or investigational new drug applications.

[Slide.]

INDs.

[Slide.]

I am just going to give you a quick recap here on INDs because of time constraints. We have recently promulgated on March 26, 2002, a final guidance document for the submission of electronic investigational new drug applications, commonly called an IND.

This guidance can be found on our web site. It features pretty much the BLA thought and philosophy and functionality, but it has a twist. The twist is that there are five individual folders that are of tremendous importance, and they are analogous to the review disciplines.

Those folders are Administrative, CMC, Pharm Tox, Clinical, and everybody has to have an Other because you never know what you may have to deal with, but those four folders, being analogous to the review disciplines, individuals will be challenged to bring forward the information in the appropriate folder, so you not only have the roadmap file, which delineates the entire history of the correspondence, but if a reviewer so

desires, they can go to their folder, which will never change or move, which will have all the amending information tagged by amendment number.

To keep the folder static, we have implemented a new naming convention, so if you have files coming in your second amendment, that amendment will have the prefix 0002, the contents as far as the file name, .PDF, .XPT for assess transport file. They will be able to search these file folders.

They will be able to use submission indexes, and for the clinical review area, which has the majority of the amending submissions, we have the highlight called a Cumulative Table of Contents for protocols and for adverse events.

That Cumulative Table of Contents is the same roadmap file within the clinical folder, but only delineating protocols and revised protocols and adverse events.

This way, if a clinician needs to quickly see the status of a protocol on-line, they can go through the hierarchy, find this Cumulative Table of Contents for protocols, and click on that, pull up the appropriate protocol, the same thing for the adverse events.

I thank you for your time and do you have any questions?

DR. NELSON: Any questions?

DR. ALLEN: I have got three or four questions, which I will just do one and let you respond to it.

I think this is a tremendous effort and applaud the effort to move in this direction. I hope it goes well. I was talking with one person who is working on some of the AIDS vaccines, and I know that that is a separate area, but he was indicating that their submission is going to be somewhat higher than the Statue of Liberty. I think it was 344 feet of paper. So, this is the right way to go.

What type of secure backup arrangements do you have in case there is a catastrophic occurrence with the servers or the primary servers where these are kept?

MR. FAUNTLEROY: Well, naturally, we had redundancy as far as when the message comes in, we are archive the message in a naive state. Then, we run it through the process, and we archive it in a different set of servers.

Joe, if you would care to elaborate on

that further, because he is the IT lead.

MR. MONTGOMERY: Actually, as Michael said, we are archiving the messages as they come in. We are staging those in the area that the administrators can get to, and we are actually maintaining multiple copies of the actual submission itself, archiving the original copy, which is one of the standards we have to abide by.

We also forward on the message into the Electronic Document Room as the final repository for it, and that is where our reviewers can access it.

DR. ALLEN: Second, I noticed you described earlier on that we are using HTML format, and then I noticed in one of the later slides, you are talking about PDF.

Are you using both?

MR. FAUNTLEROY: Yes. HTML in the web interface. PDF is the document standard for text presentations. The assess transport is the standard for the data presentation. We do accept ASCII files for the pharm tox information in the BLA because of the software program we utilize for the analysis of pharmacodynamic and bioequivalence data, which is WinNonlin.

DR. ALLEN: When the reviewers go in, they can add comments or make notes as they are reviewing, or what is the process for their feedback?

MR. FAUNTLEROY: Two ways of accomplishing it. They add their annotations to the file on-line and then save their annotations if they so desire, as an PDF file, and bring that to the PDF iteration that they are reviewing, or most commonly, as we instruct most reviewers to do, is download the file, a copy of it, and do their annotations, copy, paste, whatever they need to from that file.

The reason we suggest this strongly to reviewers is that the file on the server is read-only, and so it is an unadulterated copy of the submission at all times.

DR. ALLEN: Final question. Is there a mechanism for keeping a permanent record of everyone who accesses the documents and modifies or adds comments as part of the review process?

MR. FAUNTLEROY: In our 3.0 release of the EDR, we will have a fully robust audit trail that will allow us to know what reviewer touched what part of the file, how long they were there, and what they did.

DR. ALLEN: Thank you.

DR. HOLLINGER: Can I just follow up on one of Jim's questions? The backup, is the backup also off-site as well as on-site in several areas, or just one off-site or what?

MR. MONTGOMERY: We have an off-site location where we are sending tapes, as well. We are backing them up on archived media, DOT media, and then we are sending them off-site, so we do have an off-site location.

DR. HARVATH: I wanted to ask about the adverse event reporting because, as you know, that is a major issue with many investigators, especially studies involving oncology patients, and the National Cancer Institute has developed the ADEERS reporting system, which is already I believe readily accepted by FDA, at least in the Oncology Group.

So, will this be fully integrated with that system, so that one can use the adverse event reporting systems through ADEERS, and have that accepted with the format that you are using?

MR. FAUNTLEROY: We are not integrating it into the IND submission. Now, if you want to send us the electronic file in the appropriate PDF

version, we will readily accept it as an adverse event report, but as far as integration where a reviewer through a link submitted would go out from our server site and access that database, that will not happen. That is a real term security issue for us.

DR. HARVATH: Is FDA thinking of having a more consistent form for reporting adverse events, is there any movement in that area that you have heard of?

MR. FAUNTLEROY: Not to date. When I do hear of it, we will move more towards that standardization in line with the additional policy decisions.

DR. FITZGERALD: I realize that this isn't a medical device, but I just wondered if, since you are designing this, and FDA, are you planning to internally comply with your own 510(k) requirements.

MR. FAUNTLEROY: Well, at this point in time, I can't tell you if we plan to comply because I am not familiar with the 510(k) requirements. I have to learn then to write the guidances and to get the feedback from the reviewers, so we are complying with our 21 CFR requirements, 21 CFR 11

requirements, which I would imagine are just as stringent easily.

DR. NELSON: Any others?

Thank you, Mr. Fauntleroy.

We are at the coffee break period, and we will return at 11 o'clock.

[Break.]

DR. NELSON: We are switching topics now. For the next bit, we will be discussing Standards for Recovered Plasma. As introduction and background, Elizabeth Callaghan from FDA.

I. Standards for Recovered Plasma

Introduction and Background

MS. CALLAGHAN: Thank you, Dr. Nelson.

My name is Elizabeth Callaghan and I work in the Division of Blood Applications.

Because of the concerns for the safety, purity, and potency of products made from recovered plasma, FDA is asking the committee's advice on developing standards for the product. I would like to give you a brief summary of some of the issues that FDA has seen regarding recovered plasma.

[Slide.]

Recovered plasma is a by-product derived from whole blood collection and used for further

manufacture into injectable and non-injectable products.

It is distinguished from source plasma by the mode of collection and by the requirements for testing, storage, pooling, dating, and labeling.

[Slide.]

Source plasma is collected by plasmapheresis, either manual or automated, and is frozen immediately after collection. Recovered plasma, on the other hand, may be separated from individual units of whole blood by aseptic techniques up to five days after expiration or obtained from fresh frozen plasma collected by apheresis that has expired.

[Slide.]

Recovered plasma has no expiration date. Source plasma, on the other hand, has a 10-year dating period.

Both recovered plasma and source plasma are used for further manufacture into the same final products, IVIG, Factor VIII, Factor IX, albumin, IVD components.

[Slide.]

There are four cites in the Code of Federal Regulations which pertain to recovered

plasma. The first, 606.100(b)(18) is under the Standard Operating Procedure section. It says that if you manufacture recovered plasma, you must have procedures in place that detail the separation, pooling, labeling, storage, and distribution of the product.

[Slide.]

606.121(e)(5) is under the Labeling Section for blood and blood components. It says that recovered plasma labels shall include: (i) In lieu of an expiration date, the date of collection of the oldest material in the containers. (ii) The statement "Caution for Further Manufacturing Use Only" for recovered plasma being made into injectable products; or "Caution for Further Manufacturing into Non-injectable Products Only" is applicable.

[Slide.]

(iii) continues with the labeling requirements, and it says, For recovered plasma not meeting the requirements for manufacture into licensable products, the statement "Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act."

This is usually for products such as

chemistry controls for chemistry analyzers.

[Slide.]

606.160(b)(2)(iii) is in the Records Section, and it says that blood establishments must have records of separation and pooling of recovered plasma.

606.106(d) is everybody's personal favorite, I am sure. When there is no expiration date, the records shall be kept indefinitely.

[Slide.]

To allow for recovered plasma to be shipped in interstate commerce because it is an unlicensed product, the manufacturer of the recovered plasma must have a short supply agreement with the consignee. These short supply agreements should stipulate the conditions for production, storage, and shipping of the product that is agreed upon between the manufacturer of the recovered plasma and the consignee who is buying it.

[Slide.]

Some of the compliance issues associated with recovered plasma include: misbranding of plasma units; lack of shipping and disposition records; inadequate quarantine and destruction of unsuitable units; shipment of untested,

therapeutic, or autologous units.

[Slide.]

Lack of short supply agreements; lack of product quality and consistency due to storage, temperature, and preparation failures; non-uniform labels - registered facilities do not have to send their labels to CBER for review, so the labels can be very inconsistent, and not give the information that we would require if we had reviewed them. Obviously, that leads to labels that are incomplete or inaccurate.

Sharon O'Callaghan and Kay Lewis from the Office of Compliance will give you further information following my presentation about compliance issues.

[Slide.]

Some of the manufacturing issues associated with recovered plasma include:

Lack of consistency in Standard Operating Procedures. Registered facilities who make recovered plasma do not have to even send their Standard Operating Procedures in to FDA for review, and being that there are no standards, there is no consistency in what people are putting into the SOPs for making the product.

Complexity of the donor screening procedures. Recovered plasma should be collected from donors who meet all normal donor suitability requirements. Unfortunately, autologous donors in a lot of cases do not meet this criteria. In addition, they are frequently screened with abbreviated questionnaires, and if this happens, you shouldn't be using this product to make recovered plasma for further manufacture into injectable products. Keeping track of which units you should or should not use can be a major problem in logistics.

Infectious disease testing requirements. Source plasma and recovered plasma have different disease testing requirements. By virtue of the fact that recovered plasma is made from whole blood units, they are tested for all required infectious disease markers. Source plasma is not required to be tested for hepatitis B core antibody or for HTLV-I or II. These differences in testing can create some questions.

There are minimal labeling requirements, as you can see from the regs that I presented in the previous slides. Storage and shipping requirements defined under short supply agreements

are not always consistent with each other, and if a manufacturer has more than one short supply agreement with several manufacturers, he might have a hard time keeping track of who needs what and their short supply agreement, and giving consignees inappropriate units.

[Slide.]

To allow for the manufacture of a more consistent product, FDA is considering developing standards governing the manufacture and shipping or recovered plasma.

In addition, voluntary standards or recovered plasma are under discussion within the blood industry and FDA will need to decide whether to adopt industry standards through agency guidance or rulemaking.

Would you like me to go through the questions? Okay.

[Slide.]

The first question we have is: Should FDA develop specific product standards for recovered plasma?

[Slide.]

If yes, should the standards for recovered plasma include:

(a) Negative screening test results for anti-hepatitis B core and for anti-HTLV I/II?

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

(c) Labeling requirements similar so source plasma to distinguish appropriate use for manufacturing tin injectables versus non-injectables based on the preparation and storage conditions?

[Slide.]

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

DR. NELSON: Thank you. Questions?

The next presentation, also by the FDA, is Sharon O'Callaghan, and I guess she is not related to the first speaker, only by name, the same county in Ireland, I guess.

Presentations

MS. O'CALLAGHAN: No, there is a difference, there is an O in front of my name.

I am in the Office of Compliance and Biologics Quality in the Division of Inspection and Surveillance. I manage the Biological Product Deviation Reporting System in the Office of

Compliance. I wanted to present some information and data from the reports that we received in FY 2001, that involved recovered plasma.

These are not my slides. This is another presentation that I do, that some of you probably have seen.

Does everybody have the handouts then? Okay.

DR. NELSON: Is it feasible to do this?

MS. O'CALLAGHAN: I can provide you with the handouts I guess later. It is going to be a little more difficult, but we can manage this I think.

The data that I wanted to show really depicted the number of reports that we received in 2001, almost 24,000 reports, and of those, about 30 percent of them involved products of recovered plasma.

The most frequent type of information or type of BPD report that we received is post-donation information, and that is really the one that is representative of the recovered plasma issues, as well.

The most frequent one involving recovered plasma is travel to CJD risk areas especially with

the new implementation of the CJD guidance recently.

Also, a number of reports are submitted related to a donor having a history of cancer, donors receiving tattoos, history of disease in surgery, IV drug use, and male-to-male sex.

In all of these, not only is recovered plasma reported, but also the other products, as well, but one of the things that we have noticed with the recovered plasma is that there has been a lot of inconsistencies among the establishments as far as the action that they are taking on the product when they get this type of information.

For example, with the history of cancer, FDA does not have requirements for history of cancer, but there are some standards with AABB that identify history of cancer issues, but there are some firms that are recalling plasma based on the fact that they recalled the red cells or platelets or other products, some because it is recovered plasma, they are not taking any action.

That is true in some of the other areas as well, like under donor screening is another area that we received a number of reports involving recovered plasma where the donor history question

was incomplete or incorrect.

That could range from any of the high-risk behaviors such as tattoos, male-to-male sex, that type of thing, to the history of disease, history of surgeries, history of cancer. Also, donor-giving information which warranted deferral and the donor wasn't deferred, for example, taking medication, again history of cancer and history of disease.

These seem to be the most problematic areas as far as what the establishments are supposed to do with the recovered plasma. Also, another area that we have seen a number of reports is under quality control and distribution, specifically related to unsuitable units being distributed where the red cell was clotted or hemolyzed, and there seems to be some confusion or discrepancies between whether or not the recovered plasma is really affected by having the clot in the red cell.

Some places, like I said, will recall those products and get them back and destroy them. Some places will say because it's recovered plasma we will just go ahead and let it go and not notify anybody.

In other cases, the notification for recovered plasma is based on what the customer has requested. In some cases, the plasma fractionaters may say only notify us of these particular situations, anything else we don't want to know about, which makes it very problematic for the blood establishment if they have multiple customers that they have to try to keep track of, when they are going to notify, when they are not, and that type of thing.

So, without having any numbers, that is really the point that I wanted to make here, was that there is this inconsistency, and based on the action that the firm takes is going to depend upon whether or not we would consider it for recall, which Kay Lewis is going to talk about, you know, if the firm doesn't take any action, then, we are not going to classify that, because there is no action to classify, as I recall.

I will let Kay do her thing, hopefully, her slides are here, unless you have questions right now. I don't know whether it is better for Kay to present and then we can handle questions together.

DR. NELSON: Questions? Mary.

DR. CHAMBERLAND: A couple. I was wondering, and maybe it was on your handout, are you able to do a side-by-side comparison between recovered plasma and source plasma with respect to postdonation information issues, and are there clear differences between the two in the kind of information that comes back. That was my first question.

MS. O'CALLAGHAN: One of the biggest differences with source plasma and whole blood collection in general, is that there is a lot more tattoos and piercings, there is a lot more incarcerations, where in the whole blood industry, there is more travel to the CJD risk areas and travel to malarias, which the malaria travel doesn't impact on the source plasma.

DR. CHAMBERLAND: My second question was you mentioned one of the problems is the inconsistency from blood collector to collector in terms of how they deal with postdonation information like history of cancer or some of these issues.

In the source plasma industry, is there more uniformity as to how this postdonation information is addressed? What do they use in

terms of assist in decisions?

MS. O'CALLAGHAN: I think, for the most part, the source plasma industry is pretty consistent across the board as to when they are going to notify and retrieve products, where we really don't see that consistency in the whole blood industry.

You know, the whole blood industry will be more consistent with red cells, platelets, even FFP in most cases, but it is the recovered plasma that varies.

DR. CHAMBERLAND: Is that something that is done out of their professional organization, you know, do they promulgate some sort of standards or guidance, whatever you want to call it, but is it published information about how to deal with postdonation information?

MS. O'CALLAGHAN: I don't know if they have. I think there is other people that are probably in a better position to answer that, but just from the reports that I see, they are pretty consistent across the board, you know, from even one firm to another, making sure that they are notifying when they need to.

DR. NELSON: Actually, the recovered

plasma, really, there are two different categories. One is the autologous and the other is the recovered. You mentioned that there is a substantial difference in screening, and I understand that, but would it be an option of the committee to consider those as two different categories of recovered plasma, because I think they are.

MS. O'CALLAGHAN: A number of years ago, we did see a fair number of reports where the recovered plasma from an autologous donor who didn't meet allogeneic criteria was released. We haven't really seen that in the past, I would say probably the past two or three years we haven't seen that, so I don't know if other things were put into place to prevent that from happening or why they are not reporting those, but, yes, that might be--because there are some things where it wouldn't really affect even though the donor wasn't screened completely because of being a autologous donor, that may not impact on the recovered plasma. It might be possible to separate those.

Anything else?

DR. ALLEN: Is a question such as a prior history of cancer, a concern from the perspective

of donor safety or of infusion transfusion recipient safety?

MS. O'CALLAGHAN: It is probably a little of both. Like I said, FDA has not required screening for cancer, but industry has accepted that as deferral mechanism, because if they accept a donor who has a history of cancer, it would be something that would be reportable. History of cancer is just another whole ball of wax anyway because there are so many varied opinions about how that type of thing impacts on products.

DR. ALLEN: I realize that there are demographic differences between source plasma donors as a group and your blood recovered plasma donors as a group.

Is there any evidence that a requirement, such as the periodic physical examination by a physician, that that increases the safety or would be something that would be necessary in any way for blood donors? I mean it hasn't been, it seems to have worked well, but what is the FDA's thought on that based on information that might be available?

MS. O'CALLAGHAN: Well, based on the information that I see through the BPD reports, in the source plasma industry, when the physical is

being performed, that is typically where the postdonation information is obtained, where the tattoos and piercings are identified, and even though the donor is being asked the same question every time, the donor is not providing that, and it is only until they get to that physical that they match up the body map and see that there is new tattoos and new piercings, and then the donor will say, oh, I guess I did have that, you know, I forgot to tell you.

In the blood industry, there doesn't seem to be a point in time in a donor's history where this information will most likely come out. So, that is big difference in the source plasma.

DR. DiMICHELE: I just wanted to ask a question of clarification. You said that certainly donor deferment issues were different for recovered plasma and source plasma. Based on what you said, though, they seem to be a little bit more stringent for recovered plasma, which comes from whole blood components, than they are for source plasma, is that correct?

MS. O'CALLAGHAN: More stringent meaning?

DR. DiMICHELE: In other words, there are more deferment criteria potentially for recovered

plasma than there is for source plasma, is that not correct?

MS. O'CALLAGHAN: Well, for example, like the malaria deferral would apply in whole blood, but not in source plasma.

DR. DiMICHELE: Right. Certainly, some of the screen tests, like you said, for hep-B core and HTLV-I/II, et cetera.

MS. O'CALLAGHAN: And there is HBC and HTLV-I.

DR. DiMICHELE: So, the issue in recovered plasma, then, is not the stringency of criteria for donor deferment, and even the compliance issues are really donor deferment compliance issues in general, correct?

MS. O'CALLAGHAN: Right.

DR. DiMICHELE: So, the real issue that we are discussing here, just so I can put it in some sort of frame of reference, is that where the lack of standardization is and where the potential for error is, is that once that plasma is recovered, that is where you go into a gray zone in terms of what goes into what and where it goes from there, is that correct?

MS. O'CALLAGHAN: Yes, and I think that is

what Elizabeth pointed out, with the labeling differences and at any point--

DR. DiMICHELE: Storage differences and what have you.

MS. O'CALLAGHAN: Right. Once it becomes a recovered plasma unit, then, all bets are off.

DR. DiMICHELE: So, it is more processing issues.

MS. O'CALLAGHAN: Right.

DR. DiMICHELE: And the potential of stability of certain components vis-a-vis processing issues rather than infectious issues.

MS. O'CALLAGHAN: Yes, I think so. I think that is a fair statement.

DR. DiMICHELE: Thanks for that clarification.

DR. SIMON: Since the cancer issue has been brought up, I just wanted to point out the FDA did have a conference on this several years ago, and I think Elizabeth Callaghan organized it, and I believe there was a pretty strong consensus that it was not a safety measure of significance either for the patient or the donor.

So, I don't think that these postdonation reports need to be of concern other than the issue

of inconsistency.

DR. NELSON: There are very few proven issues on this, but there are like 12 percent of cancers are related to infections, many of which aren't screened. I would say HHV-VIII is perhaps one example, and, you know, whether or not cancers that have not been identified as virally related or infection related, in fact, are. I am sure we will find more examples in the future.

So, there may be some circumstances where deferral of a patient with cancer might be appropriate, I don't know.

DR. EPSTEIN: Toby, I would agree that the finding of a previous workshop was that there was little direct evidence for transmission of cancer by transfusion, however, FDA's point of view has been that the scientific question is unresolved, and we have recently developed a funded contract with the NCI to do a major epidemiologic study to get the answer.

DR. LEW: One of the things I was impressed upon when I went through at least the literature that was provided on this issue, is that I am having a hard time trying to figure out exactly some of the differences that have been

brought up through the questions here in terms of what truly are the infectious disease issues, because I don't know what the different questions are exactly for recovered plasma, source plasma, and the different types of recovered plasma.

There is clearly a lot of different ways of collection and also some things that could have to do with manufacturing and processing that are different, that may have an effect.

A table might be useful just to look at those differences because when I try to answer the questions, each question, I have other questions to ask before I can answer it.

MS. O'CALLAGHAN: So, what you are looking for is kind of a comparison between recovered plasma and source plasma, a listing for each one.

DR. LEW: Right, all alluded to saying, well, there is different questions that we ask the donors before collection, but I don't know exactly which questions are different, and is alluded to there is different infectious disease testing, but it doesn't say exactly which.

Also, you just brought up today in passing the different populations for these types of collections. I think all those things are very

important in answering some of these questions.

MS. O'CALLAGHAN: Okay.

DR. SIMON: We can give some information. The suitability criteria set by FDA and the ones that are different, ones specifically applied to red cells or platelets, so, for example, plasma donors wouldn't be asked about aspirin, which is an issue with platelets, or about malaria because it is an issue with red cells, and then the other major differences that the plasma donors can donate with greater frequency and have these be annual physical examination and are checked by serum protein electrophoresis every four months.

Then, the testing differences, the tests that aren't required for plasma safety, particularly HTLV-I and II because of the white cell transmission, and then core has been omitted because of the desire to have hepatitis antibodies in the plasma.

DR. NELSON: Are there any issues beyond the infectious disease issues related to the storage, that might make recovered plasma different in terms of whatever it might be made into, would the storage affect its suitability?

DR. SIMON: My understanding is, because

of the short supply, then, the manufacturer would set the storage requirements, isn't that correct?

MS. O'CALLAGHAN: Yes, that is what the short supply agreement would lay out with the manufacturer that they would be sending the recovered plasma to.

DR. SIMON: In my mind, the advantages of moving to standards would be to eliminate the short supply and have a very well established set of standards that would apply, that everybody would understand, would be uniform.

DR. DiMICHELE: Given that you brought that up, I was just wondering, for some of the newcomers who don't understand this very well, is there any reason for us to understand the short supply agreement a little bit better than certainly people like me do?

MS. O'CALLAGHAN: Elizabeth, do you want to explain that? You are probably in a better position to do that.

MS. CALLAGHAN: Short supply has been a major boondoggle since I have been at the FDA. What it says essentially is that the consignee of the product that is in short supply, and if you want to consider recovered plasma in short supply,

sets the standards that the manufacturer of the product will adhere to, so that he can sell the product to the consignee.

The short supply agreement should outline how the product is processed, how it is stored, how it is shipped, and the consignee oversees this to make sure that the manufacturer of the recovered plasma is making the product according to the specifications.

FDA has no control over any of these, and a lot of times does not even see the short supply agreements. That is why we are concerned about shipping and storage temperatures and lack of consistency because whatever the manufacturer and the consignee agree to is whatever they want to do.

Does that make it any easier?

DR. DiMICHELE: Why has this product been considered in short supply just from a historical perspective?

MS. CALLAGHAN: Because that was the only way we could get a nonlicensed product to be shipped in interstate commerce.

DR. SIMON: Just to clarify, so that if we set standards, then, that would allow you to have the product licensed, is that correct?

MS. CALLAGHAN: Well, we could either just set standards and keep with the short supply agreement, or we could, in fact, make it a licensed product, in which case the short supply agreements would disappear.

DR. SIMON: I mean, for example, at one time, there was a fair market for so-called room temperature plasma, and you didn't have to have the plasma frozen. I think that may have disappeared, but there was a lot of concern about the microbiological impact of that, so it has been something that hasn't had the same stringent requirements in terms of things like storage, temperature.

MS. CALLAGHAN: Right, hence, the lack of consistency.

DR. SIMON: Right, and that has been the case with source plasma, because it's a license product, so it has been there.

DR. KLEIN: But I don't think anybody knows, Toby, as to whether it has gone away or it hasn't gone way, because those are agreements between institutions and their fractionater.

DR. ALLEN: Two other questions that come up. When a blood center collects recovered plasma

and ships it to a fractionater for processing, I have always been under the assumption that it has all been mixed in together in huge lots, that the lot will contain both recovered and source plasma.

Is that correct?

MS. CALLAGHAN: That is my understanding, too, but perhaps the fractionaters could answer that question better. Do you mix source plasma and recovered plasma together?

DR. WHITAKER: In general, they are not mixed.

MS. CALLAGHAN: Okay.

DR. ALLEN: That is interesting. The second, with recovered plasma, if a unit of blood, let's say is found to be core antibody positive, the cellular components obviously would be discarded.

Is the plasma still then acceptable for recovered?

MS. CALLAGHAN: Yes, it is.

DR. ALLEN: I had just always made the assumption that the whole unit was discarded, but the components still might meet one criteria, but not the other?

MS. CALLAGHAN: Right.

DR. NELSON: But the processing and viral inactivation procedures are the same for recovered and source plasma, if they are kept separate?

MS. CALLAGHAN: Yes, they are.

DR. NELSON: They undergo the same process.

Kay Lewis is next, FDA.

MS. LEWIS: Good morning. I am Kay Lewis with the Office of Compliance in CBER.

I am the branch chief for Blood and Tissue Compliance. Within my branch, we also handle recalls, which is considered a voluntary compliance action.

I just want to give you a few numbers today on recalls and recovered plasma.

[Slide.]

The slide that I have here shows the number of recalls for FY 2000 and FY 2001, specifically for recovered plasma, the Class II's and Class III's.

Now, the Class II's are the aqua color, and the Class III's are the dark blue.

As you can see, there have been a greater number of Class II's than Class III's, and the intervening between FY 2000 and 2001, the number of

Class II's has increased slightly. That is probably due to the overall number of increase in recalls, and has no real effect on recovered plasma per se.

The only other thing that I want to say about the recovered plasma is that for Class II's, we currently audit those here at CBER rather than have the field audit those, and basically, by "auditing," what I mean is that the fractionaters send us information regarding lot numbers and products that the recovered plasma has been manufactured into, and we review that data, the viral inactivation steps, et cetera, to make sure that the product is still safe for its intended use.

That is basically all I have on recalls and recovered plasma. Are there any questions?

DR. NELSON: Could you describe the difference between Class II and Class III?

MS. LEWIS: The difference is in the health hazard evaluation, and that is done by our product officers. Without going into my recall talk, basically, when we receive a recall recommendation, we ask our product officers what is the hazard involved with whatever is wrong with the

product, whatever it is being recalled for.

They come back with whether or not it is a danger to health or whether it is a remote possibility of adverse health consequences, whether it is medically reversible, or whether it is not likely to have a hazard.

Based on that information, we will classify it as Class I, Class II, or Class III. So, Class II's are either a remote possibility of adverse health consequences or medically reversible health consequences, and Class II is not likely to produce any adverse health consequences.

DR. DiMICHELE: Do you repeat that one more time? Which is worse?

MS. LEWIS: Class II is worse than Class III. Class I is the most egregious. That is the danger to health. Class II is either a remote possibility of adverse health consequences or the consequences are medically reversible. Class III, there is not likely to be adverse health consequences.

DR. FITZGERALD: The numbers that you are reporting then are, by FDA definition, and by FDA guidance documents and requirements, recalls based on requirements for the product versus the things

we heard about in the talk like--

MS. LEWIS: Postdonation information?

DR. FITZGERALD: --the red cell unit was recalled, so they recalled the plasma, too.

MS. LEWIS: That is a lot of what we see if the transfusable products are recalled, then, the recovered plasma is also recalled.

DR. FITZGERALD: So, that would be included in these numbers also?

MS. LEWIS: No, these are only recovered plasma products. It does not include transfusable products.

DR. FITZGERALD: No, but was the plasma that was recalled, but is included in these numbers, recalled because the transfusable product was recalled?

MS. LEWIS: Yes.

DR. FITZGERALD: Okay. So, these numbers include all the units that were recalled regardless of whether you think it was a valid recall or not?

MS. LEWIS: By "valid recall," what exactly are you alluding to?

DR. FITZGERALD: Okay. They recalled the red cell, there really wasn't a reason to recall the plasma, but they did. Malaria.

MS. LEWIS: In the case of malaria, no, we would classify that as a market withdrawal rather than a recall, because there is no hazard to having recovered plasma out there because of malaria reasons.

DR. FITZGERALD: That is what I am trying to get to. Have you screened out of these numbers, those units that were the manufacturer instituted a recall, but the reason for the recall may not have been because of an FDA requirement?

MS. LEWIS: Yes, we have. The only numbers that I have here are recalls of recovered plasma where the reason for recall was valid to include the recovered plasma.

DR. HOLLINGER: Also, on the left of the screen, are those in units or lots or what?

MS. LEWIS: Those are actual number of recall events.

DR. HOLLINGER: Recalls, but it could be multiple units.

MS. LEWIS: Yes, it could be.

DR. HOLLINGER: Do you know how many units that represents?

MS. LEWIS: Not offhand, no.

DR. LEW: Just to get a better

understanding of this increase, do you have like the percentage for overall use? We already saw data of increased use for IVIG products, you know, other types of products. Could this just reflect increased production and use, but the same percentage is being recalled?

MS. LEWIS: No, because our overall recall percentage increased from FY 2000 to FY 2001. There was an overall increase in the number of recalls that we processed.

DR. LEW: What I am trying to get at, is it a reflection of because there is more production now, it is still--I am going to make this up--5 percent are recalled, 5 percent were recalled in 2000, 5 percent were recall in 2001, and do we have any sense of--

MS. LEWIS: No, I don't.

DR. CHAMBERLAND: What you are looking for is the denominator. Is there an appropriate denominator to affix with this numerator? I don't know if there is or not, but I think that is what you are looking for.

MS. LEWIS: I don't know there is an appropriate denominator. We haven't evaluated the number of recalls or the increase to determine

whether or not it was due to a specific reason or a specific number of reasons. We haven't evaluated that data.

DR. NELSON: Where would you put CJD, would that be a Class II or Class III, because clearly, you know, I mean somebody traveling to--

MS. LEWIS: I am sorry, I can't answer that question. We would have to ask our product officers, Office of Blood or--

DR. EPSTEIN: We treat postdonation information for BSE exposure as a voluntary market withdrawal, and we do not classify it as a recall because there has been no proven transmission.

DR. HOLLINGER: Do the blood banks send off individual units of plasma to the plasma manufacturer or do they pool it and send it off?

MS. LEWIS: As far as what we have seen, it has been individual unit numbers is what we see.

DR. FALLAT: Can you get an estimate of the denominator from the source plasma industry as to what percentage of the source plasma is, in fact, or what percentage of the plasma that is used by the source plasma people is recovered plasma?

MS. LEWIS: No, I don't have that.

DR. FALLAT: Is that information at all

available from the industry?

MS. LEWIS: At least not through the recall process.

DR. SIMON: Well, there has been estimates that it is approximately 80-20, I believe, yes, approximately 80-20, approximately 80 percent source plasma production, approximately 20 percent in the American market is recovered.

DR. FALLAT: That would give you some idea of the denominator then.

DR. SIMON: Well, the denominator here, I was just going to say we know that the amount of blood drawn in the United States has not increased substantially, so it is about the same in 2000 and 2001, so I think your denominator would be about the same in those two years.

DR. ALLEN: What is the length of time between the donation and the recall on average or what is the range? The corollary to that is are some of these recalls actually of manufactured product, so what we are seeing is not a unit being called back for disposal, but actually manufactured product that is being recalled.

MS. LEWIS: The majority of the recovered plasma recalls are of actual manufactured product,

which is why we actually review the lot number information and the products that it was manufactured into from the fractionaters for the Class II's, because by the time whatever violation has occurred or the actual blood bank acknowledges that that violation exists and does the recall, many times the product has already been manufactured into product.

DR. DiMICHELE: You may have alluded to this before, but let's say if you look at the number of recalls in 2000 and 2001 for source plasma, how does it compare or can you compare it?

MS. LEWIS: I probably could compare it, but I don't have that data with me, but I could make that comparison. I could look at all the source plasma that was recalled in those two FY's, and do an actual comparison. I could do that and maybe get it to the exec sec.

DR. DiMICHELE: Okay. Thank you.

DR. FALLAT: I would like to return to that question about the difference between autologous and non-autologous. Do you have any data as to how many of these recalled ones were autologous versus not?

MS. LEWIS: No.

DR. FALLAT: That would be the one area where some of the source information is deficient, and therefore, wouldn't be just a processing problem.

MS. LEWIS: Exactly. The blood banks and people that manufacture recovered plasma don't send the information in to us that way. It is just labeled as recovered plasma.

DR. SIMON: I don't believe autologous is being used. I get the right signs back there yes. I think this is a non-issue. Autologous plasma is not being used, this is allogeneic for further manufacture.

DR. NELSON: Yes, I think he is saying they throw this out or if they don't use it, the autologous.

DR. SIMON: A lot of it is kept as whole blood for the patient who is supposed to receive it. Also, autologous is going down substantially in the United States right now, the so-called pre-deposit.

DR. LEW: Actually, I had a question for Dr. Simon because he seemed to have these answers. You said that the rate of blood donation is the same, but the other question would be, if there is

a rising demand for these type of blood products recalled, do you know if industry or various places are increasing their production of recalled product, because again that might affect the denominator.

Is there a great need?

DR. SIMON: I think the amount of product, as we saw in the first presentation, is being increased, the production of product, but the amount of actually recovered plasma has not I don't believe increased significantly in that time frame.

DR. FITZGERALD: I don't know if we can say that, Toby, because the market has changed and the price has gone up, and there is a difference between what you get for injectable versus non-injectable, so there may be more recovered plasma being produced and sold than there was.

DR. NELSON: Thank you.

MS. CALLAGHAN: I have some overheads that might help clear up some of your questions.

[Slide.]

As far as testing requirements, the differences between source plasma and recovered plasma donors, source plasma donors are not tested for anti-core, they are not tested for anti-HTLV I

or II.

There is no deferral for travel to malarious areas for source plasma donors, and the VCJD deferral for five years in Europe is not required for source plasma donors. All of these things are required for recovered plasma donors.

[Slide.]

As far as syphilis testing goes, source plasma donors are tested every four months for syphilis, initially, every four months for syphilis, where recovered plasma is tested on every unit.

[Slide.]

Some of the differences between source plasma and recovered plasma donors. Source plasma donors have an annual physical, recovered plasma donors do not. They have a little, mini-physical, if you want to call it that, at every donation, but they do not have an actual physical by a physician every year.

Source plasma donors have a total protein done at every donation, recovered plasma donors don't. Source plasma donors have a serum protein electrophoresis performed every four months, and recovered plasma donors don't.

Source plasma donors can donate twice a week as long as the donations are 48 hours apart, and recovered plasma donors donate every 56 days.

Does this help any, I hope?

DR. NELSON: Are there any specifics mandated on the physical exam? I mean what does it conclude?

MS. CALLAGHAN: The physicals are like an annual, like a physical you would have at a physician's office. They do everything that a physician would do.

DR. NELSON: My physician probably wouldn't look for tattoos.

MS. CALLAGHAN: He might if they were infected.

DR. NELSON: I guess they map out tattoos that were there previously, because tattoo donation is one year for both source plasma and recovered?

MS. CALLAGHAN: Right. What the physician does at an annual physical, they note on a chart, on a little diagram of a person where the tattoos are or the body piercings, and if a new one shows up that is not on the little diagram, they will question the donor as to when they got it.

DR. NELSON: But as far as the FDA is

concerned, if the plasmapheresis center said we did a physical, that would be it, it is not like the donor questionnaire saying you have to ask this question this way, right?

MS. CALLAGHAN: No, it's an actual physical.

DR. NELSON: Yes, it is an actual physical, but it is not mandated as what is recorded or is it? Does the FDA mandate what should be in the physical?

MS. CALLAGHAN: Oh, yes, it has to be part of the donor's chart, and everything that is found or in the physical is on there.

DR. NELSON: But the content.

DR. SIMON: Yes, there are certain requirements.

MS. CALLAGHAN: There are requirements.

DR. SIMON: Like, for example, auscultation of the heart and lungs, palpation of the abdomen, at least some neurological exam, so there are certain features that are required, and then FDA inspectors routinely sit in on one or more physicals when they come to do the inspection.

DR. NELSON: As an aside, the first AIDS patient I saw had a physical exam, and he was a

transsexual who had had surgery, and it was reported that this patient had normal female pelvic exam, but when we went back, it was not done very well or very completely.

So, a physical is a physical, you know, it can differ.

DR. SIMON: Plasma donor centers don't do pelvic exams.

DR. KLEIN: There are also storage differences or potential storage differences between recovered plasma and source plasma, is that not correct?

DR. SIMON: It is correct, but you may want to elaborate on that.

MS. CALLAGHAN: Source plasma, when it is collected, must, according to the CFR, must be frozen immediately. There are no storage requirements at all for recovered plasma. So, it is whatever the consignee and the manufacturer of the recovered plasma agree upon.

DR. LEW: Just for my education, what is the purpose of the electrophoresis that you require for the source?

MS. CALLAGHAN: To make sure that the donor is not being overpheresed so that their

protein levels become abnormal.

DR. EPSTEIN: I just want to comment. The FDA permits both source plasma and recovered plasma to be fractionated. There are issues in two different directions on the table. I think to a certain extent we have got the committee confused whether what we are worrying about are the infectious disease control issues or the donor safeguards. Those are really not the issues.

The issue that we are concerned about is the quality of the plasma as a raw material for fractionation. On the one side, you have source plasma where the conditions of preparation and storage and labeling are rigorously defined. It's a licensed product, it meets well-defined standards.

On the other side, with recovered plasma, although we go about the donor safeguards and the donor screening in a different way, the issue at hand is that that product is not a well-defined product. It is not subject to product standards defined by the FDA in regulations or guidance.

It has variable storage conditions related to temperature and time. It does not otherwise meet any standards related to protein content. It

is entirely governed by these agreements with the fractionater.

Let me just say that the short supply is based on the concept of short supply of the end product, not short supply of the raw plasma material. In other words, it isn't because the plasma is in short supply, it is because the derivative is in short supply. We permit the fractionater to engage in short supply agreements for raw materials.

So, the issue is really thinking of the plasma and what should be the specifications as a substrate for fractionation.

Now, what is on the table from the FDA side is the FDA is of a mind-set that we really ought to be substituting product standards for the short supply agreements and define this material similar to the way we define source plasma, but you are going to be hearing that there is a whole other set of issues from the side of the industry.

The industry would like the FDA to relax the conditions under which a plasma by-product can become salable, because even though the specification on the product for recovered plasma is not well defined, there are some limitations

that are troublesome to the industry.

For example, if you are doing a cytapheresis, you can only sell surplus plasma, say, for making platelets, as expired fresh-frozen plasma. You can't just directly take the plasma and sell it as recovered plasma. Industry would like us to relax that condition. Then, there are others that you will hear.

So, I think part of the problem is that the committee has not yet heard the full spectrum of presentations, but the issue of stringency is should we raise recovered plasma to a processing standard and a labeling standard that makes it pretty much the same thing as source plasma except for the nature of how it got collected, and then conversely, should we relax stringency. The industry will be asking should the FDA relax stringency, so that there are more ways to get to a recovered plasma as a salable product.

Let me just say that there is an issue there which has to do with intent of collection. One of the differences that we have not highlighted, source plasma is intended knowingly and deliberately to be used solely for fractionation. It is dated and sealed. It is for

the manufacture and use, period, full stop.

The concept with recovered plasma is that the blood or component that was collected, was collected with the intention of transfusion, not with the intention of further manufacturing, and that, therefore, the plasma that may arise is a by-product, not deliberately made.

Again, what the industry would like us to do is to try to relax or even erase that distinction, such that you could willfully generate recovered plasma when you know you are going to be creating excess plasma from other collections, or you could simply capitalize on the opportunity.

So, if you know you are going to make platelets, can you knowingly make a surplus plasma and then just sell it upfront, why do you have to go through the drill of freezing it as FFP and waiting for it to expire, for example.

But the nuance there is deliberate collection of something that the FDA has legally regarded as an accidental or incidental by-product. So, the whole mind-set on recovered plasma historically and in the regulations and in the guidances is that it was an unintended by-product which became useful, whereas, the concept for

source plasma was that it was a deliberately collected raw material for further manufacturing, and that is one of the distinctions that we are being asked to modify.

So, the issues on the table are should we have a product standard like source plasma applicable to plasma obtained from whole blood collection, should we relax the standards on recovered plasma, so that there are more varieties that are salable and so that the collections can be done knowingly upfront. Those are the real issues.

I think the other background on how these things are distinguished is useful and its matters of fact, but it is taking us away from the question and why it is on the table.

I think a lot of this will become clearer after the industry presentations.

DR. NELSON: Thanks for the clarification, Jay.

Barbara.

Industry Presentations

PPTA

DR. WHITAKER: Good afternoon. I am Barbee Whitaker with the Plasma Protein Therapeutics Association.

PPTA is the global trade association and standards-setting organization for the world's major producers of plasma derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for source plasma and protein therapies.

These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat complex diseases in persons with immune deficiencies, and individuals with alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy.

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

Over the past two years, PPTA and its predecessor ABRA, have been engaged in dialogue with the whole blood industry about the possible establishment of specific criteria uniquely applicable to so-called "recovered plasma."

This dialogue was born out of an acknowledgment of the important public health benefits to be gained through utilization of high quality recovered plasma for the production of

plasma-derived medicinal products.

While recovered plasma is currently used in the production of safe, high quality plasma therapies, the major producers of plasma therapeutics sought to harmonize starting material requirements between recovered plasma and source plasma to the greatest extent practicable.

This ongoing dialogue has proved valuable. Following initial meetings, representatives of the American Association of Blood Banks, the American Red Cross, American's Blood Centers, Blood Centers of America, and PPTA, with participation by an FDA representative, continued to meet over the 2000-2001 time period.

Although consensus among all participants was not attained, much common ground was identified. Areas with the greatest potential for harmonization include donor documentation criteria, quality assurance practices, the National Donor Deferral Registry, among others.

This initiative grows out of a PPTA identified need for harmonized standards for plasma for fractionation, whether derived from whole blood or apheresis. Further, such standards for recovered plasma are consistent with PPTA's other

quality programs: the International Quality Plasma Program (IQPP) for Source Plasma and the Quality Standards for Excellence Assurance and Leadership (QSEAL) program, launched in 2000 for plasma fractionation.

PPTA is committed to continuous quality through programs like IQPP, QSEAL, and now, recovered plasma standards. Other quality initiatives under development include criteria for plasma fraction intermediates and harmonized guidelines for NAT testing laboratories.

Once again, PPTA is encouraged by the productive dialogue regarding recovered plasma that has taken place to date. We anticipate that a workable set of standards and criteria can be achieved by January 2004.

It is worthwhile to note that this same exercise is underway in Europe. A gap analysis of recovered plasma practices in Europe has just been completed. We look forward dot continuing this dialogue and moving ahead toward the implementation of appropriate criteria for recovered plasma on a global basis.

Thank you for the opportunity to present this information. The objective of establishing

high standards for plasma therapies is clear - to assure a consistent supply of safe, high quality human plasma for the use in the manufacture of plasma-derived medicinal products.

Thank you.

DR. NELSON: Thank you.

Questions? Mary.

DR. CHAMBERLAND: Can you briefly tell us what some of the areas were that you were not able to reach a common understanding?

DR. WHITAKER: Some of the IQPP standards that are applied to source plasma include the qualified donor, drug testing. Those were the major issues.

DR. FITZGERALD: You mentioned from the floor that lots of source plasma and recovered plasma are kept separate. Is there a difference in the quality of the products or the efficiency of manufacturer from those two different products?

DR. WHITAKER: I can't really address that.

DR. HARVATH: I was curious as to whether there is a difference in the consent for an individual donating for source plasma as compared to those who would come to a blood bank, donate for

a cellular component, and that would be used for recovered plasma.

Is there any difference in the donor consent for those two types of products?

DR. WHITAKER: I believe there are differences in the donor consents. Every collection company has its own informed consent, but our consent includes the possibility of being registered in the National Donor Deferral Registry among other things, and, of course, the intended use of the product.

DR. NELSON: But aren't both types of donors registered? This is if they have an I.D. marker?

DR. WHITAKER: Yes. Currently, that's in use by the source plasma industry, but it has not been expanded to include the whole blood industry, and that is one of the areas that we are undergoing dialogue about as a part of this process.

DR. NELSON: I am surprised.

DR. KLEIN: There is no National Registry is what she is saying for volunteer donors.

DR. SIMON: Just in Dr. Fitzpatrick's question, conventionally, in the literature, in general, factor VIII levels are higher in source

plasma donors and albumin levels are higher in recovered plasma and possibly gamma globulins, so there is some difference in the starting product from that point of view.

But I was going to ask Barbee, would the answer to this question, the FDA as opposed to us, and the creation of standards by the FDA, would you look at that as supporting your volunteer efforts, or would you prefer to move voluntarily instead?

DR. WHITAKER: We feel that our standards are in addition to the criteria set forth by the FDA, and to this point we have not gotten into specific criteria for the production of recovered plasma. However, those things are still in the process of discussions.

DR. FINLAYSON: John Finlayson, FDA.

I would like to go back to Dr. Fitzgerald's question and amend that which Dr. Simon said.

If one reads the literature of the late 1970s, and I strongly suspect that I am the only person in this room that does such a bizarre thing, one sees reports of a number of differences in products made from recovered or source plasma.

If one looks at a workshop that was held

in 1977, and which was followed by one which was held in 1978, one would see that the tendency for elevated levels of a pre-kallikrein activator in plasma protein fraction was considerably more common in plasma protein fraction made from recovered plasma than in that made from source plasma.

That is not to say that source plasma could never be the starting material for a plasma protein fraction that had elevated levels of a pre-kallikrein activator, but it was a rarer event.

If one moves to 1978 to a paper on stability of immunoglobulins, and modesty forbids my mentioning of all the authors, one sees that the likelihood of fragmentation during storage was greater in the case of immune globulins made from recovered plasma than that made from source plasma. Again, it was not absolute.

If one continues into 1979, there were some elegant studies by Dr. James McIver [ph] of the Massachusetts Department of Public Health, which showed exactly the same thing.

Now, if one knows these things, there are steps that one can take to circumvent them, but this was certainly the case as it existed in the

1970s; when the storage of recovered plasma was at best heterogeneous and was rarely equivalent to that of source plasma, which as has already been said, is collected by plasmapheresis and immediately frozen and is stored at minus 18 degrees Celsius or colder.

Now, the question large devolves then to the one that has been discussed here, but which, as Dr. Klein said, we really don't have an answer to, is what is the usual storage condition of recovered plasma at present and how soon does it get into that storage condition.

DR. ALLEN: In your studies, were you able to look at the differences in the units and apply any differential based on length of storage or freezing and thawing, and so on?

DR. FINLAYSON: As somebody's analogy was, it's not like using a shotgun, it's like using a rifle at a shooting gallery. You have to pick ducks off one at a time.

One has to look at specifically what it is one is worried about. If one is worried about elevation of plasma kallikrein activator--again this is a generalization--pre-kallikrein activator is one of the components of the--I am not saying

this for your benefit because you know, but for the benefit of the audience--is one of the components of the contact activation system.

Mother Nature has been very, very good in supplying plasma with a number of protein proteinase inhibitors, which are very good at inactivating the active forms of the contact activation system, however, these things work very well at the temperature that Mother Nature intended it to be, which is 37 degrees Celsius or slightly below, whereas, if one puts it in the refrigerator, the association constants between the protein proteinase inhibitors and those proteinases, which is the things that we are talking about, these inactivated enzymes of the contact activation system, those association constants become considerably lower.

So, a great deal of activation can take place of factor XII to pre-kallikrein activator upon storage in the cold, and, of course, the longer one stores in the cold, the more this can happen.

Now, on the other hand, if one moves over to considering stability of immune globulins, what one there is concerned about is related to, but

expanded upon, that of the activation of the contact activation system.

What one is ultimately worried about for the fragmentation of immune globulins, other words, IgG, is the presence of plasmin, but that can happen in a variety of fashions. One is that the plasminogen gets activated to plasmin while the plasma is still plasma, and then the plasma, which rides along with the final product, chews at the IgG, and what one is there concerned about is how long is the immune globulin stored.

Now, the activation of plasminogen to plasmin proceeds very nicely at room temperature, and in the old days, there certainly used to be room temperature storage of the liquid recovered plasma. It occurs more slowly, considerably more slowly in the cold.

On the other hand, kallikrein, which is the result of the action of pre-kallikrein activator on pre-kallikrein, which is also in plasma, kallikrein can convert plasminogen to plasmin.

If you ask the people who are contact activationologists, if there is such a word, they will tell you that kallikrein is a terrible

activator of plasminogen, and that is certainly true, but these people do enzyme experiments that take an hour or two hours or three hours.

When you are storing the final product, you are storing it for years, and so if it turns out that plasminogen gets into the final product, that is, the IgG-containing product, and there is a little bit of kallikrein, it can gradually activate the plasminogen to plasmin, which will chew on the IgG.

So, it is a very heterogeneous mix. You first sentence again, have you studied, yes, we have studied, but we have not gotten to the point where one can give you a nice short answer, which is what you were looking for.

DR. NELSON: Thanks, John.

Are there other questions for Dr. Whitaker?

Thank you.

The next presentation is Kay Gregory of American Association of Blood Banks.

AABB

MS. GREGORY: Thank you. My name is Kay Gregory and I am representing the American Association of Blood Banks, which is the

professional society for over 8,000 individuals involved in blood banking and transfusion medicine and represents approximately 2,000 institutional members, including blood collection centers, hospital-based blood banks, and transfusion services as they collect, process, distribute, and transfuse blood and blood components and hematopoietic stem cells.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety and availability of the nation's blood supply.

The AABB agrees that the FDA should reevaluate its requirements for recovered plasma. Disease facto regulation, through the requirement for a short supply agreement that sets the requirements for this product, is not an appropriate method of control, and FDA should set standards for licensing recovered plasma.

The AABB specifically included recovered plasma in its 21st edition of Standards for Blood Banks and Transfusion Services. These BBTS Standards were implemented by our members effective

May 1st, 2002. However, in setting these standards, the AABB worked within the constraints of the FDA requirements and identified concerns that we now know need further consideration.

While we will continue to use the term recovered plasma in these comments, it is probable that new terminology should be adopted to describe the various kinds of plasma licensed by the FDA.

The AABB's first concern is the definition of recovered plasma. Currently, this term is applied to plasma that is removed from whole blood. Source plasma is defined as plasma that is collected by plasmapheresis and is intended for further manufacture.

The primary distinction in definition appears to be the intent of the collection and the method of collection. These definitions are no longer appropriate and should be revised or discarded. Use of intent as a criterion severely limits the flexibility needed to maximize the utilization of collected blood.

New technology now permits collection of plasma concurrent with other blood components that are intended for transfusion, for example, plateletpheresis or red cells by apheresis. This

plasma is collected for fresh frozen plasma that is intended to be transfused.

However, this plasma is also suitable for use in further manufacturing and could be converted to that use at a later date if the need for the fresh frozen plasma in inventory no longer exists.

Currently, that is not possible because the plasma does not meet the existing definition of recovered plasma, i.e., it was not collected with the intent of being used for further manufacture, nor was it obtained from whole blood.

Alternatively, concurrent plasma, that is, plasma collected concurrently with other blood components, can also be collected and used for further manufacture, but this can only be done if the facility has a license to collect source plasma.

Because source plasma donors may donate much more frequently than whole blood donors, FDA has established additional requirements to protect the donor's health. These requirements include physician examination prior to the first donation and at subsequent intervals of not more than one year, and determination of total serum or plasma protein and a plasma or serum protein

electrophoresis or an equivalent test to determine immunoglobulin composition of the plasma or serum at least every four months.

FDA has issued guidance stating that infrequent plateletpheresis donors may donate every four weeks, including concurrent plasma donations, without any requirements other than those applied to whole blood donors.

Because most blood collection facilities utilize only infrequent plateletpheresis protocols, there is no need for them to obtain a source plasma license. Note, however, that if blood collection centers do permit plateletpheresis donors to donate more frequently than every four weeks, then, they must meet the same requirements as for source plasma donors.

The AABB believes that FDA should permit the use of concurrent plasma for further manufacturing without requiring a source plasma license, when the concurrent plasma is collected using an infrequent donation protocol. Further, such plasma should be acceptable even if it was originally labeled and intended for use as FFP.

Following this same logic, it should be acceptable to convert plasma that is derived from

whole blood donors that was originally collected and labeled as FFP to plasma for further manufacture. The current requirements permit this only after the FFP reaches the expiration date, and for FFP, this is one year after collection. However, plasma fractionaters will not accept year-old plasma, so the FFP is wasted.

A second concern relates to the confusion about record retention requirements. Because recovered plasma is not a licensed product, it does not have an established expiration date. Blood banks are now required to keep records indefinitely for any product without an expiration date. All licensed blood components have defined expiration dates and these dates determine the record retention requirements. Recovered plasma should be assigned an expiration date.

Third, the AABB believes that there is no need to distinguish between recovered plasma and source plasma based on donor suitability. Recovered plasma donors have established donor suitability requirements, as they must meet the same criteria as whole blood donors. These same requirements apply to plateletpheresis and concurrent plasma donation.

As you will hear later today, the plasma industry has worked closely with the whole blood community to develop a new donor history questionnaire. The proposed new questionnaires will simplify the questions and make them more readily understandable.

There will remain some differences in that questions that are applicable to components containing red cells are not always applicable to donations of plasma, but the donor questions are comparable, and the distinction between recovered plasma and source plasma is no longer necessary.

Likewise, requirements for testing for infectious disease agents for both recovered plasma and source plasma are comparable. FDA may wish to continue the requirements for testing designed to protect the health of frequent plasma donors, and the AABB would support that approach.

Finally, the AABB points out that facilities collecting recovered plasma are subject to stringent voluntary standards, including standards for quality assurance.

The AABB has been setting voluntary standards for blood banks and transfusion services for more than 50 years. Our standards include

quality management concepts with the quality management system providing the framework for the organization of the standards.

The general quality standards appear at the beginning of each of the 10 chapters followed by more specific requirements that address the elements of the facilities' day-to-day operations.

The technical standards are based on current scientific and medical data when available, and are developed using an evidence-based decision making process when possible. The BBTS Standards are updated on a regular basis based on input from AABB members, the public, and recognized experts in blood banking and transfusion medicine.

Therefore, recovered plasma is subject to the same standards as whole blood. Other products such as FFP have been licensed by the FDA and recovered plasma should also be eligible for licensure. The AABB does note that the Plasma Protein Therapeutics Association has implemented standards for source plasma collection. Therefore, source plasma also meets stringent standards.

The AABB appreciates this opportunity to present our thoughts on standards for recovered plasma. We are prepared to cooperate with the FDA

and others in developing comprehensive up-to-date standards for this valuable resource.

Thank you.

DR. NELSON: Thank you, Kay.

Questions? Yes, Judy.

DR. LEW: Has the AABB started studies to look at the difference between recovered plasma and source plasma?

MS. GREGORY: I think, as you heard from Dr. Whitaker, we have been in a dialogue considering some of these issues for about 18 months, I think, and we are still continuing that dialogue.

DR. LEW: But not studies have been done, you are just talking about it.

MS. GREGORY: We are just talking. We are not going to do scientific studies. We may identify studies that need to be done, but this particular group is not a group that would do actual studies.

DR. LEW: I guess the follow up to that, though, is that clearly, there may be differences, and you are recommending FDA set up some standards without good studies to guide them, unless they have been done and it just needs to be looked at.

What are these standards going to be without scientific evidence to back them up?

DR. SIMON: I think there are studies that characterize the two types of plasma in the old literature. I don't want to imply that I am back into it as much as Dr. Finlayson, but I believe that there are a fair number of studies back there, are there not, that compare the two of them?

DR. FINLAYSON: Step over to the blackboard, please. The answer is yes, but my take for the modern era would be that the fractionaters would prefer to have material regardless of what name was put on it and, as we just heard, maybe we have to use some name other than recovered plasma because maybe it implies that it was sick once and just got better.

But if it were frozen soon after collection and maintained in a frozen state, and let's say for the sake of consistency, maintained below minus 18 degrees Celsius, I would be surprised if one would be able to find any differences between products made from it and made from source plasma.

So, the answer to your original question is yes, there are studies and there are data

available, but they resulted from this heterogeneous array of storage conditions of the plasma itself, and I suspect that one could solve the problem largely by circumventing it today and just going rapidly to a frozen state.

DR. NELSON: What proportion of recovered plasma is fresh frozen plasma because that, it seems to me, would be quite comparable in storage conditions to source plasma, right?

DR. FINLAYSON: Are you directing that question to me?

DR. NELSON: Anybody.

DR. FINLAYSON: I certainly don't know the answer and, at the risk of plagiarizing, it is really Dr. Klein's question revisited.

DR. KLEIN: I can say with great confidence I don't know the answer either, John. There are some other slight differences that may not be physiologically important, and that is that there is a difference in the volume of anticoagulant, so there is a dilution difference, and in the nature of the anticoagulant, as well, between plasmapheresis, plasma, and plasma that is removed from whole blood.

DR. NELSON: As has been pointed out,

there may be some differences in the donors, but I guess the implication was that that wouldn't have a major effect on the end product.

DR. DiMICHELE: Thank you, by the way. This clears up a lot of the questions that we had, but you sure presented a catch-22 here, because, you know, at one point I am thinking that there is a lot of recovered plasma that is being sent to manufacturers. At this point, I am beginning to feel that you are hardly collecting anything because of the catch-22 that you presented.

In other words, a lot of what you would recover from whole blood that meets the standards, you can't really sell to manufacturers because they don't want year-old plasma.

MS. GREGORY: Well, that is only if we have originally labeled it as fresh frozen plasma. If, when we collect the whole blood, we don't make fresh frozen plasma, we can make that into recovered plasma.

DR. DiMICHELE: I see. Okay.

MS. GREGORY: So, I am looking for ways to augment the supply.

DR. NELSON: But if it was frozen, it would be labeled fresh frozen plasma.

MS. GREGORY: Yes, if it was frozen.

DR. NELSON: So, if it was collected and stored the same way that source plasma would be, then, it couldn't be used because it would be expired. It's crazy.

DR. DiMICHELE: My second question then is applicable. What percent of the potential additional plasma that blood banks could collect is actually being collected as recovered plasma, or, in other words, the corollary is, is how much additional plasma would be collectable if these two catch-22 issues that you referred to, the two major ones, are no longer issues?

MS. GREGORY: I think there is a potential for concurrent plasma, that is, plasma that is collected along with another product that is intended for transfusion. I think there is a fair amount of potential in that area.

There is probably less potential in what we collect now as fresh frozen plasma and then to find perhaps we don't need it for that, but the concurrent plasma, I believe there is a huge potential for.

DR. DiMICHELE: Do you have a sense of how much additional plasma that would provide compared

to what you can now?

MS. GREGORY: I don't know if anyone in the audience might have a feel for that, but I don't.

DR. ALLEN: Two questions. Just going back to the issue of the fresh frozen plasma versus recovered plasma, I am assuming that if a unit of plasma is not labeled immediately as fresh frozen plasma, that the blood centers can't go back, I mean if they then need more fresh frozen plasma, they can't go back subsequently.

MS. GREGORY: That's correct.

DR. ALLEN: That really does present a catch-22, and I guess I would like to know--and I am not asking for an answer, I am sort of stating a question--why is it an issue that one can't take fresh frozen plasma at some point X number of months, but less than 12 months, and reconvert it back to recovered plasma?

The second question then is with the increasing use of red cell pheresis and double-unit collections, my understanding is that one of the tradeoffs with being able to take off two units of red cells is that the plasma is reinfused into the patient, is that correct?

MS. GREGORY: I believe that is usually the case.

DR. ALLEN: I am just wondering if one wanted then to collect more plasma, can that be done at the same time during the double-unit red cell pheresis, or is that a physiologic tradeoff that the donor gets the plasma back. Maybe that needs to be addressed to somebody else, but it seemed to be pertinent to this discussion.

DR. KLEIN: Jim, you can't do that, but with many of the new instruments coming out, you can collect red cells in plasma, red cells, platelets in plasma, you can do a variety of different things that will allow you to collect plasma concurrently, and clearly, this is a growing area with the new instrumentation by different manufacturers, so that it is probably important to define what that plasma is and certainly not to lose it.

DR. SCHMIDT: The AABB seems to be the big objector to the name, and what name do you suggest, and what can you suggest instead of concurrent plasma while you are at it, by the way, because that is a loser?

MS. GREGORY: Yes, we think that's a lousy

name. We actually don't have a suggestion. We just think that maybe because there is so much confusion surrounding recovered plasma, that somebody could come up with a better name, and we are willing to think about it, but we don't have a suggestion to make right now.

DR. SCHMIDT: Not here.

MS. GREGORY: No.

DR. SIMON: What about just plasma?

[Laughter.]

MS. GREGORY: Well, I have to be honest. The whole definition of the various kinds of plasma is extremely confusing.

DR. HOLLINGER: Kay, just a couple of questions. The recovered plasma that is obtained, I mean when a person donates whole blood, very few people are using whole blood for transfusions, so it is separated into its components.

Is the recovered plasma invariably frozen at that point anyway, or is it kept, and if it is kept at refrigerated temperatures, why is it kept at refrigerated temperatures, what is its purpose at that point if it's not freshly frozen? That's the first question.

MS. GREGORY: I don't know. I think most

of it is frozen pretty quickly, but it depends on what is in your short supply agreement and what your manufacturer tells you they want you to do.

DR. HOLLINGER: But it could be used as fresh frozen plasma if the components are separated and it's frozen down immediately.

MS. GREGORY: Not if it isn't frozen under the conditions that you are required to use for making fresh frozen plasma and labeled as fresh frozen plasma. So, I think what you are asking is could I have a product and call it source plasma, and then convert it into fresh frozen plasma, and right now, no, you couldn't do that.

DR. HOLLINGER: And the plasma that is collected, the standards are, what, that it has been to be frozen at a certain temperature, but it also has to be frozen how soon after collection?

MS. GREGORY: That depends on the method of collection, so there is no one answer, but there are defined standards that it must be frozen and what temperatures and within what amount of time.

DR. HOLLINGER: As I read sort of the things that you have mentioned here, you have several things that you would like to see perhaps done. One is you just mentioned about concurrent

plasma, you could use it as further manufacturing as source plasma, and I think the issue about whether it is called fresh frozen plasma and it is used later, that is another issue.

I take it fresh frozen plasma, if it is stored for a year, you said the manufacturers will not take it.

MS. GREGORY: Yes.

DR. HOLLINGER: And is the reason they won't take it, is there something in the standards that they have, that says they can't take it after a year?

MS. GREGORY: I can't answer that question, I don't know.

DR. HOLLINGER: You also felt that the recovered plasma should be assigned an expiration date.

MS. GREGORY: Yes.

DR. HOLLINGER: Do you have any thoughts about what expiration date?

MS. GREGORY: No, we just want there to be an expiration date.

DR. HOLLINGER: As Dr. Klein said, it depends on how it is stored.

DR. NELSON: They want to get rid of the

room full of records that they have, I guess.

MS. GREGORY: The warehouse is full of records.

DR. NELSON: Mike.

DR. BUSCH: A few clarifications. FFP needs to be frozen within 8 hours. FFP outdates in a year, so it is a fairly stable product, and blood centers are always able to sustain their required inventories of FFP, and everything else is maximized for recovered plasma, to sell it.

So, most recovered plasma is also frozen quickly. The only time it is frozen on a delayed basis, within 24 hours or slightly longer, is if there is a logistical issue, and you get less money for plasma that is not frozen at 8 hours versus 24. So, the whole system is maximized to be able to utilize the by-product recovered plasma, but there are these nuances, the FFP outdated product and the move toward concurrent plasma that do need I think the fixes you are discussing.

DR. DiMICHELE: Excuse me, can I ask you a question? So then basically, if you have a blood bank and you are sort of looking at your projections and your collections through the year, and you say, okay, a certain amount of our plasma

has to go into FFP because this is what our requirements are, the rest will go into recovered plasma for sale.

DR. BUSCH: Absolutely.

MS. GREGORY: Yes.

DR. DiMICHELE: So, the intent is not for transfusion.

DR. BUSCH: No, it will be specifically labeled as recovered plasma, so as you are hearing, you cannot label for FFP and then convert, so we will maximize the collection and the processing to maximize the amount of recovered plasma derivative.

DR. DiMICHELE: What I am saying is that the initial intent is to do just that.

DR. BUSCH: Of course.

DR. KLEIN: But the unit of blood is collected for transfusion, and so therefore, because of the intent, it is not source plasma that is recovered.

DR. SCHMIDT: I think it used to be your FFP after one year, you could change the label and call it frozen plasma, and then it had a five-year date. This would be in the hospital setting, so you would use that for your other patients.

Does that still exist, and does that enter

into this discussion?

MS. GREGORY: I believe it still exists. I can't tell you whether or not that product is actually used in hospitals.

DR. SCHMIDT: It might be an avenue to get it into recovered, but you are looking for less avenues rather than more.

MS. GREGORY: Yes.

DR. HOLLINGER: John, just a question. Were you saying that with the kallikrein and other things which might cause some activation, fragmentation of immune globulin, is that going on in the frozen state also?

DR. FINLAYSON: No.

DR. HOLLINGER: Thank you.

DR. NELSON: You didn't cite any old literature.

DR. FINLAYSON: Well, as a matter of fact, there have been studies done on both ends, both on plasma that was stored frozen and the made into product, and looking for pre-kallikrein activator, and there have been studies of the immune globulin stored out of its intended temperature range, namely, stored frozen, so that one could do a controlled experiment with immune globulin frozen

at the normal refrigerator temperature, which would be within its labeled range of 2 to 8 degrees Celsius, compared with that frozen, compared with that stored at room temperature, compared with that stored at elevated temperature.

For all practical purposes, one does not get any fragmentation whatsoever in the material that is stored in the frozen state even if that which is stored at higher temperatures shows fragmentation.

DR. KLEINMAN: Steve Kleinman. Maybe I am missing something here but both recovered and source plasma ultimately get made into plasma derivatives. Each plasma derivative presumably has to meet some kind of lot release specification. So, ultimately, whether or not you use studies on the starting material, you need to at least reduce a final material that meets FDA qualifications for release.

So, I think while it is interesting to speculate about whether these things are equivalent or not, we do have some quality in place, and that is the final released product. I am not arguing against standards for storage, but I think we are missing the boat when we think that we are not

assaying these things because I think we are down at the end, which is important.

Now, maybe the efficiencies are different from the starting material, but we do have end products that meet minimal requirements.

DR. NELSON: But I understand that currently, plasma that is collected as recovered plasma, some of it is discarded based on current regulations.

DR. SIMON: They brought up some issues where they haven't been able to optimally use it, but it is not regulation, it is the manufacturer's requirement, it is not FDA that won't let them relabel it, it is the manufacturer that won't take it at one year, and that is just the manufacturer's requirements.

DR. NELSON: Celso Bianco from America's Blood Centers.

Celso, you have changed.

ABC

MS. DARIOTIS: Thank you. My name is Jeanne Dariotis. I am the president of America's Blood Centers. We had an error in who was going to speak today.

In my other life or my paid life, I am the

CEO of a community blood center, Southeastern Community Blood Center in Tallahassee, Florida, so I am a little nervous to say that I know probably quite a bit about making recovered plasma because it is a lot of what our blood centers do.

America's Blood Centers, or ABC, is a national network of locally-controlled, non-profit community blood centers that provide half of the U.S. blood supply from volunteer donors. Collectively, we operate in 45 states and serve more than half of the nation's 6,000 hospitals.

America's Blood Centers' total blood collections exceeded 7 million donations in 2001, and we shipped over 1 million liters of recovered plasma from volunteer donors for manufacture into plasma therapeutics.. These shipments that we make are made either through ABC, through Blood Centers of America, through plasma brokers, or are shipped directly to pharmaceutical manufacturers.

American's Blood Centers thanks the FDA for the opportunity to participate in this public discussion about recovered plasma. Recovered plasma is the only blood component manufactured by FDA licensed blood establishments that does not have direct FDA oversight. Instead, recovered

plasma is regulated through "short supply agreements" signed between the supplier of the recovered plasma and the pharmaceutical manufacturer or plasma therapeutics.

The specifications in these agreements are part of a product master file maintained by the pharmaceutical manufacturer. The concept of regulation by short supply agreements was created many years ago when plasma was literally recovered from expired whole blood and manufactured into albumin and other plasma products.

This indirect mode of regulation is out of pace with FDA's more recent and extensive application of drug cGMPs to blood establishments. It is also inconsistent with the strict regulation of source plasma.

Today's recovered plasma is the plasma retrieved from whole blood collections remaining after the blood center has fulfilled its patient needs for plasma for transfusion. Plasma for transfusion produced under FDA license constitutes about 20 percent of all the plasma produced by blood centers.

Although the name recovered plasma implies a lower value, in fact, as a starting material for

manufacture into plasma therapeutics, recovered plasma generally has higher protein content and higher levels of IgG than source plasma.

Until the early 1990s, the traditional view of recovered plasma as a waste product, the lack of FDA oversight, and the low reimbursement received from brokers and manufacturers provided very little incentive for blood centers to give this product the same attention as blood components for transfusion. In the 1990s, two factors radically changed the traditional view of recovered plasma.

Shortages of plasma in the world market caused by increased demand, new donor deferrals, and the vigorous enforcement of cGMPs by FDA.

As a result, plasma therapeutics manufacturers improved their quality systems, short supply agreements became far more detailed and manufacturers initiated vendor qualification programs that included inspections of the collecting facilities.

Blood centers also made substantial investments in quality systems, software and facilities applied to all blood components, including recovered plasma. Finally, AABB has

included recovered plasma into its recently published 21st edition of its Standards for Blood Banks and Transfusion Services, and blood banking organizations and the Plasma Protein Therapeutics Association have been working together on voluntary standards for recovered plasma.

Despite the many improvements made by the private sector, ABC members believe that recovered plasma must be subjected to the same regulatory scrutiny and licensure requirements as plasma for transfusion, in order to assure the highest quality for plasma therapeutics. ABC also believes that this can be achieved through simple changes in current regulations, and we have a few suggestions.

First, we think that FDA regulations should be modified to require that all plasma shipped for manufacture into plasma therapeutics be licensed by FDA. The new regulations would also specify that such licensed products could be either source plasma or plasma for transfusion derived from whole blood or apheresis collections.

We request that FDA provide a mechanism to allow the shipment for further manufacture of certain plasmas that do not qualify for transfusion in order to meet the manufacturers' requirements

and increase the plasma availability.

For instance, plasma derived from whole blood that is reactive for antibodies to the core antigen of hepatitis B is needed to guarantee minimum levels of antibodies to ensure product safety. Also, plasma from individuals who traveled to a malarial area can be safely transfused for further manufacture because the parasite does not survive fractionation.

In order to protect blood donors, the new regulation allowing shipment of plasma for transfusion for further manufacture would only apply to infrequent whole blood and plasma collections currently licensed by FDA. FDA should continue to require source plasma licenses for establishments that perform frequent plasmapheresis.

The product name "recovered plasma" would disappear and short supply agreements would merge into plasma therapeutics manufacturers' product specifications for source material.

ABC members believe that these changes would increase the availability of high quality plasma for further manufacture, would extend FDA oversight to all products manufactured by a

collection facility and would not interfere with voluntary standards such as those developed by AABB and by PPTA.

We also believe that the change would facilitate the handling and processing of our plasma by derivatives manufacturers and relieve them, at least partially, of some of their regulatory burden.

Thank you very much for the opportunity to present our point of view. One statement that I wanted to reiterate, blood centers generally, all of our collections are driven by our need to collect whole blood or red blood cells, and so we do not normally set out to recruit more recovered plasma donors. What we are out to do is recruit more blood donors, and in the process, we end up with more plasma.

Thank you.

DR. NELSON: Thank you, Jeanne.

Mary.

DR. CHAMBERLAND: I just wanted to follow up with a question to you regarding Suggestion No. 2, your example that plasma derived from whole blood that is reactive to core antibodies would be allowed to be used for further manufacturing into

derivatives.

You also give the malaria example. It relates because one of the questions that we are going to be asked to ultimately vote on has to do, the way it is phrased currently is should standards for recovered plasma include negative screening tests for anti-core and anti-HTLV.

MS. DARIOTIS: I am not an expert in the field, but currently we provide the core-positive units for the manufacturer's benefit to have more antibody present, so that question is not something I--

DR. CHAMBERLAND: I understand that. I guess the question I actually had for you is what is your sense of blood collection centers' ability to kind of address some additional complexities, namely, that you would have blood donors that would--how do I put this--would you almost in a sense have two kinds of blood donors, those that, for example, if they travel to malarial areas, they would not qualify as a blood donor, but would be deferred, or if they tested positive for core antibody, they would be deferred.

Are you proposing that, in some instances--

MS. DARIOTIS: An explanation to that is we end up, we draw donors, and at the end of the testing, we find that some of our donors are core-positive, we would like the ability, we think that the ability should still be there to ship those, I call them "accidentally found" core units.

If you were going to set out to draw core-positive donors, I think you would then be talking about a source plasma license.

DR. CHAMBERLAND: I understand that. The malaria travel--

MS. DARIOTIS: Again, it would be the same thing, that if your blood center had the ability to control your products adequately, that you could assure that you were destroying the products that would be a risk with the malaria, then, you would have the option to supply the plasma. I think that gets back to the blood centers' ability to control, if your blood centers' systems and processes would not allow it to do that with a fair amount of confidence, then, I would think the blood center would choose not to provide those products. Some could do it, some could not.

DR. SCHMIDT: Jeanne, your statement says that recovered plasma generally has a higher

protein content and higher levels of IgG than source plasma, and my recollection is the whole idea of measuring protein levels and IgG levels when plasmapheresis got started was an idea that was based on no data, that this was an important thing to do.

I am wondering, maybe I should have asked the PPTA how functional is this with the source plasma people, are there donors who are frequently pheresed, whose total protein or IgG drops, and was that a good idea or could that whole thing be thrown out to make these two more equivalent?

MS. DARIOTIS: Dr. Schmidt, I think I will let Dr. Bianco comment, too, but I believe that the statement comes from the people that we are providing our products to, tell us that recovered plasma is more valuable to them for those issues, and I would leave it to them to establish that.

DR. WHITAKER: We have done some studies with frequent donors that have been published in Transfusion, and found that while regular frequent plasmapheresis donors sometimes have slightly lower total proteins and individual proteins, that they are within the allowed range by the regulations. Then, of course, if they are not, then they are

deferred a certain amount of time.

DR. SCHMIDT: Is it something that happens, is it worthwhile doing these tests on your donors?

DR. WHITAKER: I think that there are times when donors do or I know there are times when donors do have total proteins lower than the required levels, and they should be deferred.

DR. SCHMIDT: Thank you.

DR. KLEINMAN: I wanted to follow up on Mary's question about the anti-core content of recovered plasma. It is really a question to FDA.

I think the requirement is in place or the procedure in 1987, when anti-core testing was first done was to say if we don't ship these anti-core positive units, we will take all the anti-HBS out of the donor pool and that will give less protection for our plasma products.

But I wonder, 15 years later, now that more people are getting vaccinated for hepatitis B, whether we still need that requirement to ship anti-core positive units and whether we would have sufficient anti-HBS in a pool of products that no longer contained anti-core positive units just from vaccine-induced immunity, which, of course,

everybody knows those people will come up negative on anti-core.

So, has anybody looked at this? Are there any plans to reexamine that requirement or do studies? I mean it really should be very straightforward just doing anti-HBS levels in recovered plasma units and assaying a few pools and seeing that they meet the FDA requirements.

Celso says what about source plasma. I think you could do the same thing for source plasma. So, I guess, as long as this is being opened up into looking at plasma requirements in general, you know, I would put this on the agenda as something that ought to be looked at.

DR. HOLLINGER: Steve, just in comment, as you know, most of the vaccine is going into infants, so you are talking about a couple of decades down the line, you know, as one point. The other point is since there is no boostering of this antibody, it is going to be a fairly low concentration in my opinion by the time an infant gets to an adult age and they become a donor.

DR. KLEIN: Blaine, I certainly think you would have to look at it to know the answer, but just a couple of comments. Certainly, medical

health care workers who comprise several percent of donors, most of them have been vaccinated and within the last decade. So, I think that there may be a source of vaccinated donors, and now adolescents are being or school age children are being vaccinated, not infants.

So, I think that conceivably, there is more anti-HBS titer in the donor pools than you might think, and we just need to look at it. I don't know how it would come out, I am just suggesting that we have a possible change in the anti-HBS content of donor pools that we could study if somebody wanted to fund that.

DR. FINLAYSON: First, I would like to ask is there a representative from Bayer that would like to address that question. I guess not. The reason I asked that question is because at a meeting of the Blood Products Advisory Committee in 1989, I believe it was October 31st if memory serves, a representative from Bayer did so.

There were very nice data presented that dealt with several aspects of collection, one of which was that at the time when AIDS was on the rise and there was no specific tests for what today we call HIV, people were trying a large number of

surrogate tests.

One of those that the corporation introduced was that for anti-HBC, and the result was that the plasma pool, and consequently the immune globulin intravenous, ended up with very low levels of anti-HBS, which is what had been alluded to here.

When that information was made public, it was also accompanied by a fair amount of data showing that as other tests had been introduced, there was sometimes also a concomitant decrease in the level of anti-HBS.

The result was it was considered not only desirable, but actually necessary to include a certain number of vaccinated, that is, vaccinated for hepatitis B donors in the donor population that would be used for the pools. So, the experiment has already been done.

DR. SIMON: I just wanted to clarify. It is strictly optional to the blood center whether they ship core-positive or not units, is that not correct?

MS. DARIOTIS: That is correct. Usually, your short supply agreement will request that you ship them, but the blood center can elect not to if

they can't properly control the process.

DR. FINLAYSON: I would like to corroborate that. What the FDA recommendation is, is that it not be withheld from the pools, and that one need not label it if one is shipping it for the manufacturer, but there is not an FDA requirement to include such plasma in the fractionation pools.

DR. SIMON: The only other thing I wanted to clarify from the industry point of view, there are donors who are specifically collected as source plasma donors for their high titers, hepatitis B surface antibody, and the presumption is--some of this is proprietary information--but that that can be added to the IVIG product to raise the levels or IMIG product.

DR. NELSON: Thank you.

From the American Red Cross, Don Fipps. I think after this one, we will break for lunch. I am told that in 20 minutes, lunch will no longer meet FDA requirements for consumption.

ARC

MR. FIPPS: Good afternoon.

The American Red Cross is pleased to have the invitation to speak regarding recovered plasma standards to the Food and Drug Administration's