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C O N T E N T S

P R O C E E D I N G S

DR. HOLNESS: Good morning. Welcome to the second day of the Plasma Standards Workshop.

The morning session is primarily devoted to recovered plasma, and our first speaker will be Sharyn Orton. She is the branch chief at Blood and Plasma Branch, CBER.

Recovered Plasma Questions

Sharyn Orton, Ph.D.

DR. ORTON: Good morning. Elizabeth Callaghan has asked me to give a brief review of the topics that were discussed in regards to recovered plasma at the June 13th, 2002, BPAC meeting.

At that time, compliance issues associated with recovered plasma were discussed. It included misbranding of plasma units, lack of shipping or disposition records, inadequate quarantine and destruction of unsuitable units, shipment of untested therapeutic and autologous units, lack of short supply agreements, incomplete and inaccurate labels, storage temperature and preparation failures not consistent with SOP.

In addition, manufacturing issues associated with recovered plasma were discussed, and some of the issues included lack of consistent SOPs for preparation prepared from donors who do not meet all suitability

criteria, incorrect labels if short supply contracts have different criteria.

So, the questions for the panel discussion today include what shall we call the various plasma components distributed for further manufacturing use, how should they be labeled, according to time and/or rate of freezing? If so, what stratification is most appropriate, according to what intended use, and what distinction should be made from source plasma?

DR. HOLNESS: Assuming no one has any questions for you, Sharon, our next speaker is Susan Wilkinson, who is speaking on behalf of AABB.

Recovered Plasma Issues

Susan L. Wilkinson, M.D.

AABB

DR. WILKINSON: Thank you very much and good morning to everyone.

Approximately two years ago, the American Association of Blood Banks created a task force that includes multiple organizations that are involved in the production and shipping of recovered plasma.

Members of the task force include individuals from the AABB, America's Blood Centers, the American Red Cross, BCA/Hemerica, the Canadian Blood Services, the Department of Defense, the European Blood Alliance, and Hema-Quebec.

Again, we convened this task force to address those issues related to recovered plasma, some of which you have already heard from Sharyn Orton.

From our perspective, there are a number of issues related to recovered plasma that really need to be clarified in terms of regulatory activities. First of all, it is outdated terminology. Recovered plasma, as currently written, is applied to plasma removed from whole blood and intended for further manufacturing.

On the other side of that coin, source plasma is defined as plasma collected by plasmapheresis and intended for further manufacturing. We all know that there have been a number of technological changes in our industry, and again, one of the things that we do routinely when we collect components intended for transfusion via apheresis, is frequently to collect a concurrent plasma product.

This plasma product is suitable for further manufacturing, but regulations preclude the use of such material because, first, it is not produced from whole blood, nor was it intended for further manufacturing.

It could be used if a collection facility has a license to collect source plasma, but I think it is a fair statement to say that other than those blood centers that are currently involved in source plasma collection,

there is not a huge number of facilities clamoring to get into that line of business.

The other problem with recovered plasma is the outdated system of regulation. Currently, a short supply agreement sets the regulatory requirements for recovered plasma.

In terms of controlling this product, the task force clearly would support the concept that this product should be licensed, and we believe that this would be a more appropriate strategy to handle recovered plasma.

I will now present for you what we are proposing for this product. Our current thinking is that we would call this product plasma for manufacture in distinction from source plasma.

In terms of donor qualifications, first, they would be the same as allogeneic whole blood donors, however, we need to take into account that plasma is collected concurrently with automated collections, and we believe that this can be easily addressed in the FDA memorandum from March of 1995, as it addresses requirements for infrequent plasmapheresis.

This would also apply to those situations where we plasmapherese donors, for example, for the AB plasma, again following an infrequent plasmapheresis donor program.

The methods of preparation for this product would be three different methods. First of all, obviously, we could separate that plasma from whole blood, as we currently are permitted to. The infrequent plasmapheresis concurrent with automated collection of cellular products for transfusion, or infrequent plasmapheresis, would also be a rubric that would apply to this scheme.

Again, converting plasma for transfusion, that is, FFP, to plasma for manufacture would also encompass the third method of preparation.

Here are a couple of caveats to the methods of preparation. First of all, plasma for manufacture prepared by separation from whole blood could be made anytime during the dating period and labeled at time of preparation.

Secondly, plasma for transfusion may be converted to plasma for manufacture anytime during its dating period, or up to one year after outdate as a transfusable component.

We are proposing a two-year expiration date, and that two years would begin from the date of collection.

In terms of testing for infectious diseases, we would apply those that are already applicable to whole blood donors except products don't necessarily have to be negative for core or for HTLV I and II.

Labeling is obviously an important issue, and we would propose the following labeling strategies. First of all, the product name would be Plasma for Manufacture. There would be a statement of freezing time on the label, and it would state, "Frozen Within (so many) Hours) After Phlebotomy," and the statement, "Caution: For Manufacturing Use Only into Injectable Products."

We would apply product codes as we currently do to other licensed products, and these would either be from the Uniform Labeling Guidelines or ISBT 128.

The amount or the volume or weight of plasma would be clearly stated on the label.

For those products produced or derived from whole blood, the name and volume of the source material, such as from 500 ml of CPD whole blood, would also be identified on the label.

For plasma for manufacture collected by infrequent plasmapheresis, and this would either be concurrent cellular or the plasmapheresis, we would include the total type and volume of anticoagulant used.

I almost hate to mention the next item. We are currently proposing a storage temperature at minus 18 degrees or colder, but that is open to dialogue.

For labeling, for facility identification, the name, address, and license number of the collection facility, and the name and address and license number of

the institution where separated, if it were different, would also appear on this label.

There would be a statement that testing has been negative by FDA required tests.

It would also include the collection date, and this would be month, day and year would also appear on the label.

In terms of component retrieval, we would propose the component retrieval, based on subsequent test results or other donor information, would be consistent with those currently applied to source plasma or recovered plasma, and would recommend that, consistent with other records, that they be retained for 10 years.

Several additional comments. This proposal does not specify freezing within a specific time frame as there are multiple types of products that can become plasma for manufacture, as we are proposing.

By specifying the time on the label, that is, the time of freezing, the fractionator can determine suitability for intended use.

Short supply agreements as a regulatory strategy would no longer be necessary.

While the collection date on the label is currently proposed, we would ultimately request only an expiration date on the product, once that expiration date is established for plasma for manufacture.

Of course, we would require or ask that we have adequate time to obtain a license for this product, and there may be some potential for an abbreviated application process.

We feel that this is a strategy to address some of the issues for recovered plasma that were raised at the June 2002 Blood Products Advisory Committee meeting, and we believe that working together, we can make this happen.

Thank you very much.

DR. WILLIAMS: Thanks, Susan. Alan Williams, CBER, Office of Blood.

There are a large number of collectors of whole blood that don't carry U.S. licenses, they are registered only, and I wonder if you could comment to the extent that they contribute recovered plasma to the manufacturing process and what the impact of licensure might be on these facilities.

DR. WILKINSON: I am afraid I can't personally comment. Maybe somebody else in the audience might be able to.

DR. BIANCO: Alan, maybe you can help us in the sense that I don't believe they can ship if they are not licensed for manufacture of injectables, can they? They can.

DR. WILKINSON: Does anybody have any sense of how many hospitals that might be?

DR. PAGE: Peter Page, American Red Cross.

A large number of hospitals collect some whole blood to supplement their red cell inventory needs and to contain their costs.

It is unusual that a hospital can meet all its red cell needs, and so the plasma that comes from the whole blood that they collect, they use, I believe most, and often all of it, for FFP, so with the exceptions of some very large collectors, I don't know that there is really that much on a practical basis available, but we could look at that through a survey.

DR. WEINSTEIN: Mark Weinstein, Office of Blood, CBER.

We heard yesterday about the effect of temperature before freezing as having a potential effect on yield. Would it be helpful--I don't know if you would be able to answer this, but perhaps manufacturers would be able to tell to tell us whether indicating the temperature that it is held at before freezing would also be something that could be on the label rather than just the time until freezing.

Is there anyone in the audience at this point that would be able to tell us about that?

MS. GLANTSCHNIG: Yes, I would say from our perspective, of course, the preferred temperature of storage of whole blood before fractionating would be 22 degrees, so the temperature that is suitable for platelets, platelet preparations, that would be our preferred temperature range.

However, I am not sure if this is really practical in all cases, so that would have to be determined, but if we would have to have an input, I would say this is what we would like to see.

DR. WEINSTEIN: Of course, again, asking for information as we go along outside of this conference, and that will perhaps be one of the questions that will come up.

DR. WILKINSON: Thank you.

DR. HOLNESS: I would just like to remind you that if you are making comments from the audience, please identify yourself and your affiliation.

Our next speaker will be Celso Bianco. Celso is the Executive Vice President at America's Blood Centers.

Celso Bianco, M.D.

ABC

DR. BIANCO: Good morning and thank you for bringing up such an important subject.

Yesterday, Mike Fitzpatrick already talked about ABC. We represent about 76 members exactly, but over 1 million liters of plasma.

The major issues that were raised at this conference or this workshop were the licensure of recovered plasma and the freezing parameters, and the questions we just heard from Sharyn Orton are questions that we have to respond by the end of the workshop.

I think that I would like to discuss a little bit why we want a license for recovered plasma. Recovered plasma is the only product for interstate commerce that is not licensed, does not require FDA approvals prior to manufacture or shipment.

It is regulated through short supply agreements between the supplier and the manufacturer, and essentially, each manufacturer or those that accept recovered plasma sets their own agreements. There, if we talk so much about harmonization, it is not just global harmonization, but it is harmonization of requirements between manufacturers.

The specifications are part of a product master file maintained by the manufacturer, and the concept we discussed extensively yesterday. It's historical and it is out of date.

At that time, and that is an issue that I would like us to discuss more later during our panel, is the

question of intent. For a number of reasons that I am not exactly aware of, but the regulations were based on intent of collection.

It is not in the frequency of, let's say, the source plasma donor, the frequency of donation versus the whole blood donor, but the whole reg is written as if the plasma is collected for manufacture, it is treated this way; if it is collected as whole blood or from an apheresis machine, it is to be used that way.

More recently, FDA has been more flexible and allowed the conversion of fresh frozen plasma to plasma for manufacture prior to its outdating, which was not allowed before, but still the plasma that is collected at the same time that we do an apheresis for platelets or for red cells are treated differently, and they cannot be shipped for further manufacture.

There was an exception made at the time of the big recall because of West Nile virus in 2003, and again FDA provided a variance, but what I wanted to emphasize is that what we have been doing now is looking for loopholes and ways to deal with outdated regulations.

To date, recovered plasma is prepared from whole blood collections much before expiration, after the blood center has fulfilled patient needs for transfusion. Red blood cell collections drive the blood center activities.

Plasma for transfusion produced under FDA license is about 25 percent of all the plasma produced by blood centers.

While the name "recovered plasma" implies a lower quality, in fact, recovered plasma generally has a higher protein content and higher levels of IgG than source plasma, and obviously, as we learned a lot yesterday, particularly from Dr. Farrugia's presentation, it has less Factor VIII.

In a sense, recovered plasma, the name, we don't like it, we really don't like it. It suggests that it is a byproduct that is not subjected to blood cGMPs, and actually, I believe that most of the issues that were raised during the BPAC in 2002, that Dr. Orton referred to, were older issues.

I think that those issues are much less frequent, I am sure that they still exist, than they were at that time, because all blood centers, all licensed facilities have their entire operation working under blood cGMPs, and it isn't inconsistent with the strict regulations that apply to whole blood and to source plasma.

The oversight of FDA is over the manufacturers of plasma derivatives, but there is no focus in the inspection process or pre-approval of the licensed establishment to ship plasma for fractionation.

I learn now, we all heard that that does not apply even to the registered, not licensed establishments, and certainly, I have not consulted them, I am not representing them, but I believe that they should be under the same rules that all of us have, because the final product is the same.

We, as an organization, fully support the AABB proposal. We were part of the discussions, we contributed whatever we could, and we feel that it is a simplified proposal that would make the product a recognized product, not an orphan.

Our point of view is that essentially, plasma that is good for transfusion into a patient is good for further manufacture. That distinction that we make, that plasma collected by apheresis would require currently, under the present regulations, are source plasma licensed for shipment, that it does not make sense.

Donors, also, we keep telling them during our recruitment efforts that each unit that they donate may save three lives because of the red cells, platelets, and plasma, and certainly, we are not being totally honest with them if we produce a plasma unit that ultimately is not used, which is ethically I think unacceptable.

There is one point that we did not discuss and that I think is important. We do not have consistency in our informed consents. Some blood centers will tell the

donor in the informed consent that their plasma may be used for research or may be used for the manufacture of plasma derivatives.

We could, and I believe that that would be part of what FDA will do, require that, and it is not something that would be difficult to comply, and would increase the disclosure that we make to our donors of what is the final destination of the product that they voluntarily donate.

The other issue is the way that currently, and I am coming back to the question of intent of donation, I think that there was at a time in the '70s, concern that if there wasn't real strict control, that blood centers could simply set up shop somewhere and start collecting plasma, and that would not be under good regulatory oversight.

I think that Dr. Page made very clear what drives what we do is the red cell. What the hospitals yell about that they don't have enough is red cells and platelets. That is what the patients need.

The plasma is always produced in excess to what the patients need. So, there is no interest, there is no value, and there is no economic pressure that would drive a blood center to simply collect plasma for manufacture.

The industry has very well set up their side of the source plasma that certainly supplies the needs of

the market, together with the plasma that comes from whole blood collections.

So, we would like to see the distinction made, not in terms of intent of donation, but in terms of donor protection, that obviously, if we were to collect a unit several times a week of plasma from our donors, I think we should do exactly the same thing that the plasma industry does, and follow the source plasma regulations, apply for a license.

If we make plasmapheresis collection that is infrequent, like we make the platelet collections, we feel that they should follow the rules for whole blood platelet in frequent donors.

Again, the standards for us in terms of the recovered plasma, as the AABB proposal is, should be the same for plasma for transfusion and plasma for further manufacture, and AABB included already plasma standards in their accreditation program.

We have been working together on other voluntary standards, and I think we should be careful and leave additional specifications left to the manufacturers. They have taken years to develop their procedures, optimize their production, validate their processes, and go through a very rigorous review by FDA of not only their processes, but their final products.

So, they must have the choice of which product they are going to use to manufacture what, and they choose the raw material according to their final product, not necessarily that will create a standard raw material that then will drive their processes.

It is the other way around. They ask us what they want their plasma, how much they want of this type, how much they want of that type, and they come and inspect us and tell us if we are doing what they want from us.

I don't think that I have belabored this. I think that those questions were asked yesterday, and I hope that we will discuss them a little bit today, but there is some concern that there wasn't a specific event that drove us.

I think that obviously, what is driving FDA with those is what we would call continuous improvement, and I think that we have to be careful to review and see the impact of those.

But I want just to remind us some of the things that were discussed here and some of the points in contrast with some of the points made, particularly by Dr. Farrugia, that is, the vast majority of the plasma for fractionation is used for the manufacture of stable proteins in this county and in Europe.

There is a decline in Factor VIII with increasing time to freeze and time in storage. There is a changing yield, but no documented change in efficacy of the final product. Fresh frozen plasma is not indicated for replacement of Factor VIII.

We did not discuss here, but my sense of the recent FDA workshop on inhibitors did not show a correlation or there was no documentation of a correlation between the development of inhibitors in patients with hemophilia and the type of plasma that is used for the product, but the correlation that was found were patients that were using many products that could not be maintained on a limited number of products or types of products over the years.

In general, plasma for transfusion is not used to replace labile components. Appropriate factor concentrates and recombinant factors are used for that purpose.

I want to remind you of one paper that has been studied in detail, many of the plasma proteins, is a paper actually that was made available to us by FDA. We were not aware of it in the beginning of the discussions.

That shows that at least in the ways they measure the several proteins except for Factor VIII, there were no detectable changes in plasma proteins.

There is no clear reason why Factor VIII should drive these standards. Manufacturers specify the requirements again according to their validated procedures. They will use the best available product to fulfill their needs.

Octapharma uses fresh frozen plasma prepared within eight hours because they manufacture solvent detergent plasma in Europe and distribute around the world, and certainly, that product has to be the closest possible product to the fresh frozen plasma. It used to be manufactured here, not anymore.

ZLB uses plasma frozen up to 120 hours for the manufacture of IVIG. The European regulations have reduced that time to 72 hours, but I question whether 120 or 72 are different in terms of what the IVIG that they produce will come out.

So, in summary, I would like to say that FDA should allow the use of all plasma that is good for transfusion as plasma for manufacture. Again, ABC members support the AABB proposal for plasma for manufacture.

We would like to distinguish recovered from source by frequency of donation. We would like to see FDA focus its regulatory efforts on the things that they do well and that are their responsibility direct is donor safety, donor qualification, cGMP, including the labeling

to indicate expiration date, anticoagulant, time to freeze, freezing and storage temperature, and it is our feeling that there is no compelling reason to change requirements for freezing and storage conditions at the present time.

I am repeating what was said yesterday. It was among the slides I had already seen, but essentially, if it ain't broke, don't fix it, and I thank you very much.

DR. FARRUGIA: You have raised a lot of interesting points, and I reserve most of my comments for the panel discussion, but I take you to your Slide 13. I am interested in Dr. Gilcher's remarks on this issue, as well.

You said fresh frozen plasma is not indicated for the replacement of Factor VIII, plasma for transfusion is not used to replace labile components.

So, what is it used for?

DR. BIANCO: It is used for replacement in general, but Dr. Gilcher will respond better than I can, for components that are stable components, like in a Coumadin reversal.

AUDIENCE: I think it has been very well said yesterday that fresh frozen plasma is definitely overused. All of us in this country have demonstrated that, who run transfusion services, but where it does have an indication, as was mentioned yesterday, it is

clearly the patient with TTP where you are actually after the metalloproteinase.

Then, there are selected other patients, for example, patients who are getting ready for a liver transplant, his coagulation factors are completely out of whack and they have to be prepared for surgery, so there are some isolated instances where one can use large amounts of plasma to really replace all clotting factors, labile and other in very selected situations, but it represents still a very small part of the total amount of plasma that is transfused.

DR. WEINSTEIN: I would just like to mention a few comments about the slides that were showed regarding the Factor VIII Workshop. I think that at least one interpretation of the information that was presented is it was somewhat ambiguous about whether or not there was a relationship between inhibitor formation rather than just saying that there was no relationship between the inhibitor formation and plasma collection.

I think that was what Albert had presented yesterday, it was not entirely clear.

DR. FARRUGIA: Well, I described a study which essentially emanated from Octapharma in relation to the inhibitor incident which was well recorded some years ago, and the claim there is that poor manipulation of the plasma led to activation of coagulation, amongst other

things, and led to the development of inhibitors to Factor VIII.

I am not saying I actually endorsed the study scientifically, but it has been reported.

DR. WEINSTEIN: One other point about the Kotitschke paper that you cited, saying that there was no relationship with the storage conditions, that you are correct, however, it is important to note that all the samples were frozen at minus 40 degrees.

There was a quick freeze and then they were placed in freezers for storage at minus 20 and other temperatures, so there is this element of quick freeze in that paper.

DR. DiMICHELE: I just wanted to just make, sort of add one comment to the issue of FFP use in this country. Again, I want to remind everyone that there are no treatments that are licensed for bleeding disorders here, and among the labile factors for which we do use FFP, is for congenital Factor V deficiency.

Certainly, in correction of massive DIC, particularly in our children, we use FFP, and again part of the replacement is indeed for labile Factor V, so although we don't use FFP for the specific replacement of Factor VIII, we do need active labile components in our FFP.

MS. HUME: Heather Hume from CBS.

I would say that we have been looking, as I said yesterday, we have been looking into the use of FP-24, and do offer FP-24 as a product in Canada. Prior to even beginning to use that again, we consulted with a number of coagulation experts to know if they would find this an acceptable product for the current uses of FFP today.

We actually anticipated that we would get a fair bit of pushback, and, in fact, among coagulation experts, there was really quite a large degree of acceptance of the use of FP-24 instead of FFP for the vast majority of uses for which we would wish.

As you know, we would just, I think, almost never use it for replacement of an isolated Factor VIII deficiency or for von Willebrand's disease. With respect to Factor V, we haven't actually studied in our hands what the level of Factor V would be in FP-24, but at least from the literature, it doesn't decrease as quickly within the first 24 hours as does Factor VIII.

DR. DiMICHELE: That was my question, as to whether you would characterize Factor V. I also just want to say that in Canada, you have managed to also license a lot more clotting factor concentrates for rare disorders, and so your position in Canada is a little different than ours in the United States.

MS. HUME: That is true, and also what is available through special access. We have measured

Factor V in the way in which we will be preparing FB-24 if we eventually move to the buffy coat, and actually, the levels I think our clinicians will find very acceptable.

DR. GOLDSMITH: Jonathan Goldsmith, Immune Deficiency Foundation.

I was just wondering if you could clarify a piece of the proposal that you are making with the AABB, which deals with the production of plasma for manufacturing at anytime within the dating period of the whole blood unit that it has been collected with, just to clarify that, is that in storage the whole time, in contact with red cells?

That is one thing, and then when is it actually separated, so the storage would be 4 degrees?

Maybe the manufacturers could make a comment on the impact of that storage, on the kind of plasma that they want for further manufacture.

DR. BIANCO: The proposal was written in a very flexible way, and it doesn't reflect the reality that the manufacturer sets the specification.

Today, most of the plasma is either 8-hour plasma, that is, frozen within 8 hours of collection, frozen within 15 or 24 hours of collection, and then the plasma that goes exclusively to immunoglobulin

preparation, that is, for Octapharma is 72-hour plasma, for ZLB is up to 120-hour plasma.

The rest, if plasma was left without that, it will go for the manufacturer of non-injectables.

AUDIENCE: I was just going to say that that was one reason the proposal that our group made to FDA left a blank in the label, so that particulars about the collection of freezing could be filled in as requested by the manufacturer for the product they have license with FDA, so that again we can disclose fully to the manufacturer what the conditions were, and the manufacturer can then select what is appropriate for that licensed product they are producing.

DR. BIANCO: One other comment that I would like to make in response to the rather compelling and somewhat intense comments by Dr. Farrugia. The fresh frozen plasma issue was not raised in terms of patient treatment. Fresh frozen plasma will continue to be produced and will be there.

What we are talking about is the other 75 percent of the plasma that goes for further manufacture, and what we want this plasma to look like, and essentially, that is what we are discussing here. Fresh frozen plasma will be there, because many physicians want it, it is needed, and that is why we make it.

Thank you.

DR. HOLNESS: Our next speaker is Dr. Peter Page. Peter is the Senior Medical Officer for American Red Cross.

Peter Page, M.D.

American Red Cross

DR. PAGE: I will be very brief. American Red Cross was a participant in the AABB group that developed the proposal, and we fully support that proposal.

A couple of years ago, at the end of a West Nile virus season, we appreciate the FDA's one-time granting of time-limited variances to permit us to convert plasma by pheresis originally intended and labeled for transfusion to that for fractionation inasmuch as we did not want to continue to distribute that plasma that was collected during times and places of West Nile virus endemicity prior to the availability of testing.

So, those donors' plasmas got utilized rather than wasted, and while we appreciate that, we think that precedent should help justify being able to convert back and forth as long as the proper criteria are met.

Thank you very much.

DR. HOLNESS: Questions?

[No response.]

DR. HOLNESS: Well, we can take our coffee break early, I suppose.

Our next speaker will be Mary Gustafson. She is the Director of Global Regulatory Affairs at PPTA.

Mary Gustafson

PPTA

MS. GUSTAFSON: If I repeat something that some of our colleagues from the blood industry said, or unintentionally contradict, I am sorry. I just walked in a few moments ago. I was experiencing one of my very favorite Washington activities, which is sitting on Route 50 and the Beltway.

Because I didn't hear the presentation, I think we do support the AABB Task Force recommendation, if it is how it was written before. Also, going back to the June 2003 BPAC, where there was a suggestion of redefining source plasma based on time to freezing, we recommend that the source plasma definition not be changed.

Since we know that FDA is looking towards making new standards, we caution against the use of meaningless metrics, and also in terms of expiration dating, that FDA consider specialty immunoglobulin to assign an expiration date, and also keep in mind what Dr. Page just mentioned, that sometimes there are times when you need to have product available and flexible.

At the risk of sounding really geeky, regulatory-like speak, I would suggest that FDA look at--

and this goes a little bit further than what the AABB proposal had--was to look at the definition of plasma in terms of finding a home for recovered plasma in standards, and look about changing the intended use.

Right now, plasma is defined in 640.30(a) as a product for transfusion only, and look to redefining that as transfusion or further manufacturing. That would allow the definition of source plasma to remain the same.

I think, as Dr. Bianco, I was walking in right about this time, but that would allow the distinction in products to remain based on the frequency of collection and the associated donor monitoring provisions that are in place for source plasma based on the frequency.

Now, whether these distinctions should be made in terms of the name that is on the label, I think that is debatable, but taking into account what was mentioned yesterday by Dr. Dodt, is that in Europe, the standards are the same for the products that go for further manufacturing.

They do have different labeling names, though, and they seem to co-exist quite well in that way.

Also, I think in terms of looking at different labeling distinctions, although the ISBT 128 has not been fully embraced for further manufacturing products, it would be good to go back and review the guidance document that was developed for ISBT 128.

Dr. Holmberg mentioned some of this yesterday, but a lot of really good effort and work went into the naming conventions, the use of product characteristics and attributes that are used along with the proper name of the product, and it would be well to look at that in terms of seeing where some of these things that we have talked about for two days would go into the labeling convention.

My next topic about beware of metrics that are unachievable or overly specific as you go into rulemaking or standard-setting, right now source plasma has the wording that immediately after filling the plasma that is intended for manufacture into injectable products shall be stored in its freezing temperature.

As we know, "immediately" is not achievable. In this day of doing a lot of tests, there is quite a bit of processing that has to take place in terms of mixing and removing sample tubes before the product goes into the freezer, even with the automated apheresis.

FDA's own guide to inspections of source plasma establishments interprets immediately to mean without undue delay, whatever that means, and I think Roger Brinser, you heard him yesterday say that they kept getting cited by auditors about using "as soon as possible."

So, another interpretation, and I don't think it is written down at FDA, but I know it has been used a lot, and also within companies, is that 30 minutes would be a good way to define "immediate," but unfortunately, what happens is 30 minutes becomes an absolute, and auditors love metrics. At the risk of someone from the American Society for Quality coming and ripping my certifications from me, I have to say it, that just because you can measure it, doesn't make it important.

So, make sure that whatever metrics are defined in standards, that they actually do have a meaning.

For a metric that has meaning, Cinderella's fairy godmother warned her to not stay after midnight at the ball, and we all know what happened. Her beautiful dress turned into tatters, and her carriage turned into a pumpkin, and the horsemen became mice again, so violating that metric had real consequences.

As far as I know, plasma doesn't turn into a pumpkin at 30 minutes, but you would be surprised to know the number of clocks that go off in processing labs and plasma centers, particularly the very, very busy ones. There is clocks all over the place, and they actually are measured against this "standard."

What is really sad is I have actually heard of places where if the plasma doesn't go into the freezer by 32 minutes, it gets relabeled for non-injectable use.

Here today, we have been talking about using 8-hour plasma, 24-hour plasma, 72-hour plasma, and so I think we need to really be aware of some of these metrics and what they really mean, that targets should not become absolutes.

A little bit about the dating. Source plasma, as you know, has a dating period of 10 years, and as you talk about dating periods for recovered plasma, I am sure you are also thinking about whether this is a realistic dating period for source plasma.

I think you have heard from our fractionators that two to three years is probably something that is used most frequently. The shortened expiration is due to inventory management, as well as changes in testing, and not to any stability issues that we know of.

The AABB is recommending two years for recovered plasma. Just bear in mind as you look at expiration dates that there are specialty immunoglobulins that may require a longer time of storage, and particularly when we are talking about the new bioterrorism products, that we may, in fact, need to have a longer dating period to accommodate some of these.

So, in summary, we support the AABB Task Force recommendation. We also recommend that the source plasma definition not be changed, and as you go into studying

standards and rulemaking, use metrics only if they have meaning and consequences.

At this time, we request no change in the source plasma expiration date.

Thank you.

DR. WEINSTEIN: One of the issues that we had been discussing throughout this meeting is doing what is practical and what is sort of the current state of manufacturing, and a topic that was part of this, or was to be part of this workshop, was the shipping temperatures.

This wasn't really discussed much yesterday, but I would be interested in knowing what the thinking might be about the apparently common practice now of shipping it minus 20 degrees, that this is what is done, what exists in the world at this point. The current regulations say I guess allows minus 5 degrees, something like that, and European regulations talk about I believe shipping it at minus 20 with the excursions allowed, and so forth.

Is there some feeling on the part of industry that this might be something that could be changed?

MS. GUSTAFSON: You may want to survey the shippers in the U.S. because there is not very many of them, and I think you saw in the slides from the fractionators yesterday that the majority of plasma is

shipped at minus 20, and that is to accommodate European requirements.

DR. HOLNESS: Now, we have a break, a half-hour break, so come back at five minutes to 10:00.

[Break.]

DR. HOLNESS: If today's speakers would come to the respective microphones, we will start the panel discussion. Don't forget to fill out your evaluation sheets at the end of the program.

Moderating today's panel discussion will be Mike Fitzpatrick, Chief Policy Officer for America's Blood Centers.

Panel Discussion

DR. FITZPATRICK: What we would need to do is address the questions that FDA has raised for this session, the first of which is what should we call the various plasma components distributed for further manufacturing use.

We had the suggestion from AABB, and I guess that would be where we would open the discussion.

AUDIENCE: I don't care so much for names, but I mean why not the same name as in the EP. Human plasma for fractionation.

DR. FITZPATRICK: There is not a great deal of difference between plasma for manufacture and plasma for fractionation.

MR. BULT: I think one thing that we should be aware of, with all the talk about harmonization, if we start introducing human plasma for fractionation, as described in the human monograph 893, it also covers plasma that comes from recovered plasma, as we heard yesterday. So, there is an enormous complexity to that.

The second thing that we should take into consideration is that if you look at the proposal that has been put forward, if we are going to have a distinction that is going to be based on frequency of the nation, there should be a very clear understanding of what it means, and it doesn't lead to a different perception about the quality and the safety of the products.

DR. FITZPATRICK: I am not sure I followed you with the enormous complexity to the two names.

Could you elaborate on that one?

MR. BULT: As we have heard yesterday, and you want me to talk about this harmonization, terminology is extremely important. We heard five definitions of flash frozen, for example. If we talk about plasma for further manufacture, plasma for manufacture, human plasma for fractionation, it assumes that we would choose the same terminology in the States, that it is the same as described in the monograph in Europe.

As we know, there are different plasmas covered. In Europe, those are because of recovered plasma, which is not the case in the States, and therefore, we need to make sure that if we come to one terminology, that it is the same terminology.

DR. FITZPATRICK: Right, and the underlying definition of the product would have to be the same. So, that would require a fair amount of negotiation between organizations if we did that.

DR. EPSTEIN: I think it is highly undesirable to use the European term for the simple reason that bodies in Europe will continue potentially to change the meaning of that term, and that won't be under FDA's regulatory control, and it will lead to disconnects between whether the name here and the name there mean the same thing.

I think it would be better to have a term applicable in our system, and when that product meets the European standard, that is fine, it will be recognizable, but if we use a term that could evolve differently in the two environments, we are setting ourselves up for a problem.

I also want to comment on the issue of labeling it for further manufacturing use versus labeling it for fractionation. Further manufacturing may not be fractionation, and the question is whether we are naming

now a product solely intended for fractionation, solely intended for making injectables, or suitable to make non-injectables and suitable for further manufacturing, not by fractionation to make non-injectables.

So, I kind of feel we should avoid those terms also, that we shouldn't talk about fractionation. I don't have objection to talking about further manufacturing, because that is a very broad umbrella, and the FDA's proposal was simply to call it component plasma, which would then indicate that it came from a whole blood donor.

Component would encompass apheresis, but it would come from a donor collected under the Whole Blood Donor standard as opposed to a source plasma license.

So, that is what led to the FDA proposal. We were giving it a term that would refer to the condition of collection, independent of the ultimate product use.

DR. FITZPATRICK: Any thoughts on the component plasma?

DR. WILKINSON: Well, I think the task force did speak about the FDA's proposed name, and again, and I think somebody just made the comment about apheresis or concurrent plasma as one of our issues, and it didn't quite seem to be captured in the name that the FDA proposed.

We felt, and still do today, that the term "plasma for manufacture" would be potentially more suitable, and when we say "manufacture," we are using that term in the broader sense.

DR. FITZPATRICK: Dr. Bianco.

DR. BIANCO: I don't think that we should get stuck on the name. That is probably not the most important issue. We certainly would like to have a name that deals like Susan just mentioned, deals with the plasma obtained concurrently with platelet or red cell apheresis, and that distinguishes it from source plasma, more in the sense that the donor for source plasma is a donor that goes under different criteria, different requirements than a donor for whole blood because of frequency of donation, no other reason.

So, if we keep it clean, I think that our community would accept it.

DR. WILKINSON: If I can just add we don't want to stay with recovered plasma, that is for certain.

DR. FITZPATRICK: I think what we are hearing is the goal is one name that would encompass the products, and not a variety of names to describe each product and its storage and freezing conditions, and maybe if we could suggest to our European colleagues that the name they are using might be too restrictive for our use, and

the goal for harmonization might need some dialogue there.

DR. EPSTEIN: I think the real issue is not so much the name as the definition that goes with the name and that what we are really talking about is whether we want to name a category of products suitable only for fractionation, suitable only to make injectables at the tighter end or, more broadly, for manufacture at the other end.

Now, the broader we go, the more we are going to be talking about adding text that say, you know, what its nature of manufacture related particularly to the freezing and storage.

So, I think this is really more about scope, in other words, what product are we trying to identify here, are we trying to narrow this to the product for fractionation, are we trying to narrow it to make injectables, or are we really looking at this more broadly, and does it go all the way to non-injectables not made by fractionation.

That is I think the key issue, and if we can hear some opinion on that, I think it can help inform what we ultimately name it, because the point is that the name should be somewhat transparent, and not misleading.

DR. WILKINSON: It is my understanding that the non-injectable product was not a part of this scheme,

that is my understanding. Again, perhaps that is something that needs to go back to the task force for additional clarification and then comment back to the agency, Jay.

But, again, we looked at this as plasma that would be turned into something else, principally those non-labile products where the majority of our recovered plasma is currently going.

MS. GLANTSCHNIG: I have a comment from the fractionator side. Important for us is really to have a definition on the label, what quality is this product, what type of plasma quality. It is not important for us if it says intended for further manufacture or for transfusion. For us, it has to say, for example, FFP 8 hours, FFP 24 hours, FFP 72 hours.

That is all we need to know. The rest, if it complies in detail with the specification for this type of product that we have in Europe, let's say, flash freezing at minus 30 for FFP, this is defined in our quality contracts, and if we want to use it in Europe, it has to comply to that.

But from the labeling, for us it would be the simplest to have FFP 8 hours, FFP 24, FFP 72. Just a suggestion what we would like to see.

DR. WILKINSON: And that was part of our labeling.

DR. FITZPATRICK: What industry has been describing was a product with a name and then a label that indicates the conditions under which it was frozen, the conditions under which it was stored, and the manufacturer selecting the appropriate product for manufacturing.

From the regulator standpoint, what we are hearing is that seems a little less restrictive or definitive than they would like possibly, but maybe not. I am seeing head shaking.

Mary.

MS. GUSTAFSON: Well, just in terms of having that flexibility, I think if you work at the plasma definition in the regulations and make it flexible, so that it is for transfusion or manufacturing use, you know, you can have that flexibility even to go back and forth.

Somewhere along the line, intended use does matter because that is what makes it a drug or a device component, but if you work within the regulations, I think then it can kind of flow into what labeling is important, and that is again look at the thought processes that went into the ISBT 128 proposals in terms of characteristics and attributes that may need to be on the label, or may not need to be on the label.

MR. ROBINSON: Richard Robinson, American Red Cross.

I would just like to caution against stratifying too much based on time to freezing, and rate, and so on. As we add more products, those are new product codes, and the additional complexity increases the amount of time to make software changes and increases the amount of time to implementing these changes.

So, I would urge caution and keep in mind the practical aspect of how we are actually going to implement these changes in product codes.

DR. BIANCO: I would love to hear the comments from FDA regarding what was just raised by Barbara Glantschnig from Octapharma. That is, why not just plasma and frozen within so many hours, and with the rules whatever you set. Obviously, in those rules, you could say for transfusion, the only ones that are acceptable are up to 24 hours, but at the same time, not having a distinction of what goes for manufacture or what goes for transfusion.

DR. EPSTEIN: Celso, the purpose here is information gathering, and I don't think it is appropriate for us to be expressing any sort of policy bias one way or the other, and I would make the same comment back to Mike.

We don't have a bias whether we should have delimiters based on freezing temperature as part of the label. We are here to listen. So, you know, I think Mary has put an interesting concept on the table.

The issue that is really coming to the fore is the third bullet under Question 2, which is intended use, and should that be part of labeling, and how should that bear on the licensing scheme, and that is something that we want to hear about, but I just don't think that we should be taking a position at this time.

DR. BIANCO: It is not position, but thoughts. You came with very good points a couple of minutes ago about the name and raising if it should be restrictive or not.

DR. EPSTEIN: The most I could say is I heard it and we will think about it.

DR. FITZPATRICK: That should lead us into the intended use question. Is there the need other than the distinction between volunteer and paid donor to have a distinction about intended use at the time of collection, knowing that the product, when it is collected, will be separated into components, and our goal is to use all those components to provide either patient care or do something with the material, but not throw it away.

DR. BIANCO: I would like to say something and repeat a little bit what I tried to say during the

presentation at least from how I see it, is an issue of the donor and protection of the donor.

That is, the source plasma regulations look not only at the quality of the plasma, but they look at protection of a donor of frequent plasmapheresis, and I think that they are appropriate and industry has adapted to it, and I believe that the donor is protected.

Here, I would like to see the same thing, the distinction not in terms of intended use of the product. The product is the same. The only thing that will have to be in the label is the anticoagulant and the proportion of anticoagulant in the final mixture and the time to freezing, things that would be in the label.

But from the point of view of product, it is the same. The distinction is the donor, the protection.

DR. EPSTEIN: Our current thinking is in agreement. We tend to think that the volume and frequency of collection, whether that is annual volume, but certainly frequency of collection should govern the donor safeguards, and that that is the fundamental difference between source plasma as a collection scheme and whole bleed as a collection scheme. It is the issue of the annual exam and monitoring the proteins.

So, I tend to agree with that. I think that where it gets a little bit tricky is intent at the time of collection. Now, it is our current thinking that we

are willing to consider removing that distinction as immediately governing the label of the final product. In other words, you can collect it either not knowing whether it is going for transfusion or further manufacture, or knowing it at the time.

But I think that we need a little bit more discussion. Mary, I am concerned about what you said about intended use, that is what makes it a drug or a device. That is true, but that is the label on the final product, and it is the wrong question.

The question is whether intent at the time of collection governs the label on the final product. I would say that we do want the label on the final product to state the intended use because of all the reasons you said.

So, therefore, I think that it is either part of the definition, if we call it component plasma, it is going to need to say for further manufacturing use, or if we call it plasma for further manufacture, that reflects the intended use of the product, the thing licensed, the thing in commerce.

The question here is whether we should change the regulations, so that it is not dictated by what you meant to do when you did the collection. I am going to state that FDA's current thinking is to pursue flexibility on that matter, and I know that that is what

the whole blood industry wants, but let me also point out that there is a slippery slope here, which is could it go either way.

I am not sure that we are hearing any particular drive to have what is currently collected as source plasma under our current mechanisms be immediately convertible to products for transfusion. I think that you might hear a lot of worries if we started talking about the reverse direction, but that is part of what is involved with being neutral, about being able to label and re-label.

DR. BIANCO: Well, if they have different requirements, for instance, testing requirements, certainly, source plasma would not at this point comply with the requirements for transfusion, no HTLV, no core, but I don't see if we are taking the slippery slope.

I don't see any reason if they were collected from a donor that totally qualifies, why it couldn't be used for transfusion.

MS. GUSTAFSON: If I could add something. You know, we are not asking for the definition of source plasma to be changed, and right now source plasma is defined as a product that is not for transfusion, it is for further manufacturing use only. So, that is in the source plasma regulation.

What gives you flexibility in terms of initial intended use, and not to sound like a broken record, is if you work with the section of the regulations that address plasma, which now currently says it is only for transfusion, which made the intent at the time of collection important, however, if that paragraph were changed to have the flexibility of intended for transfusion or manufacturing use, then, you have got ultimate flexibility within that regulation.

DR. FITZPATRICK: And the other, flexibility was the desire to be able to convert product that was collected and produced as fresh frozen plasma or concurrent plasma at anytime during the dating period to plasma for further manufacturing, that would fall into what Dr. Epstein said about changes to the definition of the product in the code, not necessarily a labeling change.

DR. PAGE: I could underscore that, as Dr. Epstein said, as well, because when we collect whole blood, virtually always we don't know the intended use when we do the collection. Certainly for whole blood donors, we don't know their ABO type yet, and if it is AB, it will be transfused, and if it's O, it probably won't.

Even for repeat donors that are out on bloodmobiles, we don't know the intended use, because

unless they are AB, we don't know out at the bloodmobile what our inventory of FFP or plasma for transfusion is and whether we are going to need more B's in the upcoming week or not, or need some more A's or not.

So, I believe we almost never know the intended use at the time of collection, and it is really after we get the ABO, assess our inventory, and some other issues, that we then decide later, and due to the dating, we have the luxury of some time of not deciding until after the holiday weekend is over, for example.

DR. FITZPATRICK: Any other comments from the floor, anything on intended use? Dr. Sazama.

DR. SAZAMA: I am Kathleen Sazama from M.D. Anderson Cancer Center.

There is one additional iteration of this that may bear on the discussion, and that is if you amend the regulation, as Mary has stated, then, it would appear as though you could go back and forth several times, and I don't think that that was the intent of the discussion, because we live in a world of surplus of FFP more than we need for transfusion.

Obviously, the driver are our red cells, we transfuse red cells, we don't use them for any other purpose. We transfuse platelets, and we don't use them for any other purpose, and the plasma is just a bonus, because the need simply isn't there. If that was the

reason we were collecting blood, we would have more than we need.

But I do think it is important to think in terms of, I don't think we would want to be in a situation where you flip-flop, you know, you start for transfusion, then, you decide you are going to go to manufacturing, then, oops, you have a shortage, and now you are going to put it back for transfusion, and maybe next month you want to put it back for further manufacturing.

I think we will have to leave it to the wisdom of the folks who craft these words, because I don't think that is intended. I think we really mean to say, you know, it's a one way street, so to speak.

DR. FITZPATRICK: That leads us then to the last question.

DR. EPSTEIN: Stratification.

DR. FITZPATRICK: We discussed that a little bit, specifics on stratification.

DR. EPSTEIN: The issue in stratification is whether the regulatory framework should dictate whether certain uses are allowed or not allowed.

The kinds of things that one might think about, for instance, should it be a regulatory policy not to make Factor VIII containing products from plasma frozen at more than 24 hours, should it be a regulatory policy

not to make any injectable from plasma frozen at either more than 72 or more than 120 hours post collection.

I realize that we haven't heard a lot of hard data on how older plasma may affect end products, but we have had, you know, a few glimmers that it may matter. We know it affects yield, we are not sure it affects quality. It is an open debate, what we are going to learn eventually from adverse event reporting.

We have heard a little bit about the fact that older plasma, especially with factor activation, may be associated with development of inhibitors. So, I think we have a little bit of a reason to be worried here about a completely neutral posture.

So, I think that part of the issue with stratification is whether it is stratification linked to intended use. I think the manufacturers have made clear that labels of frozen within 8 hours, frozen within 24 hours, frozen within--I am not sure whether it's 72 or 120, would be useful given the current state of affairs.

The deeper question is whether there ought to be any restrictions placed, such that you cannot make injectables if it's older than, for argument's sake, 120 hours before freezing.

And then the question is whether to be more stringent yet and link it to rate of freezing, because I think what we have learned here is that the scientific

data really lead us to be more concerned about the rate of freezing than the temperature, and certainly the temperature of the container in which it is placed is the least useful measure of all, because it says nothing about how fast it is going to reach a target core temperature.

So, the deeper question here is, okay, stratification, but should we have limitations on use based on that stratification or simply stay neutral. I mean we can always revert to dealing with it through the licensing process for the end products, we know that, but the question is whether we ought to create some standards in this field, because what we have heard is a lot of variation in practice, and unfortunately, we don't have a solid database on safety.

DR. BIANCO: Jay, I have to agree with what you said. I don't think that it is our role to define that. That role is the role of the manufacturer that validated procedures or uses it, and what type of plasma they chose.

But from our point of view, we wouldn't have objections to any of that. The same way that today they write specifications in a short supply agreement.

In a fantasy world, one day we are going to get rid of the short supply agreement, but I am sure that the manufacturer is going to give us a sheet of

specifications this is what you have to do in order to provide us plasma, so that system will continue, but they will define it regarding their final product.

I have personally, and actually as an organization, we have no objection to that, but we feel that is the responsibility of the manufacturers in a certain way to tell you what they want to do.

AUDIENCE: Well, it seems to me if the goal is to have the labeling described in some respect as Octapharma has requested, the quality of the product, then, the labeling should say the rate of freezing and the storage temperature.

As Dr. Farrugia has made it very clear, the rate of freezing is the most important item in the labile protein yields. The storage temperature protects them or doesn't over a period of time. Both of those things are easily validatable.

The other thing that I would like to say is that the pernicious use of the word "at" rather than "to" is a destroyer of confirmed quality. You can put product at a temperature. I have seen them put "at" a temperature in cartons, one-liter bottles, where 15 hours later it isn't frozen.

So, if we require that the product be frozen to a temperature, whether it should be minus 20 in an hour, minus 20 in two hours, or whatever, you now have

something that is validatable and will tell the quality of the product.

The concept that those two phenomena, storage temperature and freezing rate, are the same thing, and require the same equipment simply isn't the case. It is a big burden on storage temperature, big storage freezers, to also provide fast freezing, but they don't need to. That is an unnecessary cost to try and say that the storage freezer should do both of these things.

Our company, and many other companies, make equipment that can freeze it fast at room temperature with no danger to any employee, and once they are frozen fast, which is 80 percent of the heat removal, then, they can be transferred to the storage freezer, and that reduces the burden on the storage freezer, because it is the addition of the heat released from the unfrozen product that causes the storage temperature to go up and down like a yo-yo.

DR. FARRUGIA: I just want to indulge in some philosophizing. First of all, in relation to if it ain't broke, then, don't fix it, by the time something gets broke in this business, is generally the time when the lawsuits start, and if you have a situation whereby because of inappropriate manufacture or generation of plasma, you generate a population of hemophiliacs with Factor VIII inhibitors, just for the sake of mentioning

the most obvious example, then, I think that that is a pretty big worry.

Now, what I hear as a result of this today is there is a consensus actually here, that there is a lack of data. This business 25 years ago was very firmly focused on the issues we have been discussing today, at the stage where product development was such that it definitely mattered, definitely mattered.

You could show that if you processed the plasma inappropriately, you get low Factor VIII yields, and so on, and so forth. You might well argue whether this is a regulator's issue or not, but it is certainly something that received a lot of attention and resources.

Now, when AIDS came along, it changed everything including this. We started only feeling that the most important thing was safety, and the focus of activity, investigational research, and so on, went on safety, activation, prime clearance, and so on.

Well, it seems to me that it is time now to tread back a bit and do some more studies, because I reiterate, as a regulator now, that in the absence of evidence, we, as a community, are entitled to be conservative, because that is what history has taught us.

I would contend, Celso, that it is as much your job as the manufacturer's, because you have to show that it doesn't matter if it's stored for 24 hours than at 8

hours. The blood is in your hands, it is not in the hands of the manufacturer. What the manufacturer receives is a lump of plasma which hopefully is already frozen, and we avoided this because we don't know yet what frozen means.

So, I reckon that it is up to you folks as an industry to get together and design the appropriate studies and submit them to the FDA and the BPAC. In the meantime, I firmly believe that the FDA's own current requirements, even for source plasma, are unfortunately ambiguously worded, and I think they should have the ability as a result of these two days to get some better thinking on that.

I think there should be also the ability to define some basic conditions which are more stringent than at the moment, but certainly not too stringent to impede access to therapy. After all, what we are hearing at the same time is that this stuff is produced in excess, even though it is strangely captured under a framework which is called short supply, it is essentially a byproduct.

So, it is something which earns you money. So, I would suggest that there should be enough thinking from this meeting to set an agreed set of basic requirements, and everything else is really up to you, but don't expect the regulators to stick their neck out in the hope that

it ain't broke, because what I am hearing is that we don't actually know if it ain't broke.

DR. BIANCO: Since you mentioned my name, I agree with you, Albert, and I agree entirely. Maybe I didn't express it clearly why I put this in the hands of the manufacturer of the final product.

It is because, as always, we adapt our systems to the needs of the ultimate customer, so if it is our patient, we adapt to the needs of the patient.

If it is the manufacturer of a derivative that is going to go to patients, the manufacturer will specify to us I want so much plasma at 8 hours, because I am preparing SP plasma, I want to pay less, I want plasma, so you don't keep staff at night in the components lab because I am only going to produce immunoglobulins, and I am not as concerned.

So, that is the driver here, and that is why I left it in their hands. I have no objections to a more rational set of rules.

I think that if you guys decide to stratify, like Jay mentioned, that plasma more than 24 hours should not be used for Factor VIII production, I think all the data that you showed, and all the discussion that was here, and what the manufacturers told us, seems to be the appropriate thing to do.

MS. GUSTAFSON: I guess I just get a little bit nervous when I hear a lot of talk about putting a lot of stratifications in regulations unless they are truly not evidence based, and that is because you end up then with an overly rigid regulatory process.

The idea that if you license recovered plasma by whatever name, that then the manufacturer won't have to have short supply agreements or contracts, or whatever, is really false. The fractionator is not going to give up oversight over the supplier, that is not going to happen. I think you heard that from Daniel Albrecht yesterday.

There is very good reasons for fractionators to have specifications that go above minimum requirements, and they have audit programs that definitely go beyond FDA inspection programs.

So, that is not really going to go away, and in terms of the true regulations, let's not make them overly specific or overly rigid unless there is a real reason to do it.

DR. FARRUGIA: See, I guess I would actually follow up on that, because I guess I would concur quite strongly with most of that. I have strong doubts about this business of stratification and reflecting it in labels, for example. I mean how big do you think a label is going to be with all this information, which even the

industry, the AABB proposal has suggested to me, I think it will be a nightmare.

I think a lot of these requirements, a lot of the so-called certification should be captured within agreements between the manufacturer and the supplier. I think that what should be the basis of the regulation itself should be a basic set of conditions which will produce a uniform, standardized product, with as much science built into that as possible.

But I would also say, as I said yesterday, it seemed to be making the presumption here that the regulation is only going to be overseen through what is stated in the CFR in terms of the relevant clause.

I mean, to me, there is a hell of a lot of issues here related to GMP, and your eventual agreement, at least certainly in our system, it is the case, but your eventual agreement with Octapharma or Bayer, or whoever, is also going to be subject to the scrutiny of GMP.

It is also to be described in an appropriate way as what is meant by a quality system, so that is also going to be overseen. It is a question of where it is going to be overseen.

DR. BIANCO: And who oversees it.

DR. FARRUGIA: Them's fighting words.

[Laughter.]

DR. FITZPATRICK: I think Dr. Farrugia for that lead-in, because what I wanted to say was that the cGMP issues are that the collector who freezes the product has to comply with GMP and demonstrate to the FDA and AABB that they have freezers that can accomplish what is defined by what is on the label.

What needs to be defined, what we heard was the rate of freezing and the temperature of storage conditions. The freezers have to be validated, and we know that there is a lot of difference in freezers.

If you put 30 units of warm plasma in a freezer, the freezing rate of those 30 units is a lot different than when you put 2 units in, so the validation of the freezer to accomplish the goal is required, and it is inherent on the producer to validate that the freezer can do what the conditions require.

The AABB standards have been using a phrase, and the phrase, "a method known to" has come into the language, so rather than sometimes requiring freezing to a core temperature of minus 30 within 90 minutes, you know, using a method known to or a validated freezer that accomplishes a goal might be a good terminology.

Then, the other question that comes to my mind is which side of the coin do you regulate. From a cGMP aspect, from the collector's viewpoint, you regulate compliance, are they producing a product collected from a

donor that was frozen and stored at the appropriate temperatures and at the appropriate rate.

Do you regulate from the collector's side what that product goes into? Is FFP limited to a labeled product and is the onus on the blood collector to have a label that says that, or do you regulate from the manufacturer side and say, as the manufacturer, you are required to include in your product only plasma that was collected, stored, and frozen under these conditions?

I don't know the answer to that question from a regulatory standpoint, but it seems to me you could go on either side as to regulating what product goes into what final product, and that that is not necessarily a requirement to be on the label at the blood center when it is frozen, that it can be regulated by what materials the manufacturer uses to produce the final product.

What I am hearing is that there is a need for some stratification. Where that stratification occurs is in question, and whether, as Dr. Farrugia says, we have a label that is, as our European comrade said, it's 6 point, and you need a magnifying glass to read it, that we need obviously a better solution than that.

Freezing rate from a scientific viewpoint, this is certainly not speaking from an ABC viewpoint, but from a scientific viewpoint, freezing rate is very important, and defining how you determine rate and what rate you

want is important to the final product that it is intended to be used in. It is less important for albumin than it is for Factor VIII.

Do you have other comments on stratification?

MR. BULT: When you think about where to put a stratification, I have heard two areas. One is the regulation. I have also heard Dr. Epstein saying earlier today that at the end, there is the marketing authorization documentation that is available to the regulators.

I haven't heard anything about the plasma master file concept, Al, but you mentioned that in your presentation yesterday, that may be a third option that you accommodate.

DR. FARRUGIA: I would reiterate my words yesterday that the plasma master file concept is the most useful regulatory document which has ever come out of the European centralized blood environment, and because it captures all these issues under one framework and makes strong emphasis on things which are really important.

But, you know, I mean technical issues like the freezing rate, and so on, I don't see why they need to be specified to that extent on the label. If they are simply referred to, the general phrase, "according to FDA requirements," testing according to FDA requirements, and those requirements then will be described in the

appropriate part of the CFR, and any issues relating to further stratification should be dealt with through the agreement between collector and fractionator, but that agreement is again subject to GMP type scrutiny by the regulator, Dr. Bianco.

DR. WALKER: Tom Walker, Canadian Blood Services.

To answer the question of why you need some of this information, the information that relates to the usability of the product on the label, is so that you can keep the stuff straight in your freezers and manage your inventory easily and quickly.

If it all looks the same, and you have to go back to your files to determine what is it, you are going to have people working overtime just trying pack things correctly.

MR. BULT: I would like to make one comment on the remark that Dr. Farrugia made, when he was talking about the need to collect data. I just would like to make a very clear statement, and it is that this industry, whether it is the fractionation industry or the blood banking industry or the suppliers, have made enormous investments in relevant issues.

Let me talk about the prion removal, West Nile virus. We need to be prepared for emergent pathogen. I think it is important to realize that we have money

available for real relevant things, and we don't believe that a collection of data, as you suggested, Albert, is one of those.

DR. FITZPATRICK: I would remind the users to identify themselves, please, the speakers.

AUDIENCE: I would just like to clarify the plasma master file issue. The plasma master file is a concept which is new in the EU and which allows you, as a marketing authorization holder, to give all your information for the plasma you use for the manufacture of all your products to put together in one file, and this file is a self-standing document, and that is evaluated separately, and that is linked to all of your products.

So, if you have the choice to do so, or you have to give all that information with each of your applications, you have the choice. Either you use the plasma master file and the certification of the plasma master file, or you give that information with each of your marketing authorization applications.

I think the content of the information is the same. That is what I wanted to clarify, the content is the same. It is just the way you provide the data.

DR. FITZPATRICK: We have talked about time and rate of freezing interspersed amongst the discussions, but not specifically, so are there any other comments about time and rate of freezing?

DR. EPSTEIN: Well, I have heard that freezing to a core temperature of minus 30 degrees in something between one hour and 90 minutes is a feasible standard that is practiced already by about half the industry, if not more, that it has potential benefits in reducing the costs of storage because you don't try to do the upfront freezing in the same freezer where you store, and I guess I would like to hear an industry perspective on whether this is a feasible standard that could harmonize both the source plasma and the plasma for fractionation side.

The main distinctions that would remain between source plasma and other plasma would be the time prior to freezing, and the frequency of the donation. Also, you know, to whatever extent the--I agree with Dr. Sazama that labeling for further manufacturing use should be a one-way street, and so to the extent that it is part of the definition of source plasma, that is fine. It just means you have already walked down that road at the time of collection.

So, I would like to hear a little bit more discussion on the feasibility of a standard for plasma for transfusion use and for source plasma of freezing to a core temperature of minus 30 within--I am not sure whether to say one hour or 90 minutes--but comments on both perhaps.

MS. GUSTAFSON: I think you heard yesterday from one of the major fractionators that they do not view some existing freezers as necessary in the production of products, and probably will not continue to use those.

Then, there is also issues where now there is freezing at minus 30 in air temperature, and that doesn't necessarily get the core temperature down to minus 30 in 30 minutes or so, but that is a major investment in freezers, as well.

AUDIENCE: It doesn't say it is not feasible, Mary. You are saying people don't want to do it.

MS. GUSTAFSON: I didn't say they didn't want to do it. I said that it was not viewed as necessary in the manufacture of products.

MR. McVEY: I would just like to comment. I am John McVey with Baxter Healthcare.

Just to be clear, to bring the temperature down to minus 30 in 90 minutes is a very difficult thing to do with a conventional air freezer. That requires very specialized equipment, and that is not standard and customary to do that in that time frame.

MR. SESIC: Jim Sesic with Grifols. I just wanted to make sure that you understood that when we said that we put temperatures at minus 30 degrees, again, it was putting them into the box at minus 30, and we hadn't done the appropriate validation of what the core

temperature would be over what period of time. We expect that would be quite a task.

DR. EPSTEIN: Mary, you spoke against having regulatory standards that are not meaningful metrics, but freezing at minus 20 is not a meaningful metric.

DR. FARRUGIA: Exactly.

DR. EPSTEIN: Dr. Farrugia has educated us that that is meaningless. So, what matters is rate of freezing. We also heard what data are available, that the really critical parameter is the time taken for the phased transition at zero degrees.

We heard Dr. Walker say that there may not be a real value in freezing to minus 30 if you are going to store at minus 20 anyway, but it is a question of providing data.

I mean if the industry could show that you could freeze to minus 20 in 90 minutes, maybe that is adequate, but the problem that we are facing is that we have a meaningless freezing standard right now and we would like to put it on a scientific foundation, and I think it is hard to argue against that.

MS. GUSTAFSON: Jim's Viane's presentation yesterday said there is a lot of variables in terms of freezing. If you have got a very busy plasma center, you have got infiltration issues, you also have load issues, and those are extremely difficult to validate some of

those in terms of really finding out what the core temperature is at any given time.

DR. FARRUGIA: The question is captured by Mike Fitzpatrick saying a method shown, too, irrespective of how busy you are or how much plasma is going through.

I am just astonished at the way in which the industry seems to be comfortable with what I think is an enormously ambiguous statement. I mean as a regulator, I am always being accused that we are ambiguous in our language, and I think sometimes it's true, and I think this is a classic case of ambiguous language which needs to be resolved.

But that is not what I actually got up to talk about, because I have just heard Jan Bult saying that the industry doesn't think it is important to do these studies, and I want to join Drs. Goldsmith and DiMichele, who are here representing two of the major patient groups, as to what do they think, is it important for the industry to do a bit of study and a bit of development in relation to the issues which was discussed here, because, you know, this isn't multimillion dollar rocket science viral cultures, prion clearance studies we are talking about here, you know.

This isn't something which is going to bust the bank, in my opinion anyway, as someone who has done these things 20 years ago on a virtual budget.

So, I really think the patient representatives should comment about it.

MR. PENROD: Josh Penrod from PPTA. I don't think Jan Bult said that we weren't interested in doing it. His basic argument was that resources are finite.

But that being said, I wanted to comment on what Dr. Epstein had mentioned about harmonization. To the extent that we are interested in harmonizing, I would just like to point out that the European standard does not include quick freezing. It is freezing at minus 30 within 24 hours.

MS. GLANTSCHNIG: I would want to add to this just another comment. The source plasma centers in Germany, to our knowledge, have in the past been doing the shock freezing and probably still continue to do so if they have the equipment.

However, some of them, also Austrian centers, have now been going away from this fast freezing and allow just rapid freezing in a good air freezer.

In terms of validation of the air freezers, the walk-in freezers that are currently in use here in the plasma centers that we know, that operate at about, or a setpoint about minus 35, those freezers are not capable of having a freezing rate, bring the core temperature down to minus 30 within an hour or two hours. This is not the case currently. So, if this would become a

requirement, then, the centers would definitely have to either put in completely new air freezers or do the thermogenesis fast freezing or something like that.

So, if this would become a regulation here, this would really mean heavy investments. It is not possible with the current freezers. Just as background information.

DR. FITZPATRICK: Barbara, could you clarify, I thought yesterday you said that from Octapharma's viewpoint, you weren't seeing an appreciable difference in the final product in sources that were using blast freezers and sources that weren't--

MS. GLANTSCHNIG: I mean from the final product point of view, the parameters we measure were the same manufacturing method we applied to both types of plasma, we do not see a difference, and the product specifications are met for the final product.

The adverse reactions of the products we have on the market are generally very low, so there is no hint that there is any obvious problem associated with not shock freezing of source plasma. This is all we can say from the product experience side.

DR. FITZPATRICK: But you are still freezing at minus 30.

MS. GLANTSCHNIG: Yes. The plasma is put in at the temperature of minus 30 or minus 35.

DR. FITZPATRICK: But the freezing, you are not requiring a freezing rate.

MS. GLANTSCHNIG: For the source plasma, we don't; for recovered plasma, we do, because there we see it more of an issue, because the plasma is collected differently, stored before it is frozen longer, so there, the freezing rate is more of importance to end up with an acceptable product in terms of coagulation factors.

For source plasma, at least from the product side, we do not see this influence.

DR. FITZPATRICK: So, the rate for your recovered plasma, the freezing rate that you would recommend is what?

MS. GLANTSCHNIG: Well, we have for FFP, one hour minus 30 core temperature, and this is what is achieved in the current blood banks that supply that product to us. For the fractionation plasma, we require at least 4 hours to reach the minus 30 core temperature.

DR. GOLDSMITH: Jonathan Goldsmith, Immune Deficiency Foundation.

I have three quality issues I guess I wanted to address in response to Dr. Farrugia's comment, at least for one of them.

Yes, I think we would support studies to learn more about the effects of freezing on immune globulin and its properties at the end of the storage process, but

these studies ought to go beyond just identifying whether or not immune globulin is present or subclasses are present, but actually look at some functional aspects of these antibodies to see if they work at the end of the process, do they work differently, do they have lower affinities, so I would challenge the industry to take on those kind of studies.

There also may be a quality issue concerned with--I will just call it recovered plasma as a generic term. The donors who make their blood available, from whom this plasma is collected, may have negative antibody statuses as part of the collection process.

These negative antibodies may lead to a product that is inferior in terms of its antibody content at the end of the day. With current viral inactivations, patients may benefit by having more antibodies against human pathogens in the final product rather than fewer.

So, I think that is an issue that the group ought to address at some level.

Third, this is a very practical question. How do you think collection systems are going to perform when they have to make fine distinctions amongst products, stored for 32 hours, stored for 85 hours, what is sort of the practical aspect of this in running a blood center or in a busy hospital blood bank where a lot of this plasma

may actually come from? What is going to happen at the end of the day? What is the error rate?

So, those are the three issues.

DR. FITZPATRICK: Donna DiMichele.

DR. DiMICHELE: If I am to speak on behalf of the bleeding disorders community, I would just kind of like to reiterate what is important for us.

At this time, fully recognizing that the production of concentrates, the coagulator factor concentrates does not drive--the industry doesn't currently drive the need for plasma collection on any level.

I guess what the bleeding disorders community feels is that what we need, and what we will continue to need, and I hope I delivered that message adequately, is an adequate supply of quality product, not only for the current users, and I have to believe that this isn't a pie-in-the-sky, you know, ideal, but for a group of future users who represent 75 percent of the individuals with these disorders who currently aren't treated.

I mean that is a huge number who are going to need quality, affordable products. It is not the intent of the bleeding disorders community to ask industry or fractionators or blood collectors to be subjected to any unnecessary regulation.

We are, however, in favor of data and evidence-based information that would guide the industry with respect to safeguarding the quality product that we need now and that we will need in the future.

There has been a lot said today about the absence of evidence, but as I have said to people before, the absence of evidence is not the evidence of absence, and we have to be very careful. You know, we constantly do this in medicine, you know, there is no evidence for this, well, you know, but has anybody looked.

The issue of inhibitors, I just want to say in hemophilia A is probably our biggest safety issue now. It doesn't only relate to plasma-derived products, but it is the biggest safety issue out now, and there is a lot we don't know about the role of products.

So, to say that they are not involved in inhibitor development, I think not to correctly sort of state the level of knowledge. Again, we can't weigh in, in the absence of data, on any specific regulatory requirement, but we do--I mean I appreciate the regulators being interested on behalf of our community. We do appreciate the regulators being still interested in the issue of adequate collection and production with respect to clotting factor concentrates, and we do believe that this will continue to be a very, vary important issue.

I mean from our standpoint we would rather the collectors in industry put a lot of their time and effort into figuring out how we can get less expensive, good product and continue to produce it for the people who really need it the most rather than buying new freezers if it is not necessary.

But if it is necessary to achieve that goal, then, you know, obviously, we would be for it.

Thank you.

MS. HUME: Heather Hume from Canadian Blood Services, but if I may try to speak as a patient advocate, the other aspect to your same question of what studies would be of interest in terms of what regulations should there be, and is there any reason to think that freezing something at 120 hours versus 24 hours at the time of the other thing I am talking about is the length of time that it is in contact with the red blood cells and other aspects of the separation, would have any adverse effects for patients, for example, allergic reactions and such.

I am not aware from the hemovigilant studies that there is a great concern from this point of view, but this in terms of what one might look at as a patient's concerns for regulations, that would just be another to add to the previous two speakers.

But then again, what Dr. DiMichele I think was getting at in her final comments is access to product is also very price-sensitive at least in a lot of communities in the world, so regulations that, well, everyone knows that you need to balance that, so unnecessary regulations I don't think are in the patients' interests either.

MR. BULT: I have listened carefully to the comments of the consumers in the audience, and I take those comments back home. I just want to make very clear that this industry has demonstrated in the last decade and even more to make enormous investment in quality and safety, and I hope you can agree with me that the quality and safety levels that we have today is the highest we have ever seen.

So, it is not a matter of not wanting to invest. My point was that if we have to invest money, and we listened carefully to what has been said yesterday, the discussion about freezing temperature and the rate of freezing all focused on the yield of Factor VIII.

I think we have made it clear that Factor VIII is not a driver in this situation for this industry, and if we talk about yield, and I fully support the comments that were just made about availability and how can we make affordable products. We have other things in house

that we can use, such as yield-improving technologies what we have been developing.

Companies are shifting their fractionation activities that bring it to those places where they have the highest yield out of the fractionation process, and we believe that those investments at the end are going to serve the consumers more than investing money in the rate of freezing that is focused on one small aspect.

DR. DiMICHELE: Thank you for that and we do appreciate that, and we do appreciate the quality and the safety of our current products, and certainly the industry is largely responsible for that.

The only issue about yield is sort of the same question I asked yesterday, is at what point does the lack of yield or the loss of product, up until the time of fractionation, begin to affect product quality, and I am still not 100 percent sure that we have the answer to that.

So, I believe that yield is important only in so much as it affects the product. If you can take 40 percent of the original product in your starting material, that you have proven that that is good product, that that is not activated material, that there are no fractions in there that might be immunogenic, et cetera, and then you can maximize that yield in your fractionation process and still provide the adequate and

hopefully increasing amounts of clotting factor that we need, then, I don't think we would have a problem with that.

I think by the time it gets down to 40 percent, there is a problem with the protein, as well, and there is a qualitative abnormality, as well as a quantitative abnormality, then, that is when we get concerned.

MR. COEHLO: Phil Coehlo, ThermoGenesis.

According to International Blood Plasma News, there were $244 million worth of nonrecombinant Factor VIII sold in the U.S. last year. I am presuming that is correct. I don't know what it is worldwide. But if anyone purports to say that the cost of fast freezing is a consequential impact in the profit of that product, I would have to see the numbers. It certainly couldn't be so by the revenues in our company.

Secondly, I would say fast freezing, all the literature I have read, and what Dr. Farrugia has reported here, is fast freezing does have an effect on the labile proteins, and if 70 percent of the world's population is unable to afford them, then, it is a very difficult argument to say that improved yield won't some way or another help those people.

DR. FARRUGIA: Look, we on this side of the fence have been acting very reasonable in saying yield is not our baby, but let me just remind you what was, in

fact, stated yesterday and reiterated by comments from Gail Rock and people like that.

We are talking about the process here in terms of Factor VIII, and which by the good efforts of the collectors, plasma is delivered in a state of anything between 700 to 1,200 International Units per liter.

The fractionators trot out something which is anything between 120 to maybe 250 International Units per liter. That yield is not the manifestation of just physical loss, the Factor VIII in those final products, and anybody who has looked at this with SDS page and the immunoblots, and so on, is not exactly negative Factor VIII. Things have happened to it.

Now, I know that is debatable whether the things which have happened to it have actually done things to patients, but let's not get away too much with this business that yield and safety are totally divorced.

If a protein is lost, and that protein is found in the product in a degraded form, and if there are conditions in the manufacture and the collection and generation of the plasma which contributed to the degradation, and I would submit that there is evidence that there is, then, yield and safety suddenly start living very closely together.

MS. KIRSCHBAUM: Nancy Kirschbaum. I am a reviewer in the Division of Hematology at the FDA, and I

would like to speak in support of Dr. Farrugia and the importance of having time to freezing in the regulations of plasma because if we go back to the fundamentals of biologics manufacture and consistency of product.

I support what Dr. DiMichele said also about having science-based support for our regulations, but in the current absence of such information, if we go back to fundamentals of biologics manufacture, and implement the fact of consistency of manufacture, and having that consistency and how important that is, and the time, temperature, and pH are the fundamentals of what the conditions are as far as producing a consistent product, that can then be used maybe according to license and validated by the manufacturers.

We know that there are things that happen when plasma sits as whole blood in contact with cells, and we know that as it sits longer, it is at different temperatures, that we can think that coagulation activation and platelets activation can occur.

We know that this is affected by time to freezing and the temperatures.

I don't know if you want to add anything to that. So, I want to support Dr. Farrugia and say that it is important, I think, when we talk about regulations of recovered plasma, that we do include some sort of requirement for time and temperature to freezing.

AUDIENCE: I just want to come back to the Factor VIII yield issue, that I think that when we talk about the fact that yield is not to the production recovery of the Factor VIII per se, rather than to use a Factor VIII potency as quality attributes to measure the quality of plasma.

So, when you measure something like plasma, that you do like to find the most sensitive element that you can use to measure the quality of the plasma, and Albert pointed out yesterday that the Factor VIII, he believes is the most sensitive quality attributes that you can use to measure the quality of plasma.

Now, whether these quality attributes is a necessary risk factor to the end product, and I have heard many comments that already, today and yesterday, that we don't have a significant amount of the scientific data to support that.

Now, Albert did present some of the studies that he had done 20 years ago, that he found that Factor VIII is affected by certain process conditions, such as storage time and, you know, the freezing rate. So, I agree with Albert that we do not strictly talk about yield of the Factor VIII, but rather use the Factor VIII potency as quantity attributes to measure the quality of the plasma.

DR. FITZPATRICK: Dr. Bianco and then Mary Gustafson.

DR. BIANCO: First, I want to clarify something that was said before about the management of blood products and plasma and potential difficulties, complexities. People don't manage that, computers do, and when they are properly put together and validated, the scanning of a bar code is better than the pharmacist in the hospitals or the blood banks in the hospitals. The scanning of a bar code is going to say what the product is and how to manage it.

Even many places today use on-demand labels that will be spit and glued to the bag appropriately.

The second thing, I would ask that at some point, the manufacturers, and I ask specifically Octapharma, Barbara Glantschnig, about Factor VIII needs of the company in its market. I heard her say yesterday that they have a lot of intermediate product sitting in their freezers, and what would happen if their yield was bigger and what would they do with that.

The third thing is I want to raise a point regarding using Factor VIII as the marker for the quality of plasma. I find even as a scientist in the old times, difficult to say that it's a marker. I think it's a superb marker for Factor VIII, and it's perfect, and will tell you exactly how much Factor VIII is there, but for

overall quality, I don't think that there is enough science saying that the shape of an IgG molecule that is there or the balance between the several subtypes or things like that, is at all associated with the recoveries of Factor VIII.

DR. FITZPATRICK: Do you have evidence?

DR. BIANCO: I don't have evidence, but you don't have evidence either, so we are in the same situation.

That would be my point. So, I believe that, yes, there should be some conditions, but I believe that we have to think of how much benefit is going to come from the investment into all the new freezing equipment and all that, how much money are we going to give to Mr. Coehlo from ThermoGenesis and help his company, and what is the benefit that we are going to derive from it.

MS. GUSTAFSON: We have heard a lot about what needs to be done, what would be nice to do, what we think might be appropriate, but I think it all comes down to prioritization. There is not unlimited resources for any of us, and we have to look at what we can do with what we have.

There has been a lot of work. I think the industry has been leaders in prion removal. Just in the last couple of months, conversation with Dr. Epstein, he

would like to see more robust viral clearance methods, particularly for non-envelope viruses.

Just in the last year, we had to make sure the products were free from West Nile virus. That was no small undertaking. Also, issues with SARS that came up, the issue of the smallpox vaccines. All of these required resources, and it is an issue of prioritizing resources in a very tight economic market.

I invite FDA to review the history of the vaccine manufacturers in the '80s, and we don't want that to happen. I mean you can have a lot of product consistency if you only have one manufacturer making one product, however, you don't have access and you don't have choice.

DR. WALKER: Tom Walker, Canadian Blood Services.

I am either blessed or cursed with a long memory, and I can remember work that Bayer did about a decade ago comparing the yield that they were getting from our plasma, yield of Factor VIII at the time, to the yield that they were getting from their commercial plasma.

The plasma we were sending for fractionation was essentially FFP. It was frozen, flash frozen using either an instacle [?] or a blast freezer within 8 hours of collection. Their plasma was placed in a minus 20

degree freezer approximately half an hour after collection. It was source plasma versus plasma derived from whole blood.

They were getting better yields than we were. So, while I recognize that the rate of freezing is important, time of freezing seems to be equally important, and that is a rather long-winded route to get to a proposal that I really, sitting in the audience, I hear may be a consensus of this group, that the stratification or the freezing of this plasma for manufacture, component plasma, whatever we call it, call it Sam, could be frozen to a temperature of minus 20 or minus 30 if that really improves the locking in of the Factor VIII, frozen to the temperature within 10 hours after collection, frozen to minus 20 within 24 hours after collection, and frozen to a temperature of minus 20 within either 72 or 120 hours after collection.

That seems to be what the current practice is. It would provide codification, it would provide a framework on which we, the plasma manufacturers, could build, and it provides the information that I think the industry wants in order to be able to standardize, validate, control their processes.

AUDIENCE: I just want to make a comment about the quality attributes issue, that I agree Factor VIII potency or yield may not be critical quantity attributes

for some product like immunoglobulin product, but what we are talking about here is the quality of the plasma.

Without knowing what quality attributes is important for the IGIV, for example, what you normally do is try to maintain the quality of plasma, your study material, to the extent close to the native form as possible, or you can demonstrate under that condition this level of quality of plasma is suitable for your end product.

What I try to say is that we should really distinguish the quality of end product and the quality of plasma, so we can really, you know, to make, and then we talk about what is the relationship later.

I have not seen that much scientific data to say what quality or degrees that we can relax at a plasma level that will not affect the quality of end product.

DR. SCOTT: Dorothy Scott, FDA.

I just wanted to add to what Nancy Kirschbaum said, and Andrew Chang, as well, and to respond to the statement that there may not be any difference between plasma frozen at 24 hours versus 120 hours, or presumably versus any other time.

I think that the problem is, as we have all said, absence of data, but what we do know is that the cells in plasma release various mediators and factors, and other factors get activated over time, especially

platelet activation at lower temperatures where this may be stored.

We also know that bioburdens can increase, and while there isn't a bioburden obviously in end product plasma derivatives, the components of that bioburden can come through, and we know that there is bacterial DNA and other components of bacteria sometimes left in end products, and we can see this. There is even a level of LPS, but, of course, everybody has a cutoff for that.

So, we haven't seen any data, we haven't seen data that links products made from recovered plasma with products made from source plasma, to look at whether or not the adverse event rates are different.

Now, I do understand from Octapharma that they have looked at this, but not really with using a lot of U.S. recovered plasma. I think it would be nice to see that data, we certain have manufacturers that use both, and we haven't seen that. It may or may not be informative. I think it will be informative.

The other thing that we haven't seen, looked at side by side, is stability, because stability is a parameter for essentially unwanted enzymes in your end product, at least for immune globulins, and that might also be a useful comparison that would tell us whether or not that makes a difference.

DR. FITZPATRICK: Just a couple more comments.

MR. BAKER: I would like to thank Dr. Scott for that segue for my next comments. I am Don Baker with Baxter HealthCare.

We produce products from both source and recovered plasma. The products that we manufacture under our own brand are all from source. The products that we manufacture by contract are from recovered plasma.

I don't have answers to the questions of whether or not the freezing makes a difference with respect to quality or safety of the product. From my perspective, I don't believe they do, however, what I can tell you is what, as a manufacturer, we can do relatively straightforwardly and what information we have, and what is much more difficult and which I think might be a more futile exercise.

For example, we know from our experience that both materials produce products which meet all of our quality attributes, so, in other words, from the materials that we get now, we are perfectly able to produce product that show no difference with respect to success in the manufacturing process or differentials in terms of meeting our final product requirements.

With regards to the adverse event profiles, I can say that both materials were used in our clinical trials to license our products, and within a clinical

trial, there was no difference with respect to the adverse event rate we saw with these products.

Now, in our postmarket surveillance, and I should say I run Baxter's complaint department, which explains my normally cheerful disposition, and we do look at this as a variable, do we see differences in rates between the products.

Now, I have to tell you given the--well, let me give you a typical experience you get with IVIG. A typical manufacturing run for a lot of IGIV might be about 5,000 vials. IVIG, as a product class, constitutes about half of the adverse events we get for all of our plasma derivatives, so IGIV gives you about half. The rest of the plasma derivatives gives us the rest of our reports.

On a typical, 5,000-vial lot, we would see between, oh, zero and 4 periodic adverse events. These are your typical not serious adverse events, and zero to 1 significant adverse event.

So, if you think about that in terms of the statistics of small numbers, and realizing that IGIV gives you most of your adverse events, you can see how large of a comparison you would have to run, how many lots you would have to evaluate, how much experience you would have to look at to even get enough events that you felt you might want to be able to look at that.

Then, having decided that you were going to look at that, you would have to take into account all of the confounding variables with respect to how those products are used, and I can tell you there are differences in demographics between people that get products from the source and the recovered because of the differences in terms of how the various companies market them.

There is also significant differences potentially in how well the report is received and how vigilant the vigilance group is. So, I don't have an answer, but I just want to indicate to you how difficult this would be as a study without a hypothesis that you are specifically examining in terms of product attributes, something that was in the product.

If you are just looking at an association, this is going to be a huge trial, and I predict not a particularly useful exercise.

Thank you.

MS. GLANTSCHNIG: I just wanted to comment on what Dorothy Scott said to clarify. We do actually have more experience with immunoglobulin production from recovered plasma than source plasma. The mixture is meanwhile about 50-50, but it was more recovered in the past.

So, we have like an 8-year experience with our IVIG product, and from what we talked yesterday, the

observation of the number, the total number of adverse events that are reported, and also now within the postmarketing surveillance here in the U.S., is extremely low, and there is so far no recognized pattern as to the source.

Also, in the clinical trials, we included both plasma types. The data that we looked at, the quality assays that we used and that were discussed with the authorities were the same. So, from that respect, again, it was not a controlled study looking for such a pattern, but there is no indication at this point.

DR. SCOTT: Recovered plasma from the U.S.?

MS. GLANTSCHNIG: Yes, from the U.S., we have been purchasing that product from the U.S. for several years now.

DR. FITZPATRICK: Dr. Farrugia.

DR. FARRUGIA: Well, you know, I am a regulator, which explains my morose and distrustful nature, but I am interested in the last bit of the discussion. Certainly, in our agency, we recognize that the pharmacovigilance of plasma derivatives is not exactly state of the art, and is actually very, very difficult, and I wouldn't like to see long-term regulatory postures being shaped upon it.

But I what I got stuck to again was this vexatious issue of Factor VIII in relation to what Celso was saying. I wouldn't like to see, and I think I made

this clear yesterday, my criticism of the relevant parts of the European regulations, I would like to see blood banks doing a lot of Factor VIII assays as part of the overall release criteria for plasma for fractionation.

I think there is a lot of limitations there, but I do think that there are some basic conditions which we have tried to discuss today and yesterday, which are indicative of minimizing certain changes in plasma which are probably most related to proteolysis, and it is not just the Factor VIII.

You can measure the studies again from the same Swedish group I quoted yesterday, which show that, for example, as plasma is stored, you get the generation of plasmid, an enzyme which I believe does have an effect on immunoglobulin, and that you get the generation of pre-kallikrein and other things which are nasty things.

I showed data yesterday, which I describe as of historical interest, which are that when you get rid of issues using conditions which nowadays nobody I think wants to push like generating plasma from outdated blood, that you actually do get, over the course of storage of an immunoglobulin product, degradation.

So, what Factor VIII is, it is the most sensitive, easily accessible indicator. Probably there are more sensitive indicators like fibrinopeptide A and TROMA-3 [?] complexes, and so on, but I suspect that your

average blood bank lab can do a good Factor VIII assay these days, but might find it a bit more challenging to access these assays for which, in fact, there is very little international standardization available.

So, I would again plead for Factor VIII to retain some level of relevance in this whole debate irrespective of whether it is going to be a product, and we have heard again, Donna DiMichele say that Factor VIII is a product. I mean I am getting a bit confused. I see some ambiguity here coming from the industry.

On the one hand, they say that, you know, they have got these products, they need to sell them and they need to make the process as economical as possible. On the other hand, they say here is this product for which 75 percent of the world still doesn't have access, and that is not going to stay the situation forever, we hope.

That is, I think going to be my last comment. I think I have earned my keep at this.

MR. ROBINSON: Richard Robinson, American Red Cross.

I would like to follow Don Baker's comments about doing the studies, some of the difficulties that are involved. Once you have done the studies, communicating the information back especially to the consumer groups who have requested this information, falls into the realm of advertising and promotional

labeling, which has very stringent requirements for comparative claims, and we have to walk a very fine line.

Something as simple as the phrase "time to hemostasis" could be the subject of several paragraphs of a warning letter, and so it is very admirable to do these studies, but communicating that information back is an additional difficulty.

DR. FITZPATRICK: Dr. Wilkinson.

DR. WILKINSON: Thank you, Mike. I just wanted to make a follow-up comment to Dr. Scott and her comments, and the comments from her colleagues.

I just want to make sure that everybody understands that most of the recovered plasma that the blood industry makes, that plasma is taken off at the time those units walk in the door. We transfuse very little whole blood, and again, you know, while we acknowledge what you are saying about things leaching into the plasma from the cellular elements, that is not how we make recovered plasma, by and large.

AUDIENCE: I would like to make one comment about Factor VIII and being a general quality attribute. I am glad that Albert said he will not stand up again.

[Laughter.]

DR. FITZPATRICK: I don't think we can count on that.

AUDIENCE: So, I mean I always hear that we assume, if we have a lot of Factor VIII, that this would be beneficial for the product in general, but, of course, it could also be the other side, and since you don't have any evidence, I think we should be a little bit careful, because at least we have in our company one evidence where this could be of a negative impact meaning a quick freezing, high Factor VIII, but then for some other proteins, we have seen a negative impact. So this means it could go in both directions.

This is preliminary data, I cannot show it to everybody, but my point would be that we should be careful to assume that it could be beneficial.

DR. FITZPATRICK: Dr. Scott.

DR. SCOTT: I just wanted to respond that we have heard from ZLB Behring that they require plasma be frozen within 120 hours, which is at least several days, and we have heard from the American Red Cross that they have 800,000 units of plasma per year that are frozen after 24 hours, and we don't know how long after 24 hours.

So, I do understand what you are saying, that possibly a majority of plasma is immediately frozen. Then, there are logistical constraints on that with the mobile units and the weekends, and things like that.

DR. FITZPATRICK: Peter.

DR. PAGE: I thought the point Susan was making was that the cellular elements are separated promptly from plasma now. Certainly, the move towards leukoreduction of red cells has requirements that they be separated within 72 hours for some filters.

DR. FITZPATRICK: Dr. Chen, and then I think we need to move to our last--

DR. CHEN: It is my last comment. If I may, I would like to ask Dr. Baker a question. Let's make a hypothesis that your company wanted to make a manufacture change to use recovered plasma for one of your products which is currently licensed only with source plasma.

Your company also ask us not to do any clinical trial, because you can see that this is a minor change or not very significant change that need a clinical trial.

I would ask you what kind of a quantification that you would like to measure for the recovered plasma that is suitable for your end product, that does not adversely affect the safety and the efficacy.

So, what parameter, what quality attributes that we can look at in order to have an end product that has the same safety and efficacy.

AUDIENCE: I actually thought that was the last comment and I wasn't going to have to respond to that.

Let's say that we wanted to qualify, let's say, plus 24-hour plasma, which we currently don't use in our

manufacturing process, and we were intending to qualify it for a particular product because obviously, this would be a case-by-case basis, but let's suppose we were wanting to qualify it for IGIV.

We would, hopefully, work with the agency to develop a comparability protocol which would call out both the process and final product parameters, which we would compare for our current production, and hopefully, we would be able to make a case to the agency that the parameters, the in vitro parameters that we could measure, or the preclinical parameters that we could measure would be convincing enough to demonstrate the comparability of the protocol.

This is a tactic that we have used, a strategy we have used in the past. Now, the agency reviewers may or may not find the in vitro comparability protocol acceptable, and when I say "comparability," this would be three lots manufactured utilizing this plasma.

If the agency is not finding the in vitro case convincing, then, we would be looking at, hopefully, an abbreviated clinical trial, which might be pharmacokinetics and perhaps measurement of some selected antibody titers.

If the agency did not find that compelling, well, then, we would be looking at a more full-blown clinical trial, but to me, each one of these is a case-

by-case situation and both product- and process-dependent in terms of how one intends to evaluate that.

DR. FITZPATRICK: I have a question for the manufacturers. We are making the assumption that if we have more Factor VIII in the raw material, there will be more Factor VIII in the concentrate, and that if it's a better Factor VIII in the raw material, it will be a better Factor VIII in the concentrate.

The two questions are, one: With current technology, have you reached the limit of your capability to extract Factor VIII from the raw material, because we have seen that you have a variety of Factor VIII levels in the raw materials you receive based on Dr. Farrugia's data.

Yet, you state that the Factor VIII levels are not being impacted in the final product that you manufacture. So, that is the one question, is technology at the point that you are extracting about the maximum levels of Factor VIII you can regardless of how much is there to begin with?

The other question is more a basic science question. There has been a debate in the cryobiology literature about native protein, and we have made the assumption that when we freeze a protein, we are preserving the native structure, but there is some debate about that now, that the native structure is actually

changed just by freezing of protein, and that when you thaw the protein, regardless of how stable and robust that protein would be, is not the native protein when you thaw it.

So, when you extract and inactivate and go through all the steps of fractionation, we know that there are differences in the protein that you end up with, and that those are impacted on by the process you use to fractionate and extract the protein.

So, is providing you a better raw material really going to have any impact on the end product, because of the manipulations this goes through, and is it going to have any impact on the amount of that protein you are able to extract in the process?

DR. GLANTSCHNIG: That is not an easy question, and I am here not the fractionation expert, I won't go into a detailed answer, but a very, very superficial view on this.

Without processes that we use for our products that we sell on the market, we also produce products in the frame of certain fractionation programs, and I won't go into details which programs these are. We use plasma that is being produced under certain conditions, that have been specified for those countries, and that do differ from the situation that we have in the U.S. and in

Europe, and all I can say is that we definitely see a difference in the behavior and also in yields.

The starting material does matter. Can we improve it from the current state to another level? Probably. Are we satisfied with the current level in the U.S. and in Europe? Yes. That is what I could say from my perspective.

DR. FITZPATRICK: The last question was distinctions to be made from source plasma and plasma for manufacture, or recovered plasma, as we currently call it, and we have heard discussion about the only real distinctions are the donor qualifications from the industry standpoint.

Is there any further discussion on that?

MS. GUSTAFSON: Donor monitoring, I mean there are some donor issues like the malaria, the testing, but a lot of it has to do with the donor protection by the physical four-month samples, the protein, and the monitoring of the donors.

DR. FITZPATRICK: Dr. Page.

DR. PAGE: A different aspect of a current distinction that I was educated about yesterday is that in storage, source plasma is permitted a temperature excursion up to minus 5 for up to 72 hours, which is not an exemption we enjoy with our recovered plasma. So, consistency might be nice.

DR. FITZPATRICK: Dr. Gilcher.

DR. GILCHER: I just want to say on the front end again that we do have the dilution difference of 90 percent absolute in source versus 80 percent in current recovered, but also the difference in the citrate concentration of it being 50 percent higher in the recovered versus the source.

DR. FITZPATRICK: Are those differences in the opinions of people, do they warrant labeling differences other than in a name?

DR. GILCHER: No, I am not saying that. I am saying that there needs to be--you were asking for the differences in the plasma--this is an absolute and consistent difference between the two plasmas on the front end.

DR. ROCK: Gail Rock, Ottawa.

I would just add a comment to what Ron has just said. In the very early days when the first batch of apheresis plasma was fractionated, by what was then Cutter, and they ran the autopheresis C machine plasma through, I got a frantic phone call saying we have no Factor VIII, what can we do about it.

It turned out that the conditions of the plasma with the lower citrate, different pH, et cetera, did not respond in the same way, of course, to the first buffers that were added, and the Factor VIII had gone into a

cryogel and all floated off into their filters. So, these is some use for the manufacturers to know what kind of plasma is coming in.

MS. GUSTAFSON: The anticoagulant is already listed on the labels.

DR. FITZPATRICK: This is for Mark and Dr. Epstein. Have we covered the gamut of what you--

Closing Remarks

DR. EPSTEIN: I think Mark Weinstein was supposed to make closing comments, but I feel that we have had a very good discussion. I appreciate the fact that people have come willing to share information. I think we have managed to wend our way around the various issues that would be pertinent to any kind of a regulatory framework.

I can assure you that the FDA will think carefully about these issues, and as I said in my opening remarks, this is just one of many potential venues for us to pursue development of the regulatory framework.

We are not going to do anything rash or unexpected, that we hope to continue in the spirit of open dialogue.

DR. WEINSTEIN: Again, just to emphasize, that we do have various ways of communication here. We will have this docket available for comments, and we encourage you to submit your comments to that. We also will be

inviting manufacturers to come in and give us more information, perhaps confidential information that they would like to share with us.

We will be looking for experimental opportunities to try to answer some of these questions. Perhaps this is an area that could be raised at the upcoming October 7th Critical Pathways Initiative where there is a conversation here about what things might be appropriate to develop research programs in, and you would have an opportunity to mention that these things are important.

DR. FITZPATRICK: From our perspective, we want to thank the FDA for the workshop. There has been a lot of knowledge exchanged both ways, and continuing the dialogue is definitely something we desire.

DR. BIANCO: And we want Albert back.

[Applause.]

[Workshop concluded at 11:49 a.m.]