maybe FDA's requirements sort of are some sort of kind of minimum requirement, but that you might be required to meet different specifications depending on who you are selling to and what the ultimate end product is.

DR. WHITAKER: Every customer has its own set of criteria, so sometimes those criteria are met by the FDA source plasma regulations, and sometimes there are requirements for additional temperature and storage characteristics.

DR. CHAMBERLAND: They go above and beyond.

DR. WHITAKER: Right.

MR. FIPPS: As I understand it, these requirements are all built into their plasma master file for each of these products that the manufacturers have to maintain and keep.

MR. BULT: My name is Jan Bult. I am the president of PPTA. I would like to add to Dr. Whitaker. In this case, source plasma has to be frozen within 24 hours anyway, so I think that

answers the question.

DR. BIANCO: Celso Bianco, America's Blood Centers.

Those differences are not critical differences about infectious disease testing or things, but what they are is, for instance, for the manufacturer, those people that manufacture solvent detergent treated plasma want plasma that was frozen within 8 hours. That is the FFP standard, or frozen within 15 hours.

Other manufacturers will accept plasma that is frozen within 24 hours, and many will want plasma that was removed from the red cell that actually is a new European standard being discussed that was removed from the red cells within 72 hours. Those are the variations that you see, or how it is shipped, what kind of units will go into a container, and how long it will be stored before it gets to the manufacturer, and things like that.

DR. NELSON: Other questions or comments?

If not, it is lunch break. There is also some other testimony. I thought that if went through that, we wouldn't have lunch.

Come back at 2:30, please.

[Whereupon, at 1:25 p.m., the proceedings

were recessed, to be resumed at 2:30 p.m.]

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A F T E R N O O N P R O C E E D I N G S

[2:30 p.m.]

Open Public Hearing

DR. NELSON: Blood Centers of America. Laura McDonald.

MS. McDONALD: Thank you and good afternoon.

My name is Laura McDonald and I am the director of Scientific Programs for Blood Centers of America.

The statement today represents Blood Centers of America and its subsidiary, hemerica, and the 30 blood collection organizations in the United States that we provide services to.

These organizations conduct over 3.7 million whole blood and apheresis procedures each year. They produce 525,000 liters of recovered plasma annually, from which almost 20 million grams of therapeutic proteins are derived. Many of these blood collection organizations also distribute the therapeutic derivatives that are manufactured from the plasma.

The purpose of this statement today is to make certain points about the potential to license or to have standards for recovered plasma, and to

encourage that any rulemaking take into consideration the practicalities of how blood is collected and processed by community blood centers.

Specifically, we believe that plasma collected concurrently with apheresis procedures should be more easily directed for further manufacture into therapeutic proteins.

Blood centers currently collect blood using two diverse technologies. The first is the use of the plastic bag with integrated satellite pouches which permit the sterile separation of blood components in high speed centrifuges.

The second is the use of cell separators which permit the separation of blood components in the centrifugal field while still connected to the donor. Known as apheresis technology, this became prevalent in the early seventies for the production of platelets and is rapidly expanding today, with multiple component capacity from individual donors.

Historically, plasma derived from whole blood not required for transfusion has been sold to pharmaceutical companies that can separate the therapeutic proteins from the plasma. These transactions occur under the short supply agreement mechanism, which permits the shipment of unlicensed

products for further manufacture.

As apheresis technology improved and additional products could be produced concurrently with target products, the question of how concurrent plasma could be used was raised.

Traditionally, the FDA has ruled that plasma derived as a concurrent product from an apheresis procedure must be used as a transfusion product if it is drawn under the whole blood rules. Only if source plasma rules are used in the selection of the donor and a source plasma license is in place can the concurrent plasma be used for further manufacture.

The centers affiliated with us conducted over 350,000 apheresis procedures in 2001. This represents an incredible potential to produce concurrent plasma for further manufacture.

The current situation with dual requirements force the operator to make an either/or decision and since the primary purpose of the apheresis procedure is to produce a transfusion product, it is seldom that a concurrent plasma is even collected for further manufacture.

Our donors have made it clear they wish us to create the maximum therapeutic benefit from

their donation and given the therapeutic value that proteins derived from plasma can provide, it is unfortunate we can't easily divert plasma derived from apheresis procedures for further manufacture.

This is doubly unfortunate given the periodic market shortages of plasma proteins, such as IVIG.

We would like to strongly encourage the Blood Products Advisory Committee and the FDA to consider recovered plasma and concurrent plasma as products with identical properties when considering standards or licensure, and would further encourage that blood centers be allowed to process concurrent plasma under the whole blood rules and divert this for further manufacture when not necessary for transfusion.

Thank you.

DR. NELSON: Thank you very much.

Questions?

Thank you.

Next is Carolyn Jones for AdvaMed.

MS. JONES: Good afternoon. Thank you for the opportunity to speak on behalf of AdvaMed, the Advanced Medical Technology Association.

AdvaMed represents more than 800

innovators and manufacturers of medical devices, diagnostic products, and medical information systems. Our members produce nearly 90 percent of the health care technology products consumed annually in the United States, and 50 percent of the products purchased around the world.

Some of our members manufacture products that contribute to the national effort to improve the safety and availability of blood and blood products in the U.S.

As the committee considers standards for recovered plasma, AdvaMed would like to take this opportunity to propose to the committee a means of meeting the increasing demand for plasma without compromising donor or product safety.

Today, licensed facilities collecting whole blood and preparing fresh frozen plasma may, at any time, relabel the product "recovered plasma" and ship for further manufacturing use. No separate license is required.

Facilities license to collect FFP as a by-product of red blood cells or platelets collected by apheresis, however, do not have this option. Currently, a separate license is required to ship for further manufacturing use, plasma collected as

a by-product of cytapheresis. The plasma by-products are treated the same as plasmapheresis products, that is, source plasma, despite the fact that these products are not collected by pheresis as stipulated in 21 CFR 640.60.

The products are further distinguished from plasmapheresis products in that due to restrictions on the frequency of red cell and platelet donations, the products are collected from infrequent donors.

As you are well aware, the agency, the blood community, and industry are looking for ways to address the continuing blood shortage problems in the U.S. Increasingly, blood centers are moving towards apheresis as one means of addressing the country's blood supply problem.

Current FDA policy requiring an establishment to obtain a source plasma license in order to ship the plasma by-products of cytapheresis for further manufacturing use represents a substantial barrier to volunteer donor centers that are already licensed for apheresis collections.

We propose that FDA allow plasma by-products of infrequent cytapheresis procedures,

that is, red cell or platelet apheresis collections, to be labeled as recovered plasma.

Because these products are not collected by plasmapheresis, a formal change to the regulation is not required.

The short supply provisions of 21 CFR 601.22, which are applicable to plasma by-products of whole blood collection, can be applied to plasma by-products of infrequent cytapheresis procedures.

This would reduce the burden on the blood community and on FDA reviewers, and would increase the availability of plasma products for fractionation into therapeutic derivatives. The policy change should permit fractionaters simultaneously to amend contractual agreements to permit this change in source material definition and labeling.

We ask that the committee seriously consider this proposal and recommend this policy change to FDA.

Thank you for your consideration.

DR. NELSON: Thank you.

Are there questions or comments? Jay.

DR. EPSTEIN: Just one comment, Carolyn, thank you.

I just want to clarify to the committee that we don't have a legal opinion within FDA whether we would or would not have to change the regulation, because what is being presented here is an interpretation of existing regulation.

So, I would just suggest that the proposal that FDA allow plasma by-products of infrequent cytapheresis procedures to be labeled as recovered plasma or otherwise sold in a similar way is the essence of it, and that the mechanism is a separable issue which we don't have to really resolve today.

DR. NELSON: Thank you.

DR. HOLLINGER: Can I ask Jay another question? It could be labeled as recovered plasma, but it could also be labeled as fresh frozen plasma, as well. The reason is, is because that is what is usually ordered. I mean from a physician's standpoint, if they want something, they order as fresh frozen plasma, not as recovered plasma, and so that issue is going to be very important I think in our deliberations here.

DR. EPSTEIN: Recovered plasma is not a product suitable for transfusion. Fresh frozen plasma, which meets standards in the regulations,

is a component suitable for transfusion. Centers that prepare a fresh frozen plasma product may not relabel it and sell it as recovered plasma until it reaches its expiration date. It can only become recovered plasma after expiration.

DR. HOLLINGER: And that is a legal statement in doing that, when you say it could not be changed to a recovered plasma, is that a legal issue?

DR. EPSTEIN: Well, the issue being raised here is how much flexibility exists for interpretation of the existing regulations. The problem is that the regulations speak about recovered plasma as a product of the whole blood collection, and then they speak about plasmapheresis as the source material for source plasma when, and only when intended solely for further manufacturing use.

The problem is that we now have a practice of generating transfusable components by apheresis, and it is a question what is the legal status of the plasma, but the agency has not previously recognized the plasma as a by-product of generating a transfusable component to be recovered plasma.

The way we have looked at the regulations

is that that is a whole blood donation, and therefore, you are making only transfusable components. But what this reflects is a mind-set that goes back several decades, which was to discourage deliberate collection of a product intended solely for further manufacturing on the pretense of collecting products for transfusion.

That is why the regs distinguished it by intent. The idea was that if someone donate to make transfusion products, that is what they are for, and it is only under very restricted circumstances that anything else would be done with them.

What we are really being asked is to erase that distinction and say that products that meet a certain quality standard, for example, based on how rapidly they were frozen and what temperature they were stored and how long they were stored are equally suitable for further use to manufacture injectables or non-injectables, and that it should no longer matter what the intent was at the time of collection. It should only matter what process was followed to make that plasma. That is the essence of what is going on.

DR. NELSON: The infrequent blood donor who donates the red cells or other components of

that donation could be transfused and now it's just not permissible that any component or any portion of it be used for further manufacture, right? So, it is not violating really the agreement with the donor. I mean you still would transfuse the red cells.

DR. EPSTEIN: Okay. I mean that is one of the arguments is that there is not pretense if you are, in fact, collecting the blood component for transfusion, then, that is what you do with it, and then the fact that there is the surplus plasma is not problematic. I mean that is one possible position that could be taken.

But the situation has arisen because of the fact that we now can generate deliberately a surplus plasma product, and the question is should we allow the collection industry to do this.

DR. FITZGERALD: If a rule change were made that allowed you to convert fresh frozen plasma to recovered plasma at any point in its lifetime, that would resolve one issue, but it wouldn't resolve what seems to be more of an ethical issue within the agency of intent, even though you can draw a unit of whole blood, make the decision immediately after collection to make that

plasma recovered plasma, and there is no issue.

DR. EPSTEIN: I think you have got it right. There is the practical question should we simply allow FFP that was generated with the full intention of being FFP, to be at any point in its storage life, converted to recovered plasma through relabeling and/or should we allow deliberate collection of a plasma product for further manufacturing use concomitant with collection of components for transfusion, thereby erasing the issue of intent.

I think that those are sort of the fundamental issue in this decision.

DR. NELSON: I fail to see the ethical issue. I think if you are giving to patients who need it, you know, and not feeding it to the hogs or something like that, the person who donated the unit is helping somebody.

DR. EPSTEIN: Well, you are presuming the only reason that the donation happened was to make a concomitant transfusion component, but I can tell you that in other parts of the world, what happens is that there is donation under false pretense. The goal is to make the plasma because it is profitable to sell it.

DR. NELSON: I understand that, that is true.

DR. EPSTEIN: But we haven't had that problem because we distinguished, in the 1970s, the product is based on the intent of collection. So, what is at issue is are we going to cause the problem that we never had in this country by allowing it now, or do we think that the system we have of altruistic donation to make transfusion products is not going to become such a bonanza in surplus plasma as to create pressures on use of the donors.

I think that is the ethical side of the issue. I don't know better than you whether that is material in our system or not, but there is a reason that we separated the product streams.

DR. NELSON: The recent situation in China, I guess, is an example of a problem, a real ethical problem.

DR. SCHMIDT: I caucused with John Finlayson, and this concept of plasma in short supply, and in shuffling it off to the manufacturers, it predates FDA, and to my recollection, we were using this in 1954, plasma was in short supply and NIH let the manufacturers

decide, and it is obviously time for a change. That is 48 years that I am aware of it.

DR. CUNNINGHAM-RUNDLES: Can I just ask because I don't know, volunteer donors who give the red cells, fine, the red cells are given, but what happens to the plasma if it is not used then, it is thrown away? If it is not used for FFP in that year's window, it is discarded?

DR. SIMON: I think that we were told that the FDA allows it to be relabeled at the end of the year, but we were also told that manufacturers, that the blood centers are unable to find manufacturers who will take it at that time.

DR. FITZGERALD: Or it can be provided to a manufacturer for a non-injectable. Recovered plasma is also used for non-injectable products like controls and antibodies, and that kind of thing, but some is thrown away.

DR. BIANCO: I think I can help a little bit. It is either/or in paper, but what the blood centers do, they manage the process. You know that about 20 percent of your collections, that plasma is going to be needed for transfusion. So, what blood centers do, they try to focus those on their needs, and they focus, since the plasma has to be

removed from the red cells within 8 hours of the insertion of the needle, so they will manage actually the time that they arrive in the component's lab from the drive step that runs closest to the blood center that is going to process it, and those are the units that will become fresh frozen plasma.

When they fulfill the needs, from then on, they are going to put the product as recovered plasma. So, the amount that is wasted as fresh frozen plasma is limited. It will be some units of plasma Type A or something like that, that is in larger supply, and you are always looking for plasma of Type AB that is what you really need.

So, the process is managed. The waste is not going to be the issue. It is that from the point of view of current good manufacturing practices, as we work today, not like Dr. Paul Schmidt, I was born in '54, Dr. Schmidt, but I was not in blood banking.

At that time, it made sense, and as Dr. Epstein presented it very well, it made sense ethically. There was a lot of discussion of what is ethical in terms of a blood donor, how do you collect, what do you collect. The entire country

was on paid donations as a source of whole blood.

New York had 100 blood banks on the Bowery that was providing blood to the hospitals, and at the same time, 25 percent of the patients that received multiple transfusions had overt hepatitis. That is what caused the changes of the system in the seventies.

Today, what we are looking is from a different perspective, is the quality of the product, and the quality of the product is the same. So, it doesn't make sense now, because of the issues of intent. I understand the concerns the Dr. Epstein, could we just go in a crazy market pressure or something. No, the reimbursement for the recovered plasma is very small. It is not the major source of revenue of blood centers, and this is not going to change substantially.

The thing is that it hurts us to see that product that is so valuable not being used for a very good purpose.

DR. HOLLINGER: Celso, before you leave, in general, what percentage of the revenues in a blood center, and I will ask that also of the American Red Cross and any others about it, what percentage of the revenues come from recovered

plasma at this point, and has it been increasing over the time?

DR. BIANCO: I can give you a percent off just my head, that it is maybe 4 to 5 percent of the revenue. I can tell you what the reimbursement is. The reimbursement is on the order today, and that increased in the last year, year and a half with more requirements with introduction of NAT and all those things, is around in the 80s for a liter of plasma that will require from four to five donations depending on the value of plasma that is obtained.

So, it is in the order of maybe less than $20 a unit.

MR. FIPPS: You had asked about our revenues or percent. We, for the most part, our recovered plasma, we make into our own products and then resell them, so it is not necessarily the same analogy, but out of $2 billion annual revenues in the Red Cross, plasma sales or derivative sales represent $360 million of that.

I can't do the math right now in my head, but anyway--what's that--18 percent, okay, but that is as finished products, as plasma-derived products.

DR. ALLEN: Mr. Chairman, I would like to just ask a general question, if there is somebody in the audience or on the committee or from the FDA staff that could provide information.

It seems to me that I have heard from other sources at other times that sometimes the plasma industry requirements for recovered plasma, you know, we have already heard today that they differ somewhat, I just wonder are there other issues between the requirements of the plasma manufacturers and the recovered plasma providers that are going to get in the way or that would be impacted by possible recommendations.

I want to make sure that we have got all the information on the table.

DR. NELSON: Does anybody want to answer?

DR. BIANCO: From our point of view, we would like to see it licensed like all the other products that we distribute, and considering the short supply agreements that we have signed with many manufacturers, not many, some, because the number of manufacturers that today utilize recovered plasma is limited, most use source plasma, the specifications are not going to change.

That is their intent in general is to get

as much of fresh frozen early plasma as possible, that increases the yields. They can speak more, but my sense is that when the driver as factor VIII production or manufacture, then, it was more important the immediate 8 hour or 15-hour collection, today, the driving force appears to be IVIG that is a little bit different, because there is less time pressure.

DR. EPSTEIN: I think there is another large impact, which may be a bit subtle. Currently, if you are a registered unlicensed establishment because you operate intrastate, you still can sell recovered plasma to a fractionater, however, if recovered plasma becomes a licensed product, then, establishments that are currently registered, but want to sell recovered plasma, would have to hold licenses for recovered plasma.

Now, there are about 2,500 of those establishments. Now, they don't contribute a large fraction of the components for transfusion. I mean all together, they probably contribute no more than 10 percent of all the products, the 90 percent coming from the current licensees, but I don't know what proportion of recovered plasma they currently contribute.

I only know that is the recovered plasma is licensed, they will have to be licensed.

DR. SIMON: Well, their only representative here I guess is AABB. Do you know how the hospitals feel--these are typically hospital blood banks I think.

DR. BUSCH: I don't know about that.

MS. GREGORY: I really don't have any information on how they would feel.

DR. BUSCH: Your question about other implications, I think a licensed FFP would sort of define the standards required for safe plasma derived from a recovered source. There has been this allusion to this discussion over the last few years between the recovered and source industry about uniform standards.

We have seen enormous progress on the source plasma side with inventory hold and registered applicant donor discrimination, and obviously drug testing and a national registry, these are appropriate and have proven to be very effective safeguards that have I think brought source plasma donations into the same safety level that recovered plasma has had for a long time because of volunteer sector sourcing.

The GAO report several years ago concluded that there is really equivalence now with all of the enhanced safety standard that the source industry has brought forward.

But, nonetheless, there is an effort by the source industry to impose some of these standards on the recovered side, and many of these things just don't make sense. I mean if you only use repeat donor plasma for recovered plasma, that says you have to use all your first-time donor for FFP, so you are transfusing unprocessed, you know, non-virally inactivated product from the less safe whole blood collection pool, the first time donors, in order to meet the recovered plasma requirement that it be from repeat donors.

That doesn't make any sense. The whole issues of drug testing, et cetera, to me don't make sense, and if FDA, if this was a licensed product with clear public regulatory guidance on what is an appropriate standard, then, this behind-the-scenes, you know, debate and negotiation that is going on, that I think should be taking place in this forum, would be hopefully superseded by clear regulatory authority.

MR. BULT: My name is Jan Bult. I am the

president of PPTA.

This issue about standard setting in the industry has been discussed many times, and I have the feeling that at this moment, we are talking about two different issues. I think the issue at stake is the question of FDA, whether there should be a system that allows you to make use and to get more plasma, and have an efficient use of resources. That is one issue.

The second issue is even in this sector like PPTA, has a set of voluntary standards that includes, for source plasma, the standards that were explained by Dr. Whitaker. We, as an industry, feel it is extremely important that we have a single set of standards and that we do not use dual quality in our fractionation.

For that reason, or board of directors has made a decision to develop a standard for recovered plasma that indeed includes drug screening. The target date for implementation is January 2004, but I want to remind you it is a voluntary program. That means every supplier, every fractionater is free to participate in the program.

It is also open for public comment, and as you have heard several times today, we are

negotiating what we can do, and we have made a lot of progress, but there are some issues that still need some further discussion.

I just would like to reiterate it's a voluntary program. Nobody is forced or obliged to do so. That would be a clear violation of the legal framework in which we have to operate, and it is up to the individual fractionater to determine the criteria that they deem necessary for the manufacture of the products.

DR. NELSON: We are getting pretty late.

Steve, a short comment.

DR. KLEINMAN: Just a comment, just for perspective of the committee. You know, it is useful to look at the NAT testing paradigm because since fractionated products come from two sources, and recovered plasma comes from whole blood donors, I think everybody should recognize that because of safety concerns in the source plasma industry, the whole blood industry has implemented a series of tests, some of which would have been implemented anyway, like HCV and HIV NAT perhaps, but others of which, like parvovirus B19 and HAV NAT, which we now in discussion, probably have no value for blood donors and probably no value for the final

products, although that is debatable on the fractionated products, but basically, what I am trying to say is that what the source plasma industry does sets a standard out there some way, and it actually influences what the whole blood industry does, and in a sense, while it may not be regulatory, we have to recognize that in the current environment, in a way that has trumped FDA regulation in a variety of fashions here.

The reality is people who collect whole blood are having to do things that don't make sense in the whole blood sector, and do make sense in the source plasma sector, and it may be because they want to be competitive in the market for their fractionated product, so there is a lot of complex forces, and I guess I just offer this by way of perspective.

The last person that wanted to speak was Sue Stramer who has moved temporarily to Chiron, but she said she is going to be moving back to the American Red Cross after this talk.

DR. STRAMER: I have moved nowhere except out of my seat fortunately.

I am going to change gears a little bit and the focus of this morning's and early

afternoon's discussion has been on recovered plasma, but I am going to discuss kind of a new topic - infrequent volunteer source plasma.

So, whether we are discussing recovered or infrequent volunteer source plasma, both are plasma donations, at least in the context that I will be discussing from volunteer donors and consistency between recovered and infrequent volunteer source plasma testing standards should exist.

[Slide.]

First, I want to define what is IVSP. Starting with source plasma, it is the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use.

Volunteer donor is a person who does not receive monetary payment for a blood donation.

Infrequent plasma may be collected from healthy, non-immunized individuals who donate every four weeks or less frequently. All other collection requirements are the same as donors of whole blood other than donation frequency or minimum weight.

[Slide.]

The main difference between frequent, that

is, collections that shall not occur less than two days apart or more frequently than twice in a seven-day period, and infrequent, is that manufacturers must perform physical examinations and tests for total serum or total plasma protein on frequent donors.

Frequent donors may also be part of an immunization program.

[Slide.]

On February 27th, 2002, the Chiron Procleix HIV-1, HCV NAT assay was licensed with the following intended use - as a test for HIV and/or HCV in human plasma from donations of whole blood and blood components for transfusion.

So, donations from IVSP donors qualified as part of the clinical trial, but not included in the licensed PI, but were not included in the licensed package insert. The reasons are unknown, but I will discuss further.

Now, IVSP donations represented approximately 0.3 percent of the collections in the manufacturer's pivotal trial, as well as collections in the Red Cross' IND for pools of 16 using, at that time, the unlicensed test since September 8th, 1999, which represents over 21

million total donations.

[Slide.]

Infrequent volunteer source plasma is also not specifically mentioned in either FDA draft guidance document on NAT, and there are two documents that I have referenced here. Without inclusion in the licensed NAT package insert, testing under IND will continue because we have no mechanism to test these donations.

[Slide.]

Now, other options that exist under the current regulations, one would assume would be that we would have to identify these samples from whole blood donations versus those from infrequent volunteer source plasma donations and segregate those during processing.

So, once they are segregated, potentially, then, we would have to submit them to a different pooling algorithm and send them to the manufacturer who is licensed for source plasma NAT, which is National Genetics.

So, for a very small percent of our collections, we would have to implement two very unique processes. So, our comments to the draft guidance were provided to FDA.

[Slide.]

Why would an IVSP be included in the package insert? There are three potential reasons or three potential issues why they haven't been.

One, the manufacturer, Gen-Probe, and the FDA were unaware that these donations were included in the clinical trial and the IND data, so that no claim could be provided.

A second potential reason is questions regarding the method of sample collection, that is, is the process for IVSP different than routine whole blood collections, and thirdly, are the demographics of these donations different than whole blood donors, and therefore, no claim could be provided.

In the few minutes that I have, I am going to review those three issues.

[Slide.]

Firstly, the collection process. Samples from both whole blood and IVSP donors are collected as whole blood samples, and they are not diluted in anticoagulant, and they are obtained directly from the donor into a plasma preparation tube, which is an EDTA spray-coated plastic tube qualified for NAT.

Our plasma is collected using seven different qualified apheresis instruments. We collect plasmapheresis, plateletpheresis, aretsoapheresis [ph], and we collect either FFP or IVSP.

All samples are obtained prior to the start of the collection, and again, no anticoagulant or saline dilutes the test samples, so basically, the test samples from whole blood and pheresis donors are identical.

[Slide.]

I have just here listed, which I won't go through, but the seven licensed methods that we use for collection.

[Slide.]

To go through the specific data for the IVSP collections, the period covered for NAT on pools of 16 includes from 9-8-99 through the end of the year 2001, which includes greater than 16 million allogenic donations. In that period of time, there were 67 HCV and 5 HIV seronegative yield donations identified.

None of those were from infrequent volunteer source plasma donors, but what were from IVSP donations were 50,669 donations from 10,673

donors which included anywhere from 1 donation per source plasma donor to 28 separate donations. One donor, in fact, donated once monthly during this time period.

[Slide.]

The collections occurred at 15 geographically distinct sites, and the inclusion criteria for the analysis included collections from any region in which greater than 100 IVSP collections were obtained.

Seven reagent lots of product were used, and data were analyzed for all collection from which NAT and serology were complete, and FDA licensed methods were, of course, used for HIV and HCV.

[Slide.]

This slide shows you the 15 regions that were included in the analysis, obviously, widespread through the United States and varying numbers of source plasma collections.

[Slide.]

This graph shows you the frequency of donations per donor. So, the column closest to me represents the number of donors only donating once per this period of time versus donors on the far

left that would have donated up to 28 times.

[Slide.]

As I mentioned, the NAT testing is performed in pools of 16, so this slide shows you the number of IVSP donations that were contained in pools of 16, anywhere from one donation, that were contained in 26,191 pools to 11 IVSP donations contained in only one pool during this time.

[Slide.]

Of the 50,669 IVSP donations, 50,586 donations were tested, and 35,951 pools containing between 1 and 11 IVSP donations; 83 were tested individually, that is, never pooled. Of 35,951 pools tested containing IVSP's, 99.3 percent were NAT nonreactive, and 0.7 percent, or 244, were NAT-reactive. That included 336 IVSP donations, and the remainder, whole blood samples.

Of the 83 IVSP donations screened by NAT individually, 76 were NAT and serology nonreactive, and 7 additional samples were NAT nonreactive, but were repeat reactive by serological testing.

[Slide.]

To go through the data in composite, of the 50,669 IVSP donations, 336, those were the ones that were tested in pools, resolved to 2 NAT

reactive samples, neither of which were discriminatory HIV or HCV NAT reactive, and neither were HIV or HCV seroreactive.

So, the NAT positivity in this study out of IVSP was zero percent. To compare that with what we obtained in whole blood, the frequency is 0.004 percent. There is a zero point missing on this slide, but the bottom line is there was no significant difference between these two.

Next point. Of the 50,669 IVSPs, they contained 15 or 0.03 percent anti-HIV reactive samples, none of which confirmed. So, again, that is the HIV positivity rate for antibody of zero percent, which again is statistically non-different from whole blood donors at 0.003 percent.

For HCV, of the 50,669 IVSPs, there were 8 anti-HCV repeat reactive samples, 2 confirmed. Now, both of these had weak RIBA banding patterns suggestive of resolved infection. So, the anti-HCV positivity of IVSP in this case was 0.004 percent versus whole blood at 0.18 percent, and those two were significantly different.

So, bottom line is marker rates were comparable or lower when you consider NAT and serology from IVSP donations than from whole blood

donations.

[Slide.]

This slide just shows the breakout by pool testing the 336 reactive pools, of which resolved to 2 individual donations, neither of which were NAT reactive. This shows the composite for all of the serological data. There were the 15 HIV antibody reactives, and the 8 HCV antibody reactives, again only 2 being RIBA confirmed positive, both of which were NAT negative.

[Slide.]

To look at the population distributions of the IVSP donations tested, the population means for the NAT nonreactive pools was 0.225 versus whole blood, which is what is in the package insert or actually whole blood with a mixture of some low percentage of IVSP of 0.21. These are not significantly different.

The same thing for the NAT nonreactive individual donation samples tested, a population mean of IVSP of 0.225 versus the whole blood, what is in the package insert at 0.17. Again, not statistically different.

[Slide.]

This slide shows you the distribution of

NAT nonreactivity or the S to CO values for NAT nonreactive pools and samples for IVSP donations, and again not significantly different than whole blood.

[Slide.]

In conclusion, donation samples from IVSP donors are collected by the same processes as routine whole blood donations. Donations from IVSP donors have similar or lower marker rates than those from whole blood donors.

IVSP donations have been qualified as part of the IND process for HIV-1, HCV NAT. These data have not been excluded from the Chiron Procleix package insert data, however, they did require a separate data analysis since they are not included in the current package inserts.

[Slide.]

Since data for IVSP and whole blood donations are comparable, and both have been qualified, both should be included in the intended use statement of the Chiron Procleix HIV-1/HCV assay.

The American Red Cross has provided these data to Gen-Probe, that is, the manufacturer or license holder on May 13th, 2002, for FDA

submission as a BLA supplement labeled transmittal to their current package insert.

Thank you.

DR. NELSON: Thank you.

Questions? Jay.

DR. EPSTEIN: Susan, how does this relate to the topic at hand?

DR. STRAMER: Actually, it doesn't. It really doesn't deal with recovered plasma per se, but if we are talking about standards, and certainly testing is a standard and we are talking about all the collections from volunteer donors, be they recovered plasma or be they infrequent volunteer source, they should all be tested using the same testing algorithms, and not have to be separated in our operational processes.

DR. EPSTEIN: Are you then arguing that since you have data on unpaid source plasma donors collected under whole blood standards for infrequent apheresis, that therefore, the license for the NAT tests should extend to all source plasma donors?

DR. STRAMER: No, not to all source plasma donors, to those source plasma donors that have been qualified as part of the clinical trial for

the assay, which include volunteer source plasma donors.

DR. EPSTEIN: I don't know that we needed to do this in front of the committee because you are basically asking the FDA whether your data validated an extension of label, and we are not going to decide that here today.

DR. STRAMER: I understand that, but it was a request from Chiron and Gen-Probe to make these data public, so since we were the keepers of the data, I honored their request.

DR. EPSTEIN: All right. We hear what the implicit request to the FDA is, and I think we will discuss it at another time and place.

DR. STRAMER: Okay. Thank you.

DR. NELSON: I think we will move to the questions for the committee.

DR. HOLLINGER: Could I just ask Dr. Fitzpatrick just a minute, we never heard anything about the military. Is this an issue for the military at all?

DR. FITZGERALD: Not really. Our donor centers collect and prepared recovered plasma with short supply agreements just like other centers, so we function under the same constraints as the

industry is functioning, and we will go along with the regulation if it appears or continue to work under the short supply agreement, but we don't supply large amounts of recovered plasma.

DR. NELSON: I guess we are looking for the questions. If you can't find them, we could just read them theoretically.

MS. CALLAGHAN: I think we finally arrived.

Open Committee Discussion

Questions for the Committee

MS. CALLAGHAN: The first question to the committee. Should FDA develop specific product standards for recovered plasma?

DR. SIMON: I think the way the presentations went, it might not have been apparent but I really do think there is a consensus from industry that standards would be appropriate. I think there is a difference on what exactly they should be, but I do believe that substituting for the short supply agreements and eliminating that ambiguity and the difficulty with standardization that exists, and substituting some standards for things like storage conditions and dating periods would be a step forward.

I think we recognize it's an international industry. A lot of things are governed by the manufacturer, and there may be requirements in excess of what we said or what is set by FDA, but I think it would be appropriate to move ahead with standards.

It sounds like that comes out of most of the presentations. Then, this would allow, under the third question, it would allow the FDA to go ahead and consider some of these specific examples like the apheresis and include them as it develops those standards.

So, I would certainly favor a yes vote on No. 1.

DR. FITZGERALD: In going back to Jay's first comments and the fact that one major player that collects almost 50 percent said they didn't want regulation, I am not sure I agree totally, but I think industry appeared to be asking for the flexibility to use FFP as recovered plasma as one issue. That would take a change in a rule to do that, so that piece of regulation would be a piece that would be required.

When we look at all the other items impacted by the general statement, should there be

specific standards for recovered plasma, I think it gets complicated, and we have a lot of unanswered questions.

We have the major proponent of source plasma is paid donors, the major proponent of recovered plasma is volunteer donors, two distinctly different donor populations. The voluntary standards that have been established by PPTA have been put into effect to assure the safety of their donor population, which is a different donor population, and to assuage some of the concern and perception of the public that those paid donors are less desirable than volunteer donors.

So, I am not sure the voluntary application of all the standards that PPTA is advocating for their donors would be applicable or should be applied to volunteer whole blood donors.

The other questions that we have is you usually regulate something because there is an issue of safety or efficacy of the product on the other end. I didn't hear any data or information to imply that there is a problem with safety or efficacy of the concentrates that are being manufactured from either source plasma or recovered

plasma.

The recall information seemed to imply that there were implications of increased recalls because of postdonor information, but when we asked specific questions about the numbers of units, the percentage of units, and if there was a change, that information wasn't available, and that data is very hard to interpret and is incomplete.

Storage conditions do seem to vary between suppliers and could be an issue on the safety and efficacy of the end product, but we don't know the answer to that question.

Records was brought up, but records brings up another implication, because whenever FDA or anyone has set standards including AABB regarding retention or records, usually, there is a clause in there that says records should be retained until the expiration of the product or a period past the expiration of the in-date product.

Recovered plasma would be used to prepare an injectable in-dated product. So, now you have to give a requirement for the donor centers as to how long after the infusion of the concentrate that was prepared from the plasma should be kept. That might be less time than indefinite probably, but

that needs to be arrived at also if you are going to talk about record retention.

So, given all those indications, and the fact that there isn't an overwhelming indication to me from the industry that there is a problem with the end product, it seems like the indications are standardization of storage and a rule changed maybe to allow changing the labeling of FFP to recovered plasma at any point.

I take into consideration Jay's comments about other countries where donors were recruited under perhaps false pretenses to get plasma. We have never had the problem in this country of having excess red cells. If we got to that point, I guess we could address that, but it would be a pleasure to get to that point.

So, I don't see that there is an initial problem with recruiting thousands of volunteer donors for the sake of getting another unit of recovered plasma that you can sell for 20 to $25, which will come nowhere near covering the cost of the red cells.

I understand the ethical implication and what was done years ago because of other considerations. I am no sure it impacts where we

are right now.

If we consider regulation, I would suggest to the FDA the regulation that at first be limited to allow relabeling of FFP, perhaps address storage conditions, but that the other items, especially with the need for hepatitis B antibody in the end product, that that would require a lot more data and information to make any determination on the other questions.

DR. NELSON: The limited changes that you recommended would require a yes, that there would be then specific standards or no? There would be a change in the current regulations.

DR. FITZGERALD: To me, relabeling isn't changing --well, I guess it is, changing of product standard. It would be yes to the first.

DR. DiMICHELE: I would just like to add to what has been said already. I guess I would say yes upfront. I think I agree, there appears to be a need. I agree with what Dr. Fitzpatrick said, that there truly aren't any safety or efficacy issues that have been identified today.

I would also agree with you that I think standards should be instituted where standards are needed, and I think you iterated very well what

those problem areas were, but I do think, in my opinion, that standards are required because it appears to me that there is a precious resource out there that is going to waste because of certain ambiguities and lack of standardization, and I think that in itself creates a mandate for standards that would resolve that issue.

However, I just would like to say that I think, you know, I am a little embarrassed as a hematologist who has been working in this field for a while, that I had to learn a whole lot about a field that I thought I knew a lot about because I am a hemophilia treater and I give these plasma-derived products all the time, and it is amazing what one doesn't know.

I believe there is an issue of disclosure here and I believe that the disclosure, I hope that standardization, if the FDA does develop standards, includes standardization of disclosure, disclosure to the patient, who is coming in as a volunteer, and from whom there is a paid product, a product that is being sold. This person is donating a commodity. I think that person needs to know.

I think that there needs to be disclosure from the plasma fractionation industry as to what

exactly is in plasma-derived products, what components, what mixes, and I think that some of these issues, there needs to be--you know we understand this voluntary versus paid, but I am not sure that we have understood the full implications of this, and I think there needs to be better disclosure even to the physicians using this product.

I also, if I can just be a patient advocate for a moment, I believe that I can speak, and maybe Charlotte can actually speak for her population, but I will speak on behalf of any of those patients who are using fractionation products, that regardless of what happens, that patients and the medical system cannot bear an increase in the cost of fractionated products, whether they be IVIG or clotting factor concentrates.

This has maxed out and those of us who are dealing with this on the front lines would like to just make that point.

DR. NELSON: Thank you.

Jim.

DR. ALLEN: I concur with the comments that have been made. I personally would come down

on the side of that it is time to move towards the development of standards. I was going to raise also the point that Donna just raised at the end, and that is, I know that cost is not a primary consideration. It has not really been addressed here in terms of what the impact on collectors might be of standards and licenses with the exception of Jay's statement about the very small intrastate collectors.

I think the implication was that it would be extremely costly to them to have to go through the licensure and regulatory process, which they don't currently.

With that aside, I think that there is a cogent argument for moving ahead and addressing some of the issues that have been laid before us today.

DR. NELSON: Any other comments?

Do you want to vote on this? I guess it is yes or no.

DR. SMALLWOOD: Voting will take place by roll call. There are 14 eligible voters. So, as I call your name, would you please indicate your preference by yes, no, or abstaining.

Question No. 1 stated as read. Should FDA

develop specific product standards for recovered plasma?

Dr. Allen?

DR. ALLEN: Yes.

DR. SMALLWOOD: Dr. Chamberland.

DR. CHAMBERLAND: Yes.

DR. SMALLWOOD: Dr. Cunningham-Rundles.

DR. CUNNINGHAM-RUNDLES: Yes.

DR. SMALLWOOD: Dr. DiMichele.

DR. DiMICHELE: Yes.

DR. SMALLWOOD: Dr. Fitzpatrick.

DR. FITZGERALD: Yes.

DR. SMALLWOOD: Dr. Klein.

[No response.]

DR. SMALLWOOD: He is absent, I think.

Dr. Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Dr. McGee.

DR. McGEE: Yes.

DR. SMALLWOOD: Mr. Rice.

MR. RICE: Yes.

DR. SMALLWOOD: Dr. Schmidt.

DR. SCHMIDT: Yes.

DR. SMALLWOOD: Dr. Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Dr. Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Hollinger.

DR. HOLLINGER: Yes.

DR. SMALLWOOD: Dr. Nelson.

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Stuver.

DR. STUVER: Yes.

DR. SMALLWOOD: Dr. Simon, how would you have voted if you could?

DR. SIMON: Yes.

DR. SMALLWOOD: It takes a little longer to add up these, but I think that they are unanimous. Unanimous yes votes.

DR. NELSON: The second question.

MS. CALLAGHAN: Yes, unfortunately, you are not getting away that easy.

If yes, should the standards for recovered plasma include:

(a) Negative screening tests for anti-core and anti-HTLV I/II?

DR. SIMON: I think it is difficult because if the other components are collected, and I presume those tests would be required although plasma could be pulled out, but I am of the

opinion, scientifically and medically, to answer no to that, I don't believe that that contributes to the safety or efficacy of the final product.

We have talked about the need for the hepatitis antibody in plasma preparations. The HTLV I/II, I believe is pretty well substantiated not to be transmitted by plasma. So, I think we should answer no to that question.

DR. NELSON: Except that remember that red cells are being collected.

DR. SIMON: You still would have to have it for these other components. They would have to have it for all those other components.

DR. CHAMBERLAND: Also, my understanding is, if I heard correctly, I believe it was from the ABC statement, was that currently, if the screening test came up with a positive anti-core, blood collectors were presently sending those, the recovered plasma, for manufacture, and discarding obviously the other components.

The other half of that, though, is would the person be deferred from further donation in accordance with the current FDA guidance since they would not qualify, if you will, as a whole blood donor.

DR. BIANCO: That is correct. So, it is only for the donations. It will be one or actually two donations.

DR. EPSTEIN: I just want to comment. FDA has been of a divided mind over this, between anti-core and HTLV. In the case of anti-core, as has been explained by Dr. Finlayson and others, we do permit, indeed encourage, continued use of the anti-core positive unit in the fractionation pool, and so we allow the use of the unit collected from the donor, who would become deferred from whole blood collection, to be sold and fractionated.

However, for HTLV, we took the opposite tack, which is that we discouraged use of the marker-positive plasma. It is not in the regulations, it is in the guidance, and the reason was that we were concerned that if we allowed the product streams to go two ways under different standards, we might increase the error of use of the transfusable component, which is the point that Dr. Nelson I believe was trying to make.

So, you know, the FDA, I guess sits on the fence because we have done it one way in one setting and the other way in the other setting, but the underlying issue of concern is the

inappropriate use of the transfusable component.

We agree with Dr. Simon that we are not actually worried about the derivative as the end product because we do know that the derivatives don't transmit HTLV. So, it is really a question about how worried are we about things getting mixed up at the blood center is really what that question comes down to.

In other words, we know we exclude the unit for use for transfusion, should we be permissive about continued use for fractionation.

DR. NELSON: And given the fact that medical error, et cetera, is a substantial, perhaps one of the major contributions to significant errors. I think this is really an issue, yes.

DR. ALLEN: It is an important issue. On the other hand, the person has already donated the unit of blood, and it was the lab test, not the donor history screening, that disqualified the transfusable units.

In many instances, I assume that by the time the lab testing is completed, that the separation of the components has already occurred, and they are all in the system, and you have got to identify and recover and make a determination of

all of those components anyhow.

I think, depending on the system that it's in place in a given blood bank, one could make an argument that if there is not a safety i.e., an infection risk to allowing that unit to go into the recoverable plasma process, that that could be as easily done as discarding the unit.

They have to have a process for identifying the ultimate disposition of each of the components that were created anyhow.

I certainly wouldn't want the donor coming back in a second time. I think there could be an argument that as long as it is already in the system, it could be handled safely one way as the other.

DR. NELSON: Are you ready to vote on this?

DR. LEW: If I could just add one comment to that, though, it seems like we shouldn't be finding a lot of patients, I suspect, who are going to come up positive for the antibody, so that is a rare event. So, we are not going to lose a whole lot.

Even though it is a rare event that they might make a mistake, that would be a very bad

mistake.

DR. FITZGERALD: This is actually one of the most problematic tests we do. It has a high false positive rate, and you confirm the initial positive by putting the donor on surveillance. They come back in the second time, and are deferred after the second positive result.

So, the core antibody test is problematic in and of itself. On the next three questions, I would be inclined to abstain, because I don't think we have data to make a definitive recommendation to FDA one way or the other, and I would assume--

DR. NELSON: Are you talking about the core or the anti-HTLV?

DR. FITZGERALD: Core.

DR. NELSON: I think you were talking about the HTLV.

DR. FITZGERALD: I am sorry, I thought you were talking about core. I would assume that now that you have the recommendation to set standards, you would work on a guidance document and producing standards for comment, and we would have the opportunity to look at more data and do those sorts of things.

DR. NELSON: Do you want to vote on this,

and you can abstain if you think that there is not sufficient data. The guidance document, whatever the regulations or standards the FDA eventually comes up with may be different than what we say here, but they have asked us to comment or to vote on this.

DR. CHAMBERLAND: I just have a request for one further clarification from Jay just to make sure I understand it. Currently, what is allowed is, in the instance of recovered plasma, would be to allow a positive core, recovered plasma go forward for further manufacture, but a positive anti-HTLV, no, the guidance would suggest that it not go forward.

So, that is the current system. Do you have evidence or data that you can bring for us to consider in a more quantitative way, this important concern about mix-ups occurring vis-a-vis inappropriate release and whatever, because if I understand it correctly if we vote yes, then, we are making a change from the current practice. If we vote no, then, the current practice would not change or at least that would be our recommendation.

DR. NELSON: At the same time, we would

put this recovered plasma standards with regard to this issue similar to the current source plasma.

No, if we say yes, it will be the same as the current practice.

DR. SMALLWOOD: No, if you say no. No will be the same as the current source plasma.

DR. CHAMBERLAND: No would be the same.

DR. NELSON: Right, that's what I meant.

DR. FITZGERALD: No would be a change because you are saying that you would allow a positive anti-HTLV to go forward or a positive core unit to go forward. If you vote yes, you are making a change because you are saying a negative HTLV--either way, you are making a change.

DR. CHAMBERLAND: It is because you coupled these in one question when you consider them currently separately.

DR. EPSTEIN: This is correct, but the reason we framed it this way is what we are really asking is whether it should conform to the current source plasma standard. That is what we are really saying. You don't screen source plasma either for anti-core or for HTLV, so what we are saying is if you have done it on a whole blood donor, should we care.

So, the question really is should we harmonize the standard with source plasma.

DR. CHAMBERLAND: If you agree that you should harmonize, then the answer is--

DR. EPSTEIN: The answer would be no. The answer would be no because you do not have a requirement to the negative test. 2(a), the answer would be no.

But let's come back to the question. What do we know about errors?

MS. O'CALLAGHAN: Based on the BPD data, there are very few, if any, deviations related to the inappropriate release of units that tested positive for HTLV I. We see very few reports of those. That is just not something that has occurred.

DR. HOLLINGER: How about for anti-HBC?

MS. O'CALLAGHAN: For core? Well, because we have allowed to be released, the recovered plasma, we wouldn't see that as a deviation because it's okay to do that. It's not considered a deviation.

DR. NELSON: Unless the red cells were--

MS. O'CALLAGHAN: That is what I was going to say, that for recovered plasma, we haven't seen

that. For red cells, again, even that is very few, a handful maybe.

DR. HOLLINGER: And fresh frozen plasma would never be made from this anyway, is that correct?

MS. O'CALLAGHAN: That's right.

DR. NELSON: Okay. Let's vote.

DR. SMALLWOOD: A vote is being taken on Question 2(a) as stated. Should the standards for recovered plasma include:

(a) Negative screening tests results for anti-HBC and anti-HTLV I/II?

Dr. Allen.

DR. ALLEN: Qualified no.

DR. SMALLWOOD: Dr. Chamberland.

DR. CHAMBERLAND: No.

DR. SMALLWOOD: Dr. Cunningham-Rundles.

DR. CUNNINGHAM-RUNDLES: Not enough information. I am going to abstain.

DR. SMALLWOOD: Dr. DiMichele.

DR. DiMICHELE: I would agree with Dr. Cunningham-Rundles. I have to abstain. Same reason.

DR. SMALLWOOD: Dr. Fitzpatrick.

DR. FITZGERALD: Abstain.

DR. SMALLWOOD: Dr. Lew.

DR. LEW: Abstain.

DR. SMALLWOOD: Dr. McGee.

DR. McGEE: Abstain.

DR. SMALLWOOD: Mr. Rice.

MR. RICE: Abstain.

DR. SMALLWOOD: Dr. Schmidt.

DR. SCHMIDT: Abstain.

DR. SMALLWOOD: Dr. Stuver.

DR. STUVER: No.

DR. SMALLWOOD: Dr. Fallat.

DR. FALLAT: Abstain.

DR. SMALLWOOD: Dr. Harvath.

DR. HARVATH: No.

DR. SMALLWOOD: Dr. Hollinger.

DR. HOLLINGER: Abstain.

DR. SMALLWOOD: Dr. Nelson.

DR. NELSON: No.

DR. SMALLWOOD: Dr. Simon, your opinion.

DR. SIMON: No.

DR. SMALLWOOD: I believe I counted 5 no votes and 9 abstentions.

DR. NELSON: Okay. 2(b).

MS. CALLAGHAN: Should the standards for recovered plasma include:

(b) Specifications for allowable storage conditions and dating periods?

DR. SIMON: I would think everything has directed us to a yes on this. This would presumably be the reason for doing it. This would allow them to allow fresh frozen to be converted, for example, before a year, and so on, and so forth.

DR. NELSON: Do you want to vote?

DR. SMALLWOOD: Vote on Question 2(b). I can make this easy. If everyone is in agreement, I can call it unanimous.

DR. NELSON: Can you do a show of hands?

DR. SMALLWOOD: I will do it the right way. I will call each name.

That is the question I asked. Are there any opposing votes? Are there any abstentions? There is a unanimous yes by all voting members. Dr. Simon, you agree. Thank you.

DR. NELSON: 2(c).

MS. CALLAGHAN: Should the standards for recovered plasma include:

(c) Labeling requirements similar to source plasma to distinguish appropriate use for manufacturing of injectables versus non-injectables

based on the preparation and storage conditions?

DR. SIMON: I would have probably not thought so until I heard Dr. Fitzpatrick's comments. I didn't realize it was common within the blood centers to label things for non-injectable use, and I would think if that is going on, that we would need labeling requirements because we certainly wouldn't want anything that was unsuitable for injectable to be able to be so labeled.

So, I would think here also it would be something we would want, so it would be yes.

DR. NELSON: Vote.

[Vote.]

DR. SMALLWOOD: I just want it to be clear for the record. I am supposed to call the roll, however, if we have unanimous votes. All right.

Are there any opposing votes at all?

[No response.]

DR. SMALLWOOD: Any abstentions?

[No response.]

DR. SMALLWOOD: Then, it is a unanimous yes for No. 2(c).

Dr. Simon.

DR. SIMON: Yes.

DR. SMALLWOOD: Thank you.

DR. NELSON: Question 3.

MS. CALLAGHAN: The last question, and you are not getting away this easy on this one.

Do committee members have additional suggestions regard product standards for recovered plasma?

DR. NELSON: This one is yes, no and maybe.

DR. ALLEN: I think we have already heard a number of suggestions, and I have written down a few things, and I would just like to offer four brief statements, and then we could see what we want to do with this.

I would recommend that:

1. The issue of "donation intent" not be a fundamental principle in the standards.

2. Concurrent plasma collection, or whatever term is used, during apheresis procedures be allowed.

3. Relabeling fresh frozen plasma for use as recovered plasma at any time prior to the outdating be allowed.

4. The impact on small intrastate blood collectors of standards and licensure for recovered

plasma be studied and appropriate accommodations for these collectors be considered as part of the proposed standards.

DR. FITZGERALD: I just wanted to get again on the record retention, it is going to be problematic, so you are going to have to address whether you have to retain the donor records for the life of the manufactured product, as well as the plasma product.

DR. SIMON: I think on that one, though, they have addressed it for source plasma, if I am correct. It's 10 plus 1. I think source plasma has a 10-year.

MS. CALLAGHAN: Plus 6 months.

DR. SIMON: Plus 6 months. So, it has been addressed for source plasma, so I assume they could address it the same way for this new plasma.

DR. HOLLINGER: Jim, I guess I would agree with most of the things you mentioned about things to take into account. I am not sure that I would want to see it to be a different regulation for the group that are just doing intrastate processing even though--I mean there may be some hardships here, but I don't see how you can have a different standard.

DR. ALLEN: I basically agree with you. I think the issue ought to be addressed, however, and that some of them ought to be brought into the process and asked for comments and impact. I agree that to the extent that you can avoid any difference at all, it ought to be done, but accommodations might be considered at least.

DR. DiMICHELE: The only other question I would have is whether if more recovered plasma is used in the fractionation industry, and the ratios of source to whatever we are going to call the recovered plasma change, I think there has been some debate or certainly some old data, but not any new data, that standardization, for instance, if it is going to be used for factor VIII, what are the factor VIII levels in recovered plasma versus source plasma.

I am not sure. You know, I just don't know about this, but I am just bringing forward that maybe there needs to be, for whatever that plasma is going to be used, that there needs to be good standards, so that understand if there is a mix and a change in the mix, what that means relative to the particular product that physician or patients may have an interest in.

DR. FALLAT: I would second what you just said, and since I think I heard from industry that they do treat the source plasma differently and process it, they don't lump it together, is that right? It's the derivatives that are derived from one or the other.

I think it becomes an important issue to know what the standards are of that derived product when it comes from two different sources.

DR. NELSON: Presumably, this change, if the FDA adopted any of these regulations, they may not be in the future separate, but it would be of some advantage probably to keep them separate just because of the way they are collected and processed are different and were a problem to develop relating to that difference in processing, storage handling, or population, it might be easier to identify what the problem was if they were kept separate as they are now.

DR. SIMON: I believe the majority of the recovered plasma product in the United States is American Red Cross, so at least that portion is clearly identified, and is all from volunteer donors. So, we have experience with that being in use.

At least with factor VIII, it is measured by the end product in terms of the factor VIII assay. Now, with things like IVIG, where there is no standardization, then--I shouldn't say no, but where there isn't this type of standardization in terms of antibody levels to each of the various organisms, there could be some differences, and it would be interesting to study that.

DR. DiMICHELE: I would just like to add, though, that factor VIII is not factor VIII, is not factor VIII, and I think that there may be differences with processing differences in terms of the final biochemical product.

I just think that, you know, if there is going to be a really substantial difference in the plasma, in the fractionation mix, that we have to understand what that looks like.

I guess I would just encourage the FDA to request that.

DR. HOLLINGER: It seems to me that the most important thing that I have heard here so far has to do with storage. I mean that is really the critical thing, and it sounds like the Red Cross is doing a lot of that, I mean with their short supply agreements, that there are some really finite time

periods in which they have to freeze samples down, I think that is really critical.

If you are going to call it fresh frozen plasma, that is done very nicely, and then the question is how much further out should one go before allowing this to be used as recovered plasma, I think there needs to be a real finite level whether it is three days, four days, five days, or what.

DR. NELSON: I think the FDA probably should look at some of the short supply agreements or whatever, and take some of the requirements and criteria that seem to be applicable or useful if they are going to make it into standards, and there need to be some standards.

I think we could just vote yes, that there need to be some standards.

DR. SCHMIDT: Come up with a new name for recovered plasma.

MS. CALLAGHAN: Any suggestions?

DR. NELSON: Jay, is this discussion sufficient?

DR. EPSTEIN: I appreciate the patience and endurance of the committee, and I think we have had the discussion we need.

MS. CALLAGHAN: Thank you.

DR. NELSON: Let's move on to the final item.

We are now going to discuss the Uniform Donor History Questionnaire.

Alan.

II. Uniform Donor History Questionnaire Introduction and Background

DR. WILLIAMS: Just to establish some context, what we are going to discuss in this session is basically reviewing the product of a task force that has been looking at the donor screening instruments and has produced its final report in addition to providing cognitive studies really for the first time on a questionnaire that is used over 13 million times a year for donors of whole blood and blood components.

A really very important issue and I think some very impressive progress in tightening up the donor qualification procedure.

Because some members of the committee are new, I want to very briefly give a little bit of introduction and then introduce the topic.

[Slide.]

Why is accurate donor qualification

important? Obviously, the first reason is to maximize blood safety with respect to known agents where laboratory screens are in place, these screens are very sensitive, they there are still very rare errors associated with window periods, associated with infections, testing errors, and produce release errors.

Also important, however, are unknown threats to the blood supply when there is no laboratory screening test available. In some cases, donor questioning may be our only protection for the blood supply in deferring donors who may be carrying a transmissible agent.

The second reason is to minimize donor loss due to inappropriate deferral. There is a tendency to add questions every time we are concerned about something that might threaten blood safety, and as we all are aware, sometimes these questions are nonspecific to the point that we are losing donors that we shouldn't be losing simply due to inaccuracy in the screening process, the questionnaire process.

There is a lot of operational impact associate with donor qualification. If you get an incorrect answer, and this becomes known later,

there is what is known as postdonation information that, at the highest level, could result in product recalls, which have major impact.

Fourth, and often isn't mentioned, is the fact to minimize staff exposure to infectious donations, these bloods are drawn, processed in the laboratory, and it is simply better not to have the unit of blood drawn at all if there is a risk.

[Slide.]

There are various stages of donor qualification. The first is exclusion of risk populations. Protections that have been in place for some time are the exclusion of prisoners and the requirement for special labeling for paid donors of whole blood.

There are self-deferral where the potential donor sees educational information prior to donation, and simply concludes that they are not appropriate for a donation and doesn't appear. Similarly, that same process can happen at the blood site before the interview is actually done with a staff member.

There can be deferral by staff during the interview process. This is really the focus of today's discussion, however, some of these prior

factors are really much larger in magnitude than the actual deferral due to staff interview.

Then, there is postdonation information already commented on.

[Slide.]

Current donor qualification. There are certainly successes. We know by comparison with general population studies that blood donors coming in for the first time have lower prevalence levels than the general population, and this is certainly an impact of the education and screening process.

We know there are some failures. When a donor is found positive for an infectious marker, particularly HIV or HCV, often by interview, we can identify that this donor had a risk factor that should have prevented donation, and there are certainly hurdles to providing an accurate donor qualification - limitations in having donors read materials and apply that information to their own situation, concerns about validity assessments both for the criteria used for the deferral process, whether they are scientifically accurate, and also the methodology of the screening process, whether that is optimized to the greatest extent.

Behavior science has made great progress,

but it is still certainly considered a softer science than, for instance, the development of laboratory tests, and this has had an impact on the donor qualification process, as well, in that it is not regulated as tightly as it infectious disease testing, the science isn't quite as well defined, and the financial drivers that are there for the laboratory tests simply don't exist for the donor screening process, so the progress has been a little slower.

[Slide.]

There have been some major research advances particularly associated with defining AIDS risk factors in the general population. One of these includes the use of a computer self-assisted questionnaire with audio components.

This is probably the future of donor screening, but it is not quite there yet. There are some sites that are using some very preliminary version of this type of screening, and as mentioned, there are now available some cognitive studies of the donor screening questionnaire.

This was first done at the Red Cross through the use of focus group studies by Dr. Orton, et al., and most recently through the

National Center for Health Statistics, which we will be speaking about their studies today.

[Slide.]

I wanted to mention briefly that there is a draft guidance in the field right now for comment. It is entitled "Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires."

One particular component of this, which think you will hear discussed a little bit in the other presentations, is that this draft guidance contains FDA current thinking that self-administered questionnaire processes should not be used for brand-new blood donors at a blood center with the exception of audio, computer self-administered interview.

This is for a couple of reasons. Number one, the studies mentioned earlier by Joe Catana and Turner, and others, have shown that an audio component is important to getting individuals to recognize the content of the question.

There are also concerns about literacy, not the basic levels of whether someone reads or not, but somewhat different levels of functional illiteracy and scientific illiteracy. I think it

is a fair assumption that not every donor, reading every question, understands the full content of that question.

Also included in the guidance are a recommendation for secondary measures at the blood collection centers to assure donor understanding, provision of adequate instruction assistance and quality assurance assessment related to the qualification process, that new or modified questions which come along should, in fact, be highlighted in some way or else administered by staff interviews, so that repeat donors who have seen this questionnaire many times have new questions pointed to them, so that they can look at them with special attention.

There are special preventions in the guidance for audio, visual, and CASI technology as it grows and it harmonizes with the new final guidance for deferrals related to potential variant CJD exposure.

[Slide.]

The draft guidance was announced in the Federal Register in April and comments are due June 21st, 2002, and we look forward to receiving those comments.

[Slide.]

With respect to today's topic, the Uniform Donor History Task Force has been organized by the American Association of Blood Banks, but contains members from numerous industry and agency representatives.

Within the FDA, Judy Ciaraldi has really been I think the primary representative from the regulatory side. Robin Biswas and John Lee participated early on in the task force discussions, and Sharyn Orton and I were also members of the task force until we joined FDA and when we became liaisons to the task force.

[Slide.]

The subject was discussed just about a year ago at the Blood Products Advisory Committee, and this was kind of an interim discussion, no questions, related to the approach that was being taken by the task force and the way that the FDA would review the product of the task force.

The committee made comments about the cognitive s studies proposed, the questions proposed for elimination, the transfer of some questions out of the questionnaire itself to the written educational information.

The committee also commented on some elements of the redesigned questionnaire, and the questions were somewhat varied, but very helpful, but overall, the support for the UDHQ Task Force effort was quite strong.

Importantly, the committee strongly discussed and recognized the need for funding related to this program, and fortunately, the National Heart, Lung, and Blood Institute generously provided some funding, so that the National Center for Health Statistics could participate in the cognitive studies. I think this really helped provide definition to this whole project.

[Slide.]

The speakers for this subject, next will be Dr. Joy Fridey, who is in fact the chairman of the task force and the senior vice president for Medical Affairs at the Blood Bank of San Bernardino.

Following Joy will be cognitive studies presented by Dr. Paul Beatty at the National Center for Health Statistics. FDA's own Judy Ciaraldi will be providing an FDA perspective on the review of the document submitted by the task force or the

current status and some of the thoughts, and then finally, I will come back with a couple of questions for the committee, which I will just introduce right now.

1. Does the committee believe that the revised Uniform Donor History Questionnaire proposed by the task force is suitable to screen donors of allogeneic whole blood and blood components for transfusion?

2. What additional comments does the committee have on: (a) The validation process of the UDHQ, and (b) the specific content of the UDHQ questions.

As you consider these questions, I just want to present very clearly that these questions presented are designed for the whole blood and blood component donors, and not the source plasma donors. As you will hear from PPTA, that is a somewhat different process. It overlaps quite a bit with the current proposed questions, but will differ a little bit, so we are primarily talking about whole blood donation with respect to these questions.

Thank you.

DR. NELSON: Thank you, Alan.

Joy Fridey.

Overview of AABB Task Force UDHQ Project

DR. FRIDEY: I would like to thank Dr. Smallwood, Dr. Epstein, CBER, and the Blood Products Advisory Committee for the opportunity to be here today.

Almost exactly one year ago today, it was June 14th, I stood before this committee to present a proposal for modifying the Blood Donor Screening Questionnaire, and, in fact, by that time we already had a working draft of the revised questions that were submitted to the BPAC.

At that time, you provided insight and ultimately endorsed our approach, and today, I am here to give you a final report on the work that has been done over the past year and to ask for your input on the new donor screening materials.

[Slide.]

Briefly, I will give you an introduction and background of why we launched this project at all, what our redesign goals were, the task force members and resources, I think it is important for you to know who these people were, who are making these kinds of decisions; the new documents, there is not just one, there are actually several that we

have submitted to the FDA for review and that you all have copies of; and then the efforts that we undertook to communicate with the various stakeholders and obtain their buy-in.

[Slide.]

This has truly been an exceptional project. The FDA came to the AABB, recognizing that there were problems with the questionnaire, and asked the AABB to head up a project to redesign the questionnaires.

There has been extensive collaboration by numerous stakeholders. We basically pulled in everyone that we thought should be at the table. There has been a tremendous commitment on the part of the task force. This has been a two-year project. People have stayed with it, stayed involved.

We have used a groundbreaking approach to redesigning and designing the blood donor screening questionnaire. It is not groundbreaking from a survey design perspective because this is what is done all the time, and we have simply taken those principles and applied them to the donor screening context, and we believe that we have obtained support and buy-in from the constituents.

[Slide.]

Dr. Williams has already discussed the importance of screening blood donors through questioning. The first nationwide questionnaire was advocated by the American Association of Blood Banks in 1953.

Since that time, many questions have been added, and by the early nineties, it literally was a mishmash of non-chronological questions, quite confusing to donors, and the Blood Centers of California developed a model questionnaire that had been simplified and questions put in more appropriate order.

This was picked up by the AABB, which then requested FDA input and approval, and it became known as the AABB Uniform Donor History Questionnaire, and the BPAC members have copies of that very interesting document, which hopefully will go the way of the dinosaurs in their packet.

[Slide.]

Now, some evidence that there have been problems with the questionnaire, we find in the FDA blood product deviation reports. In 2001, nearly 80 percent of deviation reports related to errors in the donor qualification process. Also, the

American Association of Blood Banks surveyed many blood centers around the country in 2000 to find out what they were doing in terms of screening.

Now, everyone was complying with the AABB and FDA guidelines, but there was considerable variation in the format, methods of administration, and the education materials that were used.

[Slide.]

Currently, the problems that donors, blood centers, the FDA, all of us agree on, is that the questionnaire is very long, extremely complex--and I will talk about that in second--uses medical and scientific jargon, which frankly, most people can't relate to or understand, it uses non-chronological time frames, repeatedly questions donors about events that could never have been repeated if they had once already said no to them, and there has not been an abbreviated version for frequent donors with the exception of one blood center in the Midwest.

[Slide.]

The questionnaire has more than 70 informational items. Some of them are a single item question, but half of the questions are either compound questions or contain multiple items. Now,

this does not include the demographic information. That is another information set that we ask of donors.

[Slide.]

This is an example of compound, multi-item question. It is one of the worst ones. "In the past 12 months, have you had a tattoo applied," et cetera. You can read it for yourself. A donor has to sit down and wade through this and come up with an appropriate answer.

[Slide.]

Another complex question, "Female Donors: In the past 12 months --", et cetera. You can read it. This is a very complicated question, and not every question is this bad, but this is just to give you a flavor of what donors are dealing with.

[Slide.]

From a scientific perspective, however, the most fundamental problems are there has not been input from survey design experts in the designing questions. Questions do not even follow the basic rules of survey design. There are too many items in them, and they are too complicated, and there, by and large, has not been any kind of evaluation for comprehension and usability.

[Slide.]

So, we have to ask, how accurate and complete is the information provided by donors, and is there a safety issue. Now, I am not at all dismissing the questions we have been asking for years in terms of their ability to provide safeguards.

What I am saying is that I think that we can do it better and enhance at least safety and we have to ask do the complexity and length serve as disincentives to donors. This could raise supply issues.

[Slide.]

As a result, the project was launched at the initiation of the FDA in June of 2000, two years ago, and off we went.

[Slide.]

Now, a couple of months after that, in October of 2000, there was a joint AABB and FDA workshop to help provide suggestions on how the task force might attack this project. These were recurring themes of that conference.

One, there had to be a balance between safety and availability, something I have already alluded to. The questionnaire and the questions

had to be simplified. There needed to be a renewed emphasis on donor education because this is such a complicated process.

The actual mechanics of drawing a unit of blood are not complicated, but the screening process has. Validation or at least evaluation for comprehension of any questions that are asked of donors, an abbreviated version for repeat donors, and the need for blood centers to move towards CAI, computer assisted interviewing. Software right now is out there, it us undergoing refinement. A few blood centers have used it, but by and large, the majority of blood center will continue for the next few years at least to use the manual approach that is in place.

[Slide.]

So, we have five overall goals, and these are what they are.

1. To simplify the wording and questions mainly to improve donor comprehension, but also to enable self-administration by the donor.

2. To evaluate changes using accepted and appropriate research methodologies, which I will discuss in more detail.

[Slide.]

3. To reformat the questionnaire, make it easier for the donors to follow and answer to.

4. Develop an abbreviated questionnaire for frequent donors, and define what a frequent donor is.

5. To standardize the donor educational materials.

[Slide.]

Our objectives in selecting the task force members were twofold:

1. We wanted to represent, we wanted to throw out a wide net and represent as many constituents as possible from government, from industry, which would be blood centers, plasma centers, and the public, which would be blood donors and recipients.

2. Obtain the appropriate methodological expertise. We felt this was crucial to deliver a product that was scientifically sound.

[Slide.]

I am not going to read all of these, but we clearly had included the FDA and the CDC, the Department of Defense, the industry organizations - AABB, America's Blood Centers, which they are independent of the Red Cross and collect about half

the nation's blood, Plasma Protein Therapeutics Association.

We also had two research survey design specialists, one, in fact, who was a BPAC member last year, and the other one was from the National Center for Health Statistics, Paul Beatty. We will hear from him today.

There also was someone to represent the consumer, a public member. This professor is an ethicist. We had a statistician, and our neighbors to the north, who struggle with the same kinds of issues that we do, also were represented.

[Slide.]

This was work that was done predominantly on a volunteer basis. We did it through literally dozens of conference calls, hundreds of e-mails, three, face-to-face meetings. The members who participated volunteered their time and their talents. There were several pro bono projects that were done. Jerome Holland Laboratories sponsored the focus groups, Dr. Sharyn Orton did those.

We needed some data tabulated. John Boyle, the former BPAC member, his company tabulated those data, and the AABB provided administrative support and funded travel for the

members. We didn't go to Tahiti or some place like that, we came here to this area.

NHLBI provided funding for the NCHS Cognitive Evaluations. This was through Dr. George Nemo's efforts and also Dr. Barbara Alving. But I want to make a strong point here, that funding was not available for any other aspects of this project from government agencies or other entities.

[Slide.]

Now, I am going to focus on the new screening materials. You heard about these last year, but I want to tell you what we have done and where we are now with them - the full-length questionnaire, the abbreviated questionnaire for frequent donors, the pre-screening educational materials, and the user brochures.

[Slide.]

The full-length questionnaire is a questionnaire for first time and infrequent donors. It contains all of the FDA-recommended items and AABB-required items.

[Slide.]

The goals of revision are to simplify and to re-format.

[Slide.]

We basically took a very simple approach to simplifying. Taking into consideration patient safety and donor safety, we asked two questions: what is the target information of the question that we are evaluating and working on, and what is the simplest way that a question can be stated?

[Slide.]

We wanted to avoid rarified phraseology. We wanted to break down most of the compound questions and multi-item questions. We wanted to find a better way to get at the medications that the donors are taking, specifically those that are FDA-deferrable medications, and focus on the most germane of health conditions.

[Slide.]

Our thinking was that if we have better donor comprehension that there will be more relevant information and accurate information provided by the donor, there will be fewer errors and better information capture, and hopefully, improved safety.

[Slide.]

This is probably the most important slide of the entire handout because it shows the very iterative approach that we used.

First, we took the full-length Uniform Donor History Questionnaire, the AABB one which the committee members have. We divvied it up into major sections - donor safety issues, patient safety issues, infectious diseases, and a survey design expert, Dr. Boyle, worked with the subcommittees who looked at each question and asked those two fundamental things, what is the point of asking this question, what is the target information, what is the simplest way we can ask it.

When this was done, the entire task force reviewed that material and made some further adjustments. At this point in time, we had a working draft and felt that it was important for the FDA to see what we were up to and to provide us with input.

So, we sent a letter to CBER in May of last year, which contained the suggested revisions. At the same time, the focus group evaluation started, the task force refined the questions further based on that input. Then, cognitive evaluation was done by the NCHES.

We looked at that information, it was a 40-some page document that we considered when we

were making our final revisions, and finally came up with final wording and questions.

Along about September, CBER provided us with a very detailed and helpful letter, which expressed concerns and insights and suggestions for our proposed draft of the questions, and we integrated those comments in our final products.

[Slide.]

Just a few words about the focus groups. The focus group methodology was based on a methodology that was used for a published peer review article that appeared in Transfusion, written by Drs. Orton and Virvos in 2000, but there were four groups convened specifically for task force research purposes. There was a nice demographic mix.

The participants were eligible non-donors. These are people who had never donated blood before, but would qualify to donate blood, virgins, if you will. They were presented with the questions that had been reworked and asked for feedback and alternative wording.

[Slide.]

The National Center for Health Statistics then performed cognitive evaluations. I am going