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P A R T I C I P A N T S

Moderator: Dr. Les Holness

SPEAKER PAGE

P R O C E E D I N G S

DR. HOLNESS: Let's get started. I'm Les Holness. I'm with Division of Blood Applications at CBER. There are a few announcements before we start our session today.

There is no smoking anywhere in the building. The bathrooms are on the left side and both sides of the main conference room outside and upstairs. The cafeteria is on the floor above. Telephones are on the right outside.

There is a message board right outside this conference room, area code 301-496-9966.

Transcripts of the workshop will be available on the CBER website 15 working days after the meeting.

There are also evaluation sheets at the back of your handouts. If you'll fill those out at the end of the session and leave them with us, it will be very helpful.

Our first speaker today will be Dr. Jay Epstein. He's the Director of Blood Research and Review at CBER, Food and Drug Administration.

DR. EPSTEIN: Well, I don't know that I'm a speaker so much as a greeter. It's my pleasure and privilege to welcome everyone to this FDA Workshop on Plasma Standards, and I'd like to start by thanking the principal organizers, who are Dr. Holness, Dr. Weinstein,

and Elizabeth Callaghan, and also special thank to Joe Wilczek for providing logistical support for this meeting, including rescuing it when we lost our venue at Lister Hill. And I hope there wasn't too much confusion with people going to the originally planned location.

I also want to thank in advance both our speakers and attendees for their efforts to ensure a successful meeting, and especially those who have come from Australia and Europe and other long distances.

So I guess the lead question is: Why are we here? And to start, I'd like to show some of our meeting objectives which are related to information gathering that will help FDA develop an ultimate policymaking initiative. So what are the objectives?

Well, we seek to obtain information that would aid in the development of regulatory standards for the entities that we now call recovered plasma, and subjects of concern include potential labeling and the freezing, storage, and shipping conditions.

We additionally have the objective to review scientific data, regulatory requirements, and current industry practices regarding the freezing, storage, and shipping of plasma to ensure the safety, purity and potency both of the labile and the non-labile plasma components, and we have also the opportunity, if you will, to explore the potential to harmonize the

requirements with other regulatory bodies, recognizing also that in this field many of the standards are standards rather than regulatory requirements as one looks place to place.

Of course, we hope to ensure that any regulatory decisions that our agency might make will be based on a good understanding of the current science, but also a perspective on the need or lack of need for change and the practicality of any proposals that might be made.

So what are the policymaking goals? They're summarized on this slide. We seek to identify the quality of plasma based on labeling to indicate the conditions of freezing. In other words, as products are distributed in the U.S. and worldwide, it should be patent through their label exactly what condition of plasma is being offered.

We seek to remove barriers to conversion of plasma collected with the intention for use in transfusion or conversion to use in fractionation. This is a request that we have received from parts of the blood industry that are uncomfortable with the current limitations which reduce flexibility.

We do, however, feel that where we may relax some barriers, we need to retain some distinctions, and the issue is to retain only those distinctions which are important. And some of the distinctions that will need

to be considered are: labeling that would distinguish plasma coming from a whole blood collection versus an apheresis collection; product characterization based on intended use at the time of collection, which is now fundamental in the FDA regulations; as well as the aforementioned conditions of freezing.

And we want to ensure that our regulatory standards, as I stated, conform to the scientific state of the art.

Now, just a word about process. It's important to note that policymaking in this area will be a deliberative process. No one should expect a rapid change, and we will certainly proceed in a public manner with ample opportunity for notice and comment.

Now, in particular, regarding this workshop, let me just note that this is only one venue for collecting information. Additionally, there's been some concern how public are we pressing companies to be. Proprietary or confidential information will be considered through one-on-one discussions with the regulated industry. There is no intention here to impose or compel disclosure of proprietary or trade secret information. So whatever information is being shared is being done voluntarily.

Additionally, in the spirit of information sharing, it is our intention to establish a docket--I believe we have to do that by publishing an FR notice.

That has not yet happened, but we will establish a docket for this workshop that will provide a mechanism for further sharing of public information. In other words, people can write to the docket and provide information that is then made public for the ongoing dialogue. And as I said, any policy proposals will be developed through a public process of notice and comment.

Now, for the remainder of my remarks, I'd like to provide a brief overview of the program and pose some questions that I hope will be discussed at the meeting, predominantly in the panel discussions. So starting with now, Day 1, and looking at the morning, we'll first have a summary of the June 20, 2003, Blood Products Advisory Committee, where we made some proposals and heard recommendations on standards for recovered plasma, and in particular, focus on the need to develop specifications for the allowable storage conditions and dating periods of a product which is potentially a licensable product.

We will hear a consumer perspective on the need for high-quality plasma products, and then we will review manufacturing standards for plasma for fractionation, which come basically in two parts: first, a special guest invitation to review the literature on the effects of time to freezing, rate of freezing, and the freezing and storage temperature on the integrity of plasma proteins; we will then have a segment where we review our

regulatory standards around the world, starting with the FDA framework, which, as you know, does not have requirements for recovered plasma; and then the overview and rationale of the international standards for plasma freezing, storage, and shipping respectively from the Council of Europe and the European Pharmacopoeia, Canadian standards, and Australian standards.

In the afternoon today, we will then have--I guess I fell behind a little bit. The next one. In the afternoon, we will then hear about the current practices in the plasma fractionation and the blood collection industries, and this will be followed by the first of two panel discussions.

Now, the first panel will focus on the science, the current practices, and the regulatory oversight of plasma preparation, and we've famed two questions in particular:

What conditions of plasma collection, processing, shipping, and storage are necessary to ensure safety and efficacy of plasma derivatives? And a subsidiary question, whether the same standards should apply to all plasma independent of the end products that may be made from different collections?

And then the second question: Should any restrictions between placed on further use of plasma based on the conditions of plasma collection, processing,

shipping, and storage? Is there such a thing as a recovered plasma which was frozen sufficiently after the time of collection that it shouldn't be used to make an injectable? And, of course, we will be informed hopefully by current practices.

So that panel will conclude today's session, and then tomorrow, which is a half-day meeting, is mostly about straw men. I guess that's sexist, but I've never heard anyone speak of "straw women." It's probably unflattering. But the idea is that we will listen to proposals on candidate regulatory frameworks for recovered plasma, and you'll hear proposals from the FDA, from sectors of the blood industry and the plasma industry, and then once again, that will be followed by a panel discussion.

Now, the questions for this panel include the following--again, the subject being the framework issues for possible licensing of recovered plasma. So, first off, what should we call the various plasma products that are distributed for further manufacturing use? How should they be labeled? In particular, should they carry labels according to the time and/or rate of freezing? And if so, what would be a suitable stratification for such labeling? Should they continue to be labeled according to intended use? And then what distinctions should be made from source plasma? Should the

regulations be neutral, for example, if a fractionator seeks to switch wholly from source plasma to recovered plasma should we have no concerns at all about validation of end products, or should we be concerned about revalidation at some level?

Now, I am aware that a certain amount of confusion and apprehension has surrounded the run-up to this workshop, and I'm hopeful that my remarks have served to clarify the focus of the meeting. And I do look forward to a productive day and a half of information sharing and thoughtful discussion.

So at this point, I'm going to turn the podium back to Dr. Holness so that we can begin the meeting in earnest, and thank you very much.

DR. HOLNESS: Thanks Jay.

Now for a summary of the June 2003 Blood Products Advisory Committee, Liz Callaghan will give us the summary. She's Deputy Director, Division of Blood Applications at CBER.

MS. CALLAGHAN: Good morning, everybody. I hope you didn't have too much of a time getting over here from the other building. Sorry about the confusion.

I would like to give you a brief summary of the June 20, 2003, Blood Products Advisory Committee meeting. Actually, the issue with recovered plasma started at the Blood Products Advisory Committee on June 13, 2002. FDA

made a presentation to the committee and asked if we should, in fact, develop standards for recovered plasma. The committee unanimously voted yes, and they gave us some additional recommendations: come up with an alternative name; develop a strategy to allow apheresis plasma from whole blood donors to be used for further manufacture; and to distinguish this component from source plasma.

FDA then went and developed some strategies, and they were presented at the June 20, 2003, BPAC. To address the alternative name issue, FDA asked, Could we name the product "component plasma"? And to address the apheresis from whole blood issue, FDA proposed defining recovered plasma or component plasma as "plasma that is collected manually or by apheresis, either separately or concurrently with other blood components, from donors who meet all whole blood donor suitability requirements."

To address the distinction between source plasma, FDA proposals moving the requirement to freeze immediately after collection into the definition of source plasma.

FDA also proposed two additional issues: One, should the time to freezing standard be defined for plasma for manufacture into labile derivatives? And should there be a 10-year expiration date for this product?

There were several industry presentations, and this is a very short list of what was presented, and I took highlights from it, and these were some of the suggestions that industry had: They all agreed that we should license recovered plasma. There was a suggestion that we harmonize with EU standards. Some felt that we should have freezing temperatures consistent with FFP. Another suggested name was "plasma for manufacture." There was a suggestion of a 2- to 3-year expiration date. And they did not want any specific time to freezing.

The committee had discussions, and these were the recommendations we got from the committee: "Component plasma" was a possible name. There should be a different name for plasma for manufacture into non-injectable products. The committee felt that there was not enough data available to comment on the changing of the definition of source plasma to include freezing immediately after collection.

There was not enough data available to decide on the appropriate temperatures or the dating periods for the product. There was not enough data available to comment on the time to freezing as a criteria for manufacture into labile products. And they suggested that we have a workshop to collect this needed data, which is why we're all here today.

So hopefully we will be able to satisfy the Blood Products Advisory Committee. Thank you.

DR. HOLNESS: Our next speaker is Dr. Donna DiMichele. She's Associate Professor for Clinical Pediatrics, School of Medical Sciences at Cornell University in New York. Welcome.

DR. DiMICHELE: Good morning, everyone. I'm Donna DiMichele, and I'm here actually to present what I was asked to do, and that is the consumer-physician perspective on this issue. And I just wanted to say that I will do this on behalf of several organizations. I do not speak basically with my own views. I am speaking on behalf of the consumers as represented national by the National Hemophilia Foundation, as well as those represented internationally by the World Federation of Hemophilia. So in that way, I'm actually internationally representing the bleeding disorders community.

By the way, I apologize that this talk was actually sent at the last minute so you don't have a handout. As typical for physicians, they sometimes get a little busy.

Now, with respect to the National Hemophilia Foundation, we have several bodies that include the Medical and Scientific Advisory Council to the National Hemophilia Foundation, and there is a working group called the Blood Safety Working Group, which is a

subgroup of the Medical and Scientific Advisory Committee, that also has views that are represented in this discussion.

Now, I'm going to start by actually delivering the message straight out in terms of what we have to say, and basically what the message from the bleeding disorders community is is that it is incredibly important, in our view, that whatever standards are developed have the goal of both preserving the intent to produce as well as optimizing recovery of clotting factor proteins as an essential responsibility of the plasma collectors and fractionators, given national and global needs of this community. And I'm going to talk a little bit more in detail about the global needs of this community.

We'll also suggest that national and international harmonization of plasma collection, storage, and processing may indeed provide the most cost-effective way for all stakeholders to fulfill this collective responsibility to produce safe and effective as well as affordable product in adequate supply. However, we will stress that in calling for harmonization, in our minds the goal of harmonization is that of equivalence rather than uniformity of process and outcome.

Now, there are other stakeholders, there are other consumers who are not going to get a chance to speak today, and on their behalf, particularly on behalf of those patients receiving immunoglobulin and Jonathan Goldsmith of the Immune Deficiency Foundation, I also want to add that these consumer groups also have concerns and would like some input into the issue of plasma standards, especially as it relates to what we're now calling source versus recovered plasma. And their issues are multiple, including efficacy, in other words, the amount of antibody that's actually in the product, as well as safety. And safety issues including recordkeeping, adverse events rates, and donor and donation issues as well as supply are all going to be factors with respect to their goals in these discussions.

Now, back to the issue of the bleeding disorders community, I just want to say that the intent of this presentation will not be specifically to enter the debate on specific regulatory standards for plasma intended for fractionation with respect to collection, storage, and manufacturing, particularly issues that are going to be very critical in terms of time to freezing and freezing temperature. Nor are we intending to discuss the scientific basis for maximizing yield of labile and non-labile clotting factors, which we think to be important, but there are people more qualified than me to represent

those issues. And, in fact, Dr. Farrugia will continue with that discussion after me.

Now, we predicate a lot of what we say on the fact that there is a need, and the reason that we feel like we have to actually convey this message is because there is a sense in the United States that clotting factor therapy is now recombinant, and particularly for Factor VIII and for Factor IX, that there is no requirement or very minimal requirement for plasma-derived Factor VIII and Factor IX. And so, therefore, why should standards continue to be important with respect to particularly Factor VIII, which is a labile clotting factor?

And, indeed, if you actually look at the U.S. figures--I don't know if I can use a pointer here. If you actually look at the U.S. figures, indeed, 70 percent is recombinant; therefore, only 30 percent of the clotting factor that's used for hemophilia A is now plasma-derived. But the fact of the matter is that the requirements at somewhere between 1.1 billion units total or 1.4 billion units in the unit are such that even 30 percent represents a sizable amount of clotting factor, as you can see here by the approximate number of units being about 420 million for Factor VIII. And that's plasma-derived Factor VIII.

Now, similarly for Factor IX in the U.S., as well as for bypassing agents, the split is about the same. It's about 75-percent recombinant and 25-percent plasma-derived. Factor IX is a rare disease, so the requirements are only about 65 million in terms of a total number of units, but that's still sizable.

The bypass agent requirement, the numbers are a little bit proprietary and, therefore, were not included in this.

What's totally unknown is the amount of plasma-derived product that's needed to treat all the other disorders, including von Willebrand disease and the rare bleeding disorders, which I'm going to come back to, for which there are no recombinant products licensed in the United States.

Now, that's the U.S., but, however, what we're going to present here today is more of a global view because the hemophilia community and the bleeding disorders community is a global community. And if you look at the same situation across the world, excluding the United States, more like 58 percent of the clotting factor that's used--and you can see to the tune of a billion units of Factor VIII and 135 million units of Factor IX--is plasma-derived. And I want to thank the World Federation of Hemophilia for these numbers, which came from a WFH global survey. And I just want to state

that those numbers, as large as they are, represent only 25 percent of the world's hemophilia patients because 75 percent get almost no treatment whatsoever. So you can imagine that the capacity, the world capacity for this clotting factor is tremendous, and as large as it is, is minimally represented. The numbers for bypass agents as well as the plasma-derived requirement for rare bleeding disorders and von Willebrand disease is also unknown globally, but you can imagine is quite huge as the rare bleeding disorders are oftentimes very well represented in countries where consanguinity of marriage is frequent.

And, by the way, I also want to thank publicly Patrick Robert from MRB for help in putting together these numbers, which I'm sure are an approximation. But hopefully they do indicate that the need is still tremendous.

Now, I said I represented the National Hemophilia Foundation, and certainly the National Hemophilia Foundation has indeed gone on record, in November of 2000, to advocate for a movement to recombinant replacement therapy in the United States, and that's MASAC Recommendation No. 106 involving both Factor VIII and Factor IX products. And to paraphrase this recommendation, recombinant Factor VIII products, including recombinant Factor IX product, are and is the safest with respect to viral transmission and should be

considered the treatment of choice for individuals with hemophilia A and B. And I think that's what sort of set off the premise that the issue of plasma-derived Factor VIII and Factor IX is no longer important.

I do want to say, however, from a physician's perspective that ever since this recommendation came out, there has been a lively debate, a very lively debate which continues to this day, as to the merits of plasma-derived versus recombinant factor with respect to everything from the development of antibodies in individuals, what we call inhibitors, to inhibitor therapy, and then including the treatment of bleeding and immune tolerance, and even because of times of shortage as to whether the viral transmission issues are more theoretical versus real especially when we've had to resort to plasma-derived products, which we consider to be virally quite safe these days.

So the issue of recombinant, I guess it's to say the issue of recombinant is not a said-and-done issue, and you're going to actually hear, for those of you who are going to the World Federation of Hemophilia meeting in Bangkok, there's going to be a lot of symposia dedicated to that very topic.

Now, despite their going on record to recommend recombinant product, the NHF, however, has already come out in support of the maintenance of a plasma-derived

supply in their report language to Congress in 2003, and essentially it's a lot of what I'm presenting to you today.

With respect to blood safety, the NHF wrote that the committee is aware that several standards currently are followed regarding the collection of recovered and source plasma from blood and encourages the FDA to work with all stakeholders and collectors of blood and plasma to ensure equivalence of these standards in safeguarding the nation's supply. So this is something that the NHF has indeed gone on record to state.

Furthermore, Mark Skinner in his presentation in April of this year to the North American PPTA had this to say: that indeed there was a future and continuing role for plasma-derived products in the United States for rare bleeding disorders, for times when recombinant is not an option, patient preference in some cases, as a supply backstop, as we know very well, and oftentimes because of reimbursement and cost issues that don't allow recombinant therapy as an option.

Now, the Medical and Scientific Advisory Council, of course, is the one that put out Recommendation No. 106, and so it, too, has gone on record to encourage the U.S. transition to recombinant especially Factor VIII and IX. But in a letter by the Chair of MASAC, Keith Hoots, to Jessie Goodman that was

just sent this August, MASAC had this to say about its position with respect to plasma-derived products: "Despite the fact that they are on record for encouraging U.S. transition to recombinant, there are cogent arguments on behalf of the bleeding disorders community for preserving and internationally harmonizing standards for plasma colleague, processing, and storage for these reasons"--they're going to come up again and again: only option for rare bleeding disorders, such as Factor V, which is also another labile clotting factor, Factor XI, and currently the only treatments for these disorders is FFP, fresh frozen plasma. There's certainly no recombinant bundle of factor preparation. Von Willebrand disease is probably one of the most common bleeding disorders that we care for, and there is no recombinant product.

In his letter, Dr. Hoots states, "The potential for exploiting underutilized plasma and plasma fractions to increase supply, potentially lower the price for the developing world"--and this issue is going to come up, as I present the World Federation view. There's certainly a role for plasma-derived products in immune tolerance, an issue that's very near and dear to my heart. And another issue that he states is that there are implications of national standards for blood collection and processing

with respect to international needs. And, therefore, the issue of harmonization we feel is quite important.

And, of course, last but not least, we have had catastrophic shortages of recombinant Factor VIII just recently, and it was only because of the availability of high-quality plasma-derived Factor VIII that no individual in the U.S. experienced emergency bleeding for which there was no replacement therapy, and the situation was the same in Europe.

The Blood Safety Working Group of the Medical and Scientific Advisory Council is doing some long-range planning with respect to their goals, and a key goal of the Blood Safety Plan is also the availability of plasma-derived products for a lot of the same reasons that I've already stated, including something I'm going to get to later, and that is maintaining also economic feasibility for other plasma-derived products, such as IVIg.

Now, recently, in the Journal of Thrombosis and Hemostasis, the Medical Director of the World Federation, Paul Giangrande, and many others involved in the World Federation of Hemophilia, wrote a letter refuting what was written by Dr. Shanbrom indicating that the official recommendation of World Federation is to utilize recombinant products in the treatment of hemophilia. And it's often that the NHF view gets confused with the World Federation view, and so I'd like to present the World

Federation view on plasma-derived products because indeed it is not the same. And in that letter, Dr. Giangrande wrote, "It is certainly not the policy of the WFH to recommend only recombinant products for the treatment of hemophilia. There is and will continue to be a global requirement for both plasma-derived and recombinant coagulation factor concentrates, and the aim of the WFH is to ensure the availability of an adequate quantity of safe and effective products for the treatment of hemophilia across the world."

And, in fact, most recently, in 2003 and 2004, there has been some danger that clotting factors would come off the WHO, World Health Organization, essential drug list, and the WFH put through an application that was basically trying to make the case for the continuing need for clotting factor concentrates on the essential drug list.

Now, basically, as you're going to see, the application was for plasma-derived products and not recombinant products because the issue with respect to the world and the World Federation is the issue of do you have plasma-derived concentrates or do you have blood products, local blood products, where viral safety issues are very considerable problems. And, in fact, the case they make is that across the world major surgery would be difficult with blood bank products alone; that early

therapy to minimize morbidity and mortality is not possible with just blood bank products along; and that in the developing world, as I've already said, bloodborne virus screening is inadequate.

To make this point, there is the issue in Venezuela where if you look at the column on the left, where you look at years of treatment 5, 30, 60, and depending on what you consider to be the risk--low, mid, or high--in terms of the frequency, that's the estimated risk for HIV infection in individuals receiving cryoprecipitate in Venezuela.

Now, if Americans were receiving cryoprecipitate and not recombinant or plasma-derived product, they would have a risk. But as you can see in the column on the far right, that risk is considerably lower. So this is a huge issue globally.

And, in fact, their recommendation was that not only was there a requirement for factor concentrates, the nature of which would depend on the economic capacity of the country, but they estimated the minimum requirement to be one unit per head of population. What this translates into is for Factor VIII, 20,000 units per year per patient; for Factor IX, the same; and notice these are plasma-derived concentrate. So this comes back to what I said before, that the need for plasma-derived

Factor VIII and Factor IX, not only when you look at U.S. needs but certainly world needs, is tremendous.

Now, we understand, however, that there's an economic side to this, and Jan Bult in his presentation to BPAC this past July and to the Blood Safety Advisory Committee in August presented some of these issues, the reality of plasma economics to the community. And there are two sets of recent developments. One is what's going on in the industry with respect to consolidations and divestitures and the closure of plasma collection and fractionation facilities, such that there is a reduced volume of fractionated plasma for use for these products, although there is no near-term threat to plasma therapy availability. On the other hand, there's a potential for new companies, enhanced technologies, and the potential for higher yields. And that issue is an important and exciting one from our standpoint.

Indeed, although the goal of this presentation is not to discuss the technology for maximizing clotting factor yield, there is some scientific data that is available to suggest that we may be able to get more out of our products than we do already. And some of that will be touched on by Dr. Farrugia in his presentation to follow mine. And there's certainly ample data that was generated in the '70s and '80s by Gail Rock, who I

believe is also here today. And I thank her for that information.

Now, again, this is another slide that was borrowed from Jan Bult, and in this, again, this plasma economics issue, he taught us--and we need to be taught and we're happy that we're taught. But he taught us that there are drivers for plasma economics, but then there's the revenue side. And, indeed, as the lower bar shows, the current driver for plasma and plasma-derived products is immunoglobulins, and there's no doubt about that, with albumin being second. But as you can see by the magenta line, there's also a cost to manufacture products, and if there's going to be profit, it comes from the sale of multiple products, including, for instance, Factor VIII.

Now, regardless, however, he's also taught us that there's no economic gain if you make more product or if one product drives the manufacture of more product that sits on the shelf. So this product has to be used. And so with respect to clotting factors and certainly what the community is asking for with respect to achieving maximum factor yield, we think that it does make economic sense.

In, again, the continuing letter of Dr. Hoots to Jessie Goodman, he writes, "It's recognized by members of MASAC that insistence on the highest standards for plasma collection, processing, storage, and shipping come with a

price tag. And it may well be, however, that the capacity to use every plasma fraction will prove to be cost-effective and that higher up-front costs may be offset by mutually beneficial contracts for factor concentrates to developing countries."

And in its application, the World Federation does have some cost figures that don't look that bad when you're talking about plasma-derived products. And in their statement, in their application, they state that plasma-derived Factor VIII and IX have been purchased at prices as low as 10 cents a unit, with the cost usually in U.S. dollars of 20 cents to 30 cents more commonly seen. However, these costs do compare, these prices do compare with the cost of producing cryoprecipitate in some countries which can be approximately 20 cents a unit. So that there is some economic potential for the developing world to actually have plasma-derived products that are safer at potentially no additional cost.

Also with respect to the issue of making additional products, I'm very happy to say that the same bleeding disorders community has recently championed the cause of treatment for rare bleeding disorders, which actually does not exist in a satisfactory way, in our opinion, and the Blood Safety Advisory Committee recently last week did come up with a recommendation to the Department of Health that recommends the development of

products to treat individuals with blood disorders, including obtaining additional licensed indications for already licensed products, approval of licensed indication in the U.S. for European licensed products, and the development of new products. And we believe, if we can work together, that that will only help in this issue of plasma economics.

An important caveat, as I finish, and I go back to our other community of plasma fractionation users, we believe very strongly that in maximizing clotting factor production, as you talk about regulatory issues, we hope and we feel very strongly that the increased costs, if there are any, cannot and should not be borne by others who currently benefit from plasma fractionation, including patients with immunodeficiency and autoimmune disease who currently benefit from immunoglobulins and individuals with alpha 1-antitrypsin just to mention a few.

In bringing to you our views, our hope is that--our promise is, actually, that we will continue to work with the regulatory community and industry and plasma collectors to continue to make this a viable effort, like I said, not only nationally but globally, by working on issues that are currently problematic. Again, PPTA has taught us that reimbursement in the United States is a particularly big problem, and we will continue to

advocate for reimbursement of these products, again, to make this an economically viable venture.

We will work with you in terms of harmonization of regulatory requirements, and we will work with you with respect to global access to care, which is a critical issue in the hemophilia global community.

Finally, in closing, I would like to thank the organizers of this workshop and wish all the participants good luck. We applaud this meeting, and we applaud all of you coming together, and we wish you every success in consensus building.

Thank you very much for your time.

[Applause.]

DR. HOLNESS: Any questions for Dr. DiMichele?

DR. FITZPATRICK: Donna, hi. Thanks. I'm Mike Fitzpatrick from America's Blood Centers. A great talk, and you presented the case for plasma products and the need for them, and we would agree with that, and that you can increase the yield for fractionation with different storage and freezing. But what I didn't hear was anything about efficacy of the current product. Do you see a problem with efficacy with the products that are manufactured under the current standards?

DR. DiMICHELE: You know, that's a good question and thanks for that question, Mike. I think, you know, when we talk about efficacy, we can't dissociate safety

from efficacy. And I think if you want to just talk about efficacy, I guess in terms of certain licensing tests that look at the licensing of this product and certainly in our post-licensure use of this product, I don't believe that we have identified glaring--any glaring lack of efficacy, no. And are there differences in products? Probably. Do we see them in patients? Yes. There are groups of patients who actually respond better to one than another for reasons that are still not clear. And it's not always one product versus another. Sometimes it's recombinant versus plasma-derived. Sometimes they'll respond better to one plasma-derived product versus another, von Willebrand factor-containing or not.

And we also know, you know, there's been a big flap in terms of assaying Factor VIII these days and what assays are best. And we know that a lot of these products assay very differently by clotting and chromogenic methods.

So there are probably small differences in efficacy. Why we don't pick it up, however--and this has been a huge discussion as we do something else through ISTH, and that is, we're looking at global blood clotting assays to assess clotting factor efficacy. What that may show us is that at the levels at which we dose currently-

-we dose at very high levels--we're not going to see differences in efficacy.

If we can get to the point--and, again, this is to maximize availability. If we can get to the point of understanding how to do individual patient dosing based on the characteristics of an individual patient's clotting system and we're able to use lower doses, might we see differences in efficacy? At minimally effective, you know, clotting factor levels we might.

So I guess what I would say to you, to answer your question, is no, I think our dosing practices--not generally, may be based on assays, may be based on certain patients that we see, and most likely not at this time based on our dosing practices.

Are there other questions?

[No response.]

DR. DiMICHELE: Okay. Thank you very much.

DR. HOLNESS: Our next presentation will be on product quality, and here to present will be Dr. Albert Farrugia. He's a senior principal research scientist and head of the Blood and Tissues Unit, Office of Devices, Blood and Tissues, Therapeutic Goods Administration, Woden, Australia.

DR. FARRUGIA: Well, while the slides are coming up I'd just like to say good morning, and I want to thank

the FDA and commend them for this initiative, for this workshop. I think it's very timely.

Unlike Donna, I'm not representing anybody here. I'm acutely conscious that anything I say is going to be transcribed and may be taken down in evidence later on, so I'm speaking here basically to my own views, and I'm delighted to have had the chance to review a field which is very close to my heart and on which I cut my blood banking and scientific teeth 25 years ago. And now I need the slides.

Well, you know, when I submitted the first draft of this talk about three weeks ago, my generous hosts had the temerity to suggest that 85 slides in 45 minutes was pushing it a bit. So I said okay. So I sent them the handout which you actually have, which I believe is about 70 slides, and yesterday some further doubts were expressed by my good friend Dr. Weinstein. He was very gentle about it, so I trimmed to the absolutely ruthless minimum of 60 slides.

[Laughter.]

DR. FARRUGIA: Therefore, you'll see that some of the stuff which you've got in the handout is not actually here. There are things which I think are less relevant to the immediacy of the issues as I understand them now. So what I will do is I'll go over very briefly some current standards, and I won't go into these in

details. They're on the slides. I think this will be dealt with later on in the day. I'll review the scientific data. This is mostly based upon empirical observation. There is, I think, relatively little basic science. I'll attempt, mainly unsuccessfully, to wrestle with that. I think this will generate immediately the tensions which, as I say, underpin the situation, particularly in this country. And then I'll have the temerity to suggest some possible approaches.

As I've said, this is a very personal presentation. I have lapsed into personal indulgence over the course of it, and the views are entirely my own, and basically they're my own as they were about three weeks ago. I have a suspicion I'm going to change some of them before the end of these two days.

So there are a number of available standards, and in Europe, we've got, in terms of plasma for fractionation, an unusual monograph in the European Pharmacopoeia, and this is a monograph for human plasma for fractionation itself. And there is also now--and I will say something more about this in the second talk because we give this a lot of importance in Australia--a guideline for generation of a document of a so-called Plasma Master File, which does give some reference to the storage and freezing conditions as they are presented in the European Pharmacopoeia monograph.

In the European environment as well, there is a standards-based distinction between plasma for fractionation and plasma for transfusion. And the Council of Europe Guide for Blood Components, which also happens to be the Australian standard for these products, includes chapters on fresh frozen plasma and similar components, and it specifies that these are not applicable for plasma for fractionation and refers the user to the European Pharmacopoeia monograph. And, of course, in the United States you have Title 21, subpart G, Source Plasma, of the CFR, and that's about it. And I guess this is one of the reasons why we're having this workshop today, to try and bring, as Dr. Epstein said, recovered plasma into the regulatory fold.

Now, I'll continue by making what I think is a contentious statement. I was told by Mark Weinstein to be contentious to, you know, generate discussion. I think that basically--and we can debate this; I hope we will--most of these regulatory requirements which do cause some level of tension within the industry and between industry and regulators underpinning blood and plasma storage, freezing, and so on are essentially predicated on the needs of Factor VIII. And, therefore, most of this presentation in terms of the science is going to focus on the properties of Factor VIII in

relation to blood bank manufacture in relation to plasma freezing and all the issues with interest us.

I think Donna has made some statements about this, but plasma-derived Factor VIII production is becoming reasonably marginal in the developed blood economies. I think this is great news. I think plasma-derived Factor VIII concentrates have served us well and have now earned--in countries which provide the level of health care which we associate with the First World, they have earned an honorable retirement, and it is one of my personal views that this is a good thing, and we should not be too upset about it.

However, it is the case--and it has been shown by Donna--that this is still a very important product and is still basically the only product of immediate conceivable access in the developing world, and fractionators, therefore, still ship plasma for Factor VIII manufacture not just for what is becoming an increasingly limited domestic market, but also in the hope of supplying the emerging markets. As to how much this is actually impacting in the global market for Factor VIII is still a matter, I think, of some doubt. Despite the fact that it is true that you can get Factor VIII now, depending on how well you can bargain, I guess, for a relatively modest cost, it's still uncertain in my mind as to how much these products are actually

penetrating in the developing world, because what may be a modest cost for us is still, I suspect, prohibitive for most environments attempting to crank up a health care system.

Now, Factor VIII is the most labile plasma therapeutic protein. I don't know how contentious it is. I think it's still the case. I would say that conditions affecting Factor VIII, however, may affect other proteins in ways which are still unknown. And, therefore, I would say that tailoring the conditions to optimize Factor VIII preservation is still a valid goal. This can be debated, I think, very strongly, and I hope we will do so.

Now, the immediacy and the relevance of Factor VIII, I think, in terms of the standards is shown by this particular manifestation in the European environment in which in both the standard for plasma for transfusion and the standard for plasma for fractionation delineated is a somewhat curious requirement for Factor VIII levels in the resulting plasma product. I'll just use this as an illustration to link to the Factor VIII story. I personally view this as being one of the requirements in the European environment which is more eccentric than scientific, and I'll say something about this when I talk about Australia.

Now, I have chosen to essentially address the issues in relation to the stages in the part of

manufacture from the basic blood collection or the plasma collection to the end product of concentrate as far as the impact on what is of interest in this talk. And so you will notice that I'm not going to actually cover the slides which affect the issues of anticoagulant because I don't think that they are of immediate interest today, although they do have some linkage and they are very interesting issues.

Therefore, you can see that in these stages we look at the anticoagulant and its effect on preserving or otherwise Factor VIII, the collection method, whether it is true apheresis or whole blood collection; and then the things which are of interest to us today, the time and the temperature to separation and freezing, the freezing rate, storage conditions of the frozen plasma.

Now, here is a slide which is, again, old and honored, and it shows the basic properties of Factor VIII in blood bank normal anticoagulated donations. And I think there are some interesting features here which perhaps are not widely appreciated.

This slide shows the situation at three storage conditions of temperature for the blood. First of all, observe what happens in normal blood bank storage; that is, the well-characterized, very well known so-called biphasic decay of Factor VIII. If you store the blood,

however, at room temperature, here defined at 22 degrees, you will see that the drop is significantly less.

This other line here, which is entirely superimposed on the 22-degree Centigrade line, shows what happens when you store at blood bank 4 degrees Centigrade storage, and then just before you harvest the plasma through separation and freezing, you warm the blood up--I think these experiments I did were about 15-minute warming--and you get the Factor VIII basically back in the plasma.

This is essentially a manifestation of the well-known phenomenon of cryoprecipitation, and it shows that really Factor VIII is not well preserved under conditions of standard blood bank storage for whole blood. And I think this is something which needs to be kept very strongly in mind.

I think this next set of data from Jan Over from the Dutch environment shows the situation again over there, which you can see that the amount of Factor VIII when the blood is stored between 0 and 4 degrees is actually significantly less than when the blood is stored at room temperature. And there's also a bit less protein, and, again, this is entirely understandable in relation to the phenomenon of cryoprecipitation.

So immediately we start seeing doubts thrown on many of these statements which are made that we have to cool the blood quickly and go to that level.

Now, collection method. Well, there's a lot of data. This is just a summary of various studies from the U.K. and also from Australia, and essentially you see that when you are collecting generally through the recovered plasma mode, you're going to get less product, less Factor VIII in the intermediate stages of manufacture than if you collect in the apheresis low citrate or normal citrate mode.

This is easily understandable in my view from two components involving the apheresis environment, one of which is that you're certainly going to freeze faster when you are collecting through apheresis, and you are probably, because of the lower anticoagulant concentrations in most machine systems, you are going to have a lower citrate concentration. And as was shown many years ago by Gail Rock, who's been mentioned today, low citrate is good news in terms of Factor VIII.

However, I want to start immediately making the emphasis which I'll make several times throughout the slides. And I think this is unfortunate that this field actually has tended to taper off in terms of new investigations. These are somewhat old studies, and they focus on products which are not exactly representative of

the generation of Factor VIII concentrates which we are accustomed to now in the First World, the high-purity, highly viral-inactivated concentrates. These are mostly low- and intermediate-purity products, and these products--and I'll emphasize this point in later data. The question is still open as to whether you have an enhancement in yield.

In lower-purity products, it is certainly the case, especially upscale in the manufacturing process, but as you approach more closely the final product, the differences in yield accruable from the initial difference of amount of Factor VIII in the plasma starts to diminish as you can see.

Let's now talk about the important area of time and temperature, separation and freezing. This is data from our Blood Service from about 10 years ago, and it shows the various types of plasma which were being handled then. And you can see it being related to the Australian mandatory standard of the amount of donations which actually have less than 0.7 IUs per mL, international units of Factor VIII per mL. You can see that when we have freeze donations which are frozen in less than 12 hours, it's just 1 percent. When whole blood donations are frozen in less than 12 hours, this goes to 13 percent, a demonstration of the phenomenon I described earlier. When the whole blood is kept for less

than 18 hours, it goes up to 27 percent. And when it's less than 24 hours, it goes up to 40 percent.

This, as I emphasize, is simply a demonstration of the amount of Factor VIII in the plasma, and this is very well known. This is data from Jim Smith for intermediate-purity concentrates in the United Kingdom quite some time ago, and it essentially shows that when you look at plasma from different ages, you do get some levels of enhanced Factor VIII yield in the plasma. And then when you look at the effect of the pack type on the freezing on the Factor VIII, you get not such a high level of difference at all.

Now, does this matter? Does the fact that some delayed blood processing leads to frozen plasma have decreased Factor VIII levels? In other words, does this affect the yield and quality of fractionated products? I think it is quite a legitimate point to be made, primarily by the industry, that this is what needs to be the primary focus. I agree myself that this is the most important matter. Let's see what the data tell us.

This is data from Jan Hellings, a study which was done in Holland, again, more than 20 years ago, which shows that when you store the blood overnight at 22 degrees Centigrade, you get a decrease in the amount of Factor VIII, and this decrease is reflected in the

distribution of the Factor VIII in the fractions upon cryoprecipitation. This is small-scale data.

In this study as well, which formed part of a major doctoral thesis, Hellings showed that this was actually linked strongly to the fact that proteolytic degradation was occurring and having an effect on the Factor VIII molecule and, in fact, on the association between Factor VIII and von Willebrand factor as the blood was exposed to longer periods of time at room temperature. And I think this needs to be kept in mind. There is evidence that if you keep blood stored for a prolonged period of time at room temperature, it does have an effect on molecular integrity.

This is data from my lab in the Red Cross in the late '90s in Australia, in Melbourne, and you can see that there is a significant difference in the amount of plasma Factor VIII between 6-hour and 18-hour blood. This difference is retained not to the same level, at the level of the cryoprecipitate. The difference, however, although still there, loses significance when you get to the stage of a low-purity Factor VIII concentrate, as this then was. So I think here we're seeing the picture starting to emerge that differences in the plasma, which can be moderated by moderating the storage and freezing conditions of the plasma, are not necessarily retained in the final product. And I remind you that these were

products of a low purity. This was a low-purity product, about 2 IUs per milligram, and also it only had a single viral inactivation step.

And I reiterate my regret that there is not much data on this kind of situation in relation to the current generation of Factor VIII concentrates. I think it's a general case, and in some ways a pity, that fractionators certainly don't publish this data anymore. I think the focus has been entirely on safety and on generating viral inactivation capacity in the processes, and this is entirely appropriate. But this kind of study has not been shown, in my view, in relation to the very high purity concentrates which are available today. I am aware of some data which is available to me on a regulatory basis which I cannot share fully but which indicate that for high-purity Factor VIII concentrates, these differences do not exist.

Here is, again, some data from the United Kingdom, from, again, quite some time ago, showing the differences which are accruable, and at the level of these types of products, you do get some levels of differences in the recovery of the Factor VIII international units per final kilogram of plasma in the final product. Again, these are historic. These are not products which are manufactured anymore. These are low-purity products.

And does this matter? Okay. It depends. There is no doubt that the cryoprecipitate yield is affected. Low-purity and intermediate-purity products may well reflect this difference in the yield of cryoprecipitate. But as I said, there is no data for the current generation of Factor VIII concentrates.

Now, I'll sort of philosophize later on on what no data means to the regulator. But let's discuss a bit the question of freezing rate, and I think that this is really very important because it is actually a significant gap in the regulatory and scientific debate much of the time that we do not actually talk about freezing rate.

Statements are made that plasma should be frozen at some temperature or other, and here you see the ranges which are noted in the various standards and requirements. And I find the language to be remarkably ambiguous, things like, for example, European Pharmacopoeia says you should cool rapidly at minus 30 so that it is frozen at minus 20, and the CFR for source plasma, should be stored at a temperature not warmer than minus 20. There is little recognition in my view in these documents of what I think is the most important and obvious parameter, which is the freezing rate. And here is just an illustration of how freezing rates can vary on fairly similar conditions. This is data generated by Ron

McIntosh in the Protein Fractionation Center in Edinburgh, in which he is looking at plasma frozen under two different conditions, a very standard regimen, and also using the phenomenon of super-cooling. The conditions are described on the slide, but you can see that a freezing environment of minus 50 can lead to significantly different freezing profiles depending on the manipulation which the plasma has been subjected to. So I think freezing rates need to be defined much more rigorously than they are now.

Here is data from some personal studies done some years ago, again, in Melbourne, in which we compared the freezing of plasma in a minus 30 cold room compared to the freezing of plasma in a minus 30 mixture of halogenated hydrocarbons. And these are basically the kind of freezers which are used to freeze most of the plasma in Australia today. And you can see that the freezing rates vary dramatically between these, not just in terms of what you see in the plasma through appropriate temperature probes, but also what happens to the medium, and depending on the capacity of the medium itself. And these do have some effect on the eventual products which you can generate.

In these studies, again, we're only looking at the amount of Factor VIII harvested in the cryoprecipitate in the blood bank. And essentially the

message is that the faster you freeze relative to these kinds of freezing conditions, the more Factor VIII, significantly enhanced Factor VIII you can generate inside the cryoprecipitate.

I think it's extremely important to define the conditions because people say, okay, we will freeze at minus 30. Minus 30 in what? There's a hell of a difference between putting something in a minus 30 cold room and putting it in a minus 30 cabinet freezer. And there's also a significant difference, obviously, between putting about a ton of plasma in a minus 30 cold room compared to putting a couple of units. And, therefore, I emphasize the importance of the rate in the things which we're interested in.

Here's a nice study from G. Carlebjork, who I believe now the corporate affiliation is to Octapharma, done in the mid-1980s when he was still working for that time-honored company Kabi. And you can see that you can get very different freezing times between different freezing conditions. And you can then relate these to the levels of Factor VIII generated, which I'll show in a subsequent slide. And the amount of Factor VIII as harvested in the cryoprecipitate and the total amount harvestable between the fractions varies between the freezing rates.

Here is some data now from, again, work which Chris Prowse and I did in Edinburgh quite some years ago, and this is comparing, again, the yield in cryoprecipitate between fast freezing--and at that time we defined this because we had the equipment to do it--as minus 70 ethanol bath cooled with liquid nitrogen--and slow freezing, which was, again, simply sticking it in a minus 40 cabinet freezer. And again, you see--and this was done using the thaw-siphon cryoprecipitate technique, something which is basically of only historical interest these days, alas, and it basically showed us that with fast freezing we could get significantly higher levels of Factor VIII in the cryoprecipitate. But, interestingly, what this data also showed was that the Factor VIII was actually not too different in the total amount recovered between cryo and cryosupernatant plasma. In other words, there was a redistribution of the Factor VIII between the two fractions, and this redistribution could possibly have been occurring, although we lacked the means to investigate this thoroughly, to molecular differences generated as a result of the freezing rates. And, therefore, the question arises: Does this matter eventually when it hits the patient?

Again, I don't want to go over too much in detail on these slides. You have the handout. But,

again, this is data from Jan Over showing pretty much the same effect which I have shown on previous slides.

So what is important? We need to define the conditions. Rapid freezing. I would call rapid freezing, as I have gained the perspective over the years, to be the ability to attain minus 30 in about 30 minutes, and this is entirely empirical. As I'll show you, I hope, later on, there is very little basic science behind this. But achieving this level of plasma core temperature results in better Factor VIII yields up to the stage of the cryoprecipitate relative to a slower freezing regimen. And we know that the ice crystal structure and the physical nature of cryoprecipitate are affected by the plasma freezing rate. We have various data on this from the literature to which we have also contribute.

There is also data--and this was actually shown on the previous slide from Jan Over's work, amongst others, that slow freezing also increases the amount of fibrinogen in the cryoprecipitate. Now, this is obviously something which is of great interest and has its pros and con. If you are making cryoprecipitate as a fibrinogen source, which is what most people do these days, this is a good thing. If you are making it to make Factor VIII, well, you might well be indifferent today at the level of purification which is attainable as a result

of things like monoclonal affinity chromatography. It doesn't matter much. But in the old days, I can remember when a lot of fibrinogen in the cryoprecipitate resulted in headaches. It meant that you had to work much harder removing it in order to generate viral-inactivatable product.

I would reiterate that the effect of freezing rates on Factor VIII yields in the current concentrates is not well recorded. There may well be people who have data, and they may well be going to show them here today, and I stand ready to be correct.

Storage conditions, very contentious. Well, here is data again from Prowse and myself in Edinburgh in the mid-1980s, and essentially we looked at material which had been subjected to slow and fast freezing, as defined on the previous slides, and then stored at two temperatures: minus 20 and minus 40. Reiterating, the important thing was the initial freezing rate. Once the plasma has been frozen under those different conditions, it did not matter in the time frames which we studied here, which was only up to six months, what temperature you stored it between these two temperatures.

Now, I note with interest the prospect of storing plasma for fractionation for 10 years. Forget it. Why do you want that problem? Apart from anything related to the issues we're discussing today, in 10

years' time all the safety factors related to the things which really move us today are going to have shifted to the level that it just will not be usable. I'll just say as a caveat to this that at the moment we're struggling with this precise issue in Australia in relation to long-term cryopreserved products such as cord blood. It just ain't worth the headache, folks.

Of interest as well is the situation of what happens when you vary the storage temperature, and I think this is actually quite of higher significance. This is data from Ron McIntosh again which shows that when you do vary the storage temperature during storage, you get a difference in the actual weight of the cryoprecipitate, and this is easily understood in terms of the amount of fibrinogen deposited. And here is a dramatic study which Chris and I did, again, in which we deliberately subjected to the plasma during frozen storage some level of temperature challenge, some level of temperature insult. I am relating this here to the relevant statement in the CFR to show you that there is actually quite good reasons for some of the things which are in some of the standards. But essentially what happens when you do subject plasma to deliberate fluctuations in storage temperature, as you see it on this slide, is that there is actually very little effect on the amount of cryoprecipitatable Factor VIII, but

there is a dramatic increase in the amount of cryoprecipitatable fibrinogen. And when you do subject it to these temperatures fluctuations, you get much higher levels of fibrinogen. Now this, again, may be good news or it may be bad news.

Here is an interesting piece of data, though, from Jim Smith again, and this again is at the level of dried low-purity concentrate in which he went the whole hog and he thawed, absolutely thawed, and refroze again the frozen plasma and looked at the effect on intermediate-purity Factor VIII. And while the amount of plasma Factor VIII dropped significantly when this happened, when the plasma was totally thawed and refrozen, the amount recovered in the final product did not budge. Interesting.

Now, let's just review some other aspects of this which are very interesting, and if you look at, for example, what happens in terms of fractionation and how the plasma is manipulated by the fractionator. Well, what we have is plasma which is held in frozen storage for some time, and that has to be brought to the appropriate state for it to enter the fractionation process. And one of the first things which is done is that this plasma is so-called conditioned. It is slowly warmed in order to be able to handle it for fractionation. I remind you that one of the first things

which has to happen to plasma is that the plastic bags in which the plasma is stored have to be removed, and this has to be done under conditions which retain the integrity of the plasma in terms of its eventual fractionation fate. So this is what is called conditioning, and the plasma is gradually conditioned by softening it to a warmer temperature. This makes it easier to remove the pack and makes it more amenable to crushing and melting. And this is shown nicely on this somewhat diagrammatic representation by Peter Foster, again, from the Scottish Fractionation Center.

This was an issue which interested us greatly when we worked in fractionation in Australia, and we looked at how conditioning could result in having an effect on the final products. And we looked at different conditioning regimens. Essentially we looked at what happened if you are able to fractionate the plasma without any conditioning at all, i.e., if you're able to strip off the plastic packs while having that minus 40 deep frozen state. You can't do this on a large scale, but you can do it if you're doing it on a small model scale. And we did this by splintering the packs in chucking them in liquid nitrogen.

Then you could condition to a cold temperature, and I believe this was something like minus 10, or you

can condition to a warmer temperature, something like minus 5 to 0 degrees. This is published in Transfusion.

Essentially what we found was resonant with the findings which we had made years earlier in relation to temperature variations during storage, which is that when you condition to warmer temperatures and then start the fractionation process, the amount of Factor VIII, again, in both the cryoprecipitate and in subsequent stages of the fractionation process does not change. It doesn't matter. But the amount of fibrinogen is dramatically affected, and when you condition at warmer temperatures before you start the actual thawing of the plasma, you get significantly higher levels of fibrinogen. These studies, again, were done at a time when we cared about this. We did not want a high level of fibrinogen because, amongst other things, we were attempting to dry heat treat this product at 80 degrees for three days, and we found that high fibrinogen at these levels in these conditions was very bad news. You just couldn't do it.

Nowadays, of course, with things like high-purity concentrates, (?) exchange, and monoclonal chromatography, the proteins are stripped of the Factor VIII anyway. And I suspect that these effects would not be seen at all.

This is a hopelessly complicated slide which essentially says exactly what I've just said, so I'll leave you to mull over it at a later time.

Of course, you can actually exploit this effect when you are actually trying to increase the amount of fibrinogen in cryoprecipitate as a route to fibrinogen-enriched cryoprecipitate at blood bank levels. So we introduce this technique in the Melbourne blood bank in the early '90s--I hope it's still there--in which we deliberately conditioned the frozen plasma to a warmer temperature before the final thaw to generate cryoprecipitate in order to have fibrinogen enrichment in the cryoprecipitate. And this was published as well, but it basically resulted in a product which was significantly higher in fibrinogen. The Factor VIII was really not affected much. The von Willebrand factor stayed the same as well, another important consideration, and the enhanced fibrinogen allowed us to generate an in-house fibrin glue which had a significantly enhanced adhesive strength.

So what is important? I would say that as long as freezing is optimized, storage requirements appear to be very flexible in the range of minus 20 to minus 40 in the practical periods of storage possible which I think are imposed on us today. If you go for 10 years, I don't know what will happen, but I would advise you very

strongly not to go for 10 years. And maintaining a steady storage temperature is more important than the absolute storage temperature within this range. And while temperature changes can affect the quality of the cryoprecipitate, this can be not necessarily a bad thing and can be exploited to improve both blood bank and industrial cryoprecipitate.

Now, let's talk a bit about basic science. Don't worry about this hopelessly complicated slide here, but I captured this from the Internet from a Canadian site because I found it a good demonstration of the so-called theory behind much of what is reflected in the standards in relation to freezing and storage. And this relates, of course, to the concept of the eutectic point of plasma. And I don't want to give you the impression that I have any level of physical chemistry knowledge which can attempt to explain what the eutectic point is, but I will simply say that there is no such thing.

And here is one of, I think, a few studies now in the literature, but, again, I salute the elegance of the Scots in this. And this is a study in which they basically attempted to detect eutectic points in plasma through resistivity measurements in plasma which had been frozen to low temperatures and then slowly warmed. And you have a situation here--I can't see it now either. You have a situation here where you are comparing plasma

to 0.9 percent sodium chloride. And in the 0.9 percent sodium chloride, of course, you can detect a distinct eutectic, but in the plasma you can't. It is as simple as that. It does not happen.

I'm informed by physical chemists that this should not be something which should astonish anybody because eutectics and eutectic points are essentially phenomena associated with crystalloid solutions, and plasma is a solution of 5-percent colloid in crystalloid. And so we should not expect these conventional parameters to apply. And here is data from McKenzie, a very interesting series of studies, not very well reflected in the literature, available through meeting proceedings and similar types, but which show that actually plasma in the frozen state, as it is frozen and subsequently warmed, undergoes a large number of transitions apart from the transitions associated with traditional eutectics. And these may well have different levels of importance in the things which we are interested in, but has not been studied sufficiently in my view, as reflected in the literature, to allow us to delineate absolute points which are crucial. There is no such thing as a eutectic point in plasma.

So what can we do to study this? Well, here, again, is elegant data from G. Carlebjork, and you are looking here at a temperature freezing curve in which he

managed to measure calorimetrically the phase change, energy changes associated with the freezing cycle. And he then related this to the time achievable in times of the phase change and to subsequently the Factor VIII levels, and he found that the faster you go in that phase change, the time for the--the shorter the phase change, the higher the Factor VIII levels. Again, an empirical set of data which tends to underpin the thesis that fast freezing is good news.

So in terms of plasma freezing and storage, conventional eutectics offer no guidance. One should freeze so that the phase change is as rapid as possible on the basis of Carlebjork's data. And in my view, storage so that this is maintained at minus 20 degrees Centigrade appears to be adequate.

But now let me be more contentious. The argument is flung at us: Why should this be an issue for regulators anyway? Because what we've been talking about mostly has related not to safety and quality--I will not have the temerity to say anything about efficacy--but to yield, and this is our business. Is there any evidence that blood/plasma processing affects safety and quality as opposed to yield?

Well, I don't know. Here is an interesting study relatively recently in Transfusion which absolutely floored me, which indicated that the activation level in

the Factor VIII molecule as assessed to the differential measurement using the clotting and the chromogenic assay is actually higher when you so-called fast freeze under the conditions of this study. And this is also reflected in the amount of prothrombin activation product in the plasma, indicating that in fast freezing there is activation of coagulation and the resultant effect possibly on the proteins, including the Factor VIII. There is no indication from this study whether this has any effect further down in possible fractionation.

This is the only study that I'm aware of which might indicate that fast freezing might have an effect on the product quality.

But there was another interesting study in relation to this whole issue which came about when we had the famous incident involving inhibitor development in a product marketed--and I think this is public information. In fact, this is extracted from the literature--by Octapharma. And in this study, which was a follow-up on the basic clinical observation and clinical problem, the investigators looked at the effect on the Factor VIII molecular integrity of what they called collection conditions as assessed through parameters meant to detect activation, such as fibrinopeptide A and thrombin-anti-thrombin complexes. They then related this to molecular changes which they found in the final product and related

those changes to the level of inhibitor development in patients. And basically, to cut a long story short--and I again refer you to the literature--they made the correlation that plasma which showed evidence of coagulation because of what they called poor storage generation conditions resulted in molecular changes which eventually could be linked to the development of inhibitors.

Now, this is obviously a very interesting and quite potentially important observation. I would, however, make one point on this study, which is that in the study, in relation to the amount of activation markers in the plasma, at least as assessed through fibrinopeptide A, the level of fibrinopeptide A in both the normal and elevated plasma was much in excess of what is traditionally found in blood bank condition plasma. And this is data from Chris Prowse which shows that essentially the level of fibrinopeptide A in plasma is very low compared to even the normal levels which were found in the previous study.

So I would contend that in relation to this one study which I have been able to source, the amount of fibrinopeptide A there was not really something which was normally encountered, and I don't think that it is representative.

And so the question which was, I think, addressed in some ways by Donna in her answer to the question from the floor earlier on to my mind is still an open one. I hear with interest what she says about, you know, products are different and patients react differently and so on, but I could only wish to see some data in the literature which can lend itself to some level of objective assessment. And I would be delighted to be made aware of some data today.

And, of course, now I started out by saying--and I'm approaching, you'll be glad to know, the end of my talk. But I started out by saying that there are other things one can get out of plasma. It's not just Factor VIII. Here is data which was made aware to me by John Finlayson which shows that when plasma is generated from outdated blood compared to source plasma, the fragmentation of intramuscular immunoglobulin was significantly enhanced during storage of the final product in the plasma generated from outdated blood.

And here is some other data, again, from John Finlayson that albumin made from plasma from outdated blood shows higher levels of prekallikrein activator, and you know what that does to you.

I would say that these are data of enormous interest, but I suspect that the interest is more historic. But I don't think we know. Are these issues

mainly of historical interest? Are there other plasma proteins which can be affected by poor storage conditions and which are more relevant to the industry today than perhaps Factor VIII is? And we've heard--and I think quite convincingly--from Donna that Factor VIII is still relevant. Is this part of the great unknown? And what does the great unknown mean for regulators? The great unknown, when we have the great unknown, we tend to go back to our mainstay, the precautionary principle.

However, I think there is another issue, and this is: What is actually a quality product? Now, this is a definition from the Internet, from one particular area. I think it's a good definition, and I think that reliability, consistency, and the ability to continue performance in stress or volume situations, I think it's quite important to look at this. And I would say that you cannot get reliability, consistency, and the ability to constantly perform in possibly stressful and varied conditions if you don't define them very rigorously and you do not align them to some parameter which, for lack of anything else, you can say is indicative of good or bad things happening, if you like, in the plasma. And I think we need to have a defined manufacturing process, specified freezing and storage conditions, and robustness to volume and temperature changes.

In other words, I would contend what we need is that extremely important concept of good manufacturing practice. And I do not think you can get good manufacturing practice if you allow people to shelf plasma at any temperature they like for the amount of time they like purely on the presumption that it's not going to have any effect on the final product. I think the process has to be defined at the outset.

So this is my final serious slide, and I think that overall there is a need for clear and unambiguous wording in the standards which are currently used. I think that all of us in the regulatory community have failed miserably in this, and I think the wording is very ambiguous and results in confusion.

I think we need a process which results in a consistent product in terms of plasma for fractionation, and this would form the basis of any standard. And this should be a manifestation of GMP more than anything else.

However, it is the case that empirical observation appears to support greater flexibility than some current requirements. There is little evidence that any of these requirements have a bearing on product safety. Obviously, basic conditions for minimizing microbial contamination and preserving product integrity should be defined. However, I do agree that requirements such as Factor VIII levels in the plasma should basically

be left to be negotiated between the manufacturer and the supplier, and I reiterate that I think requirements such as are found in the European plasma for fractionation and plasma for transfusion requirements on Factor VIII levels are in my view difficult to justify and certainly have no sense in relation to process control type concepts.

I'd like to thank very much the FDA for the opportunity. I'd like to thank you all for your attention, and I would like to thank you all for reminding me of when I was very young. Thanks.

[Applause.]

DR. FARRUGIA: And I believe I'm on time.

DR. HOLNESS: Are there questions for Dr. Farrugia?

DR. EPSTEIN: Well, Albert, thank you for this masterful overview. I have a regulator-to-regulator question. You know, there's a lot of interest and effort at harmonization, but when you consider that some of the more stringent standards that are rigidly adhered to by various highly respected bodies may be unduly stringent, how do you attempt to harmonize? Because there's rarely incentive to harmonize with lesser standards.

DR. FARRUGIA: Well, I think that's very true, and I think we need to generate a framework, first of all, whereby we can do this because we don't have this in the blood area, and I think it's a great problem that in

terms of plasma products they seem to be at the moment outside frameworks like the ICH.

However, I'll say something about the rigor and difficulties of standards, and this is that it's actually not too difficult with good will to attain most of the requirements which there are currently available. It's less easy to justify them, but sometimes it's quite possible to minimize loss of energy by simply adhering to them. And I shall show this in relation to the Australian environment because we do adhere, we do mandate the European standards, and we find that they are actually quite achievable by our industry in what I think is logistically a challenging environment.

But I agree, and I don't have any suggestion other than that we need to generate the ability to have a framework to discuss. Once we do that, we can then agree on some basic conditions along the lines which I have tried to indicate in terms of, again, agreeing on what empirical observations support certain types of conditions.

MR. COEHLO: Yes, I had a question in regards to your fast freezing, which I thought was pretty fascinating. Since most of the heat in plasma to be removed is at the point of fusion, heat of fusion, then the fast freezing which you accomplished really did two things. It did most of the work for the storage freezer

so that you're not putting heat in the storage freezer, because you independently froze those down below fusion.

DR. FARRUGIA: That's right.

MR. COEHLO: So you stabilize your long-term storage temperature, and you do most of the work ahead of time and get higher Factor VIII yields. So would you-- I'm trying to go from what you said there. Would that be your recommendation that you accomplish that fast freezing--

DR. FARRUGIA: Yes, I--entirely, entirely, because, I mean--and you see this if you're a blood banker. I mean, if you just take a bunch of plasma bags and shove them in a minus 30 freezer, if you look into that freezer after six or eight hours, you'll see that the plasma is still liquid because the capacity just isn't there. Of course, if you pop it in a minus 30 cold room, you know, with substantial capacity and there is nothing else there at the same time, you will find that you freeze much quicker. But I agree.

What we found, which was perhaps surprising, was that at least at the level of minus 20, if you then put it at minus 20, then the amount of Factor VIII is basically staying the same. But, yes, I agree. I think the fast freezing is the crucial parameter.

MR. COEHLO: Yes, I had once noted that 12 hours after--the way the language often is is put it in a freezer.

DR. FARRUGIA: Yes, I agree.

MR. COEHLO: Presuming that something happens repeatedly in there, and often it's very--

DR. FARRUGIA: Yes, the statements are regrettably ambiguous. This is reflected in the CFR. Place in a temperature no warmer than minus 20. Well, you know, what do you mean?

MR. COEHLO: Thank you very much.

DR. HOLNESS: Would you give your name and affiliation, please?

MR. COEHLO: I am an interested party. My name is Phil Coehlo. I'm the CEO of ThermoGenesis Corporation.

DR. FARRUGIA: Dr. Rock, how nice to see you, Gail.

DR. ROCK: Gail Rock from Ottawa, Canada. I have one question and then perhaps a comment.

I was intrigued with your statement that we don't really know what other plasma proteins are going to be affected by sort of leaving things at room temperature for 12 hours or longer. Has anybody looked at the metalloprotease that's so important in the treatment of TTP? Because we only can use FFP for TTP because of this

enzyme. And being an enzyme, it doesn't seem to me that it would do well standing around.

DR. FARRUGIA: I don't know.

DR. ROCK: I guess we'll soon find out.

DR. FARRUGIA: Yes.

DR. ROCK: All right. My comment really is don't completely denigrate the double freezing or recycling of cryoprecipitate because in our hands, as you know, when we used heparin at 8 units per mL in a blood bag and did a double cryoprecipitation, we were able to produce in a blood bank a Factor VIII concentrate with 666 units of Factor VIII per liter in an intermediate-purity product. So when applied specifically and goal-oriented, the double refreezing can be very effective.

MS. GLANTSCHNIG: Octapharma, Barbara Glantschnig. I want to comment on the effect of the freezing speed for different plasma qualities, and, again, I'm speaking only from our experience there as we fractionate both qualities. For the recovered plasma, I absolutely agree that the speed of the freezing is very relevant and very important. For the source plasma, we see from experience and from comparison between source plasma manufactured in, let's say, Germany and Austria that the flash freezing is really not such a critical parameter. We don't see any big difference in yields or behavior of the different plasma from both countries, one

shock frozen and the other not shock frozen. So minus 30 big walk-in freezer requirements seems to do the job from experimental data for the source plasma.

DR. FARRUGIA: Well, you know, I hear what you're saying and I'm interested. But we had a tussle with our local industry on this issue of apheresis freezing, and we basically made the point to them that it doesn't seem to us to be sensible to have put in the enormously expensive infrastructure to generate apheresis plasma and then not freeze it at least within the time frames of the standards. And I would reiterate that point.

But we've never seen any instances of apheresis plasma, although it's difficult, we only fractionate about 35 percent of the plasma apheresis in Australia where flash freezing has proven to be detrimental.

DR. HOLNESS: Now it's time for a coffee break. You can bring food and refreshments into this room, if you like. We'll restart the session at 10:30. Thank you.

[Recess.]

DR. HOLNESS: Our next speaker will cover current U.S. requirements for source plasma, fresh frozen plasma, cryo, and recovered plasma, and Sharyn Orton is the branch chief of the Blood and Plasma Branch of Division of Blood Applications at CBER. Sharyn?

DR. ORTON: Good morning. Everybody had better get in here quickly because I only have four slides, so you'll miss it.

I actually have the easiest presentation. Elizabeth asked me just to review what we regulate, hence, the four slides.

For source plasma for injectables, I've put all the CFR citations on the slides for anybody who needs them. The CFR states to freeze immediately, store at temperature no warmer than minus 20 degrees Centigrade. The expiration is 10 years, and they are shipped at minus 5 degrees Centigrade or colder.

For non-injectables, the CFR states to freeze and store according to intended use of the final product.

For source liquid plasma, which has come up as a question quite frequently, for non-injectables store at 10 degrees Centigrade or colder and ship at 10 degrees Centigrade or colder.

Fresh frozen plasma and cryo. Fresh frozen plasma is to place in the freezer within 8 hours or within the time frame specified in the directions for use for the blood collecting, processing, and storage system; to store at minus 18 degrees Centigrade or colder; and the cryo is made, of course, from the FFP.

Expiration is 1 year, or 12 months, from date of collection, and ship at minus 18 degrees Centigrade or colder.

For recovered plasma, freeze, store, and ship, as you know. For those of you who don't know what this is, this is a black hole, and hopefully we'll get more information today that will help us move forward with recovered plasma.

Thank you.

DR. BIANCO: Sharyn, Celso Bianco, America's Blood Centers. There is one area that probably we'll come back to in the discussion, that is, the intent of collection. Do you want to talk a little bit about it?

DR. ORTON: Actually, Jay's a better person. He's talked about that before. He's not in the room at the moment. I'd rather not take that on.

DR. HOLNESS: I'd just like to announce there are additional handouts at the front table.

Our next talk will be about the current Council of Europe and European Pharmacopoeia standards for source plasma, fresh frozen plasma, cryo, and recovered plasma. And to talk about that we have Johannes Dodt. He's the head of the Blood Coagulation Factor Section at the Paul-Ehrlich-Institut in Langen, Germany.

DR. DODT: Good morning, ladies and gentlemen. It's a pleasure for me to be here and to speak about

European regulatory requirements for plasma for fractionation. I thank Mark for inviting me and giving me the opportunity to speak about this.

As you heard, I'm from the Paul-Ehrlich-Institut. This is the German Federal Agency for Sera and Vaccines, and I am here to give you my personal view on this. I'm working in Group 6B, so I'm a little bit--I have a little bit of experience with the development of the monographs, and I will talk about this later. But the first development of the monographs took place in the '90s, beginning of the '90s, and at that time I wasn't really there, and I reviewed the minutes of the meetings to give you an overview how the monograph developed and what are the requirements of the monograph.

First of all, I will start my talk to remind you about the importance of plasma for fractionation for the manufacture of blood products, and after that I will give you a brief legal background for human plasma for fractionation, and then go in detail into some issues of the monograph plasma for fractionation, which are under discussion during these two days, and finally I will summarize my talk.

The quality design of blood products is an all-embracing concept. The quality cannot just be tested at the finished product level, but the quality, safety, and efficacy of the blood products, as for all biologicals,

depends on several parameters which are, for example, the starting material, the manufacturing process itself, the control tests, and the in-process controls, specifications, the equipment, and operational standards. For the blood products, the starting material is an important factor which could contribute to the quality, and here are some of the criteria which define the quality of the blood. As in starting material, these are the donor selection exclusion criteria, the screening tests used, the epidemiology of the donation centers, and the storage and transport, equipment, and the quality system under which the donation centers are operated. And today's issues are storage and transport, and I will go into detail later.

But, first of all, I'd like to show you the legal background in the EU, and, first of all, I have to mention the Directive 2001/83 that is the general Community code relating to all medicinal products for human use. And then there is the famous Recommendation No. R(95) of the Council of Europe on the preparation, use, and quality assurance of blood components.

I'd like to mention and to point out that this is not a legally binding document. The Council of Europe is a group of more than 40 countries representing Europe, not only the EU, and this is an agreement between all these countries to have a common standard for plasma for

transfusion. But that is not a legally binding document, although it represents a common-sense and a state-of-the-art document. So in some kind it is binding, but it has no legal status. And you should know it is not intended for plasma for fractionation.

Plasma for fractionation is in the European Pharmacopoeia Monograph, Human Plasma for Fractionation, and the quality aspects are laid down there. And you can refer in general when you like to produce blood products to the CPMP note for guidance on plasma-derived medicinal products, which gives you some explanation how to manufacture blood products.

The EU has decided to give the--or to set standards for the quality and safety of collection, testing, processing, and storage and distribution of human blood and blood products, to give that a legal background, so there is a directive beginning--that came into force the beginning of this year, and that is Directive 2002/98. And this sets the standards for plasma for transfusion, or for any plasma, whether it is intended for transfusion or for the manufacture of blood products. And there are annexes to this directive. These are technical annexes, and one is Directive 2004/33 that came out also early this year, and another will follow soon. And, again, the European Pharmacopoeia Monograph applies to human plasma for fractionation. And

both with the two new directives, the recommendation of the Council of Europe will not have the same level of applicability in the European Union.

The scope of the new directive and its technical annexes cover only plasma for fractionation, the collection and testing of this plasma, but the standards for plasma for fractionation are covered by the monograph, Plasma for Fractionation. This should be kept in mind.

The directives were developed in order to ensure that there is an equivalent level of safety and quality of blood components throughout the EU, and whatever their intended purpose is, and it includes the starting materials also for medical products and that should be established by this directive. For this, you should know that directives are not directly binding documents, but they have to be transformed into national law of the EU member states, and the directives give a legal frame which has to comply by the national laws, but you can go beyond this frame. You can have stricter requirements in your national laws if you like or if there is a need. And the implementation and application of the directive or the transform into national law, transformed directives, is the duty of the member states, and the elaboration of the technical requirements, technical

annexes of the directive, involves scientific committees in the European Community.

There is a transposition phase for the member states, and the new directive should come into force at the latest the 8th of February next year.

Again, I have summarized the requirements of the Council of Europe recommendation, but remember this is for plasma for transfusion. And it relates to whole blood and apheresis plasma and there is defined the time from collection to freezing, which is 6 hours but not more than 18 hours, 6 hours for apheresis plasma, and the freezing temperature is to minus 30 degrees within 1 hour. That means a rapid freezing process to a core plasma temperature of minus 30 degrees. And the storage and expiration is also mentioned there, and it is when it is stored at minus 25 or below, 24 months.

As I said before, the legally binding document for plasma for fractionation or setting the standard for plasma for fractionation is the European Pharmacopoeia Monograph. The European Pharmacopoeia has the task of laying down common standards for the composition and preparation of substances, for example, excipients, starting materials, or finished products. The medicinal products marketed in the EU have to comply with the relevant Pharmacopoeia monographs, and that is also mentioned in Directive 2001, which is the general code

for human medicinal products. They have the force of law in the EU, and the monographs are elaborated by expert groups and expert groups dealing with the blood products is the expert Group 6B at the European Pharmacopoeia.

I'm a member of that group since 2001, so I cannot tell you everything about that. But Group 6B worked since September 1991. There have been 25 meetings, and you see it is a never-ending--plasma for fractionation is a never-ending story. And it was 18 times on the agenda, and I promise next week we have the next meeting, it is again on the agenda. So you are not the only people discussing plasma for fractionation.

So, in principle, the issue is clear. We have blood or plasma recovered from blood and plasma by apheresis, and how should we bring that into the frozen state? There are two main players: time and temperature. And time can mean time to freezing, time for the freezing process, storage, and temperature can mean to which temperature should the plasma be cooled down and how should it be stored, at which temperature, or at which temperature should it be transported.

This is the scope of the workshop. This was outlined in the announcement of this workshop, and I'd like to go now into some detail on how does the European Pharmacopoeia deal with these issues.

First of all, I will show you this slide. As I told you, the monographs should develop standards, and in this case a standard for plasma for fractionation. And the intention of Group 6B is always to provide assurance about the high quality, and that means protein integrity, of the source material for the manufacture of blood products. And we are always considering more or less scientific data and discuss scientific data, and when the monograph goes out for consultation, industry can comment on that. And in our final discussion, we also consider the need of industry for our decisions.

What I'd like to make clear is that we have only one standard for plasma for fractionation, and that is already given in the definition which is the first part of the monograph. And plasma for fractionation is the liquid part of human blood after separation of the cellular elements from blood collected in a receptacle containing an anticoagulation, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure. It is intended for the manufacture of plasma-derived medicinal products.

This means we have one standard, but the plasma for fractionation can be obtained either by apheresis or by whole blood, recovered blood by the separation of plasma from whole blood.

Now I'll try to show you how the monograph developed, and I took the third edition of the Pharmacopoeia monograph to discuss some issues which are important and are discussed during this meeting.

First of all, should it depend on the final--should the definition of the storage and the freezing temperature depend on the final product. In our first--or that is not the first, but it is the same as the first. In the third edition, we made it dependent on the final product how the plasma should be frozen. And you see for labile products, as soon as possible, but the latest within 24 hours. That is true for plasma obtained by plasmapheresis and from whole blood. And for non-labile products, it stated separation within five days of the expiry date of the whole blood. And that is plasma obtained from whole blood.

But then in the third supplement in 2001, we changed this definition. It was recognized that we should not give a definition on the--or make it dependent on the final product, but it depends whether the factor is labile in plasma or not. And so we changed the wording to make it clear that for coagulation factors which are labile in plasma, they have to be frozen as soon as possible, but at the latest within 24 hours. And for non-labile, we introduced this definition as soon as

possible, but at the latest within 72 hours. And this is for plasma obtained from whole blood.

We had a lot of scientific data. Albert presented these very nicely. And most papers, as I know, and Albert already mentioned, focus on labile components in plasma, and also in finished blood, finished policy, and they are the coagulation Factors VIII and V. And it has been shown in literature that time to freezing is a very crucial factor for the recovery of these labile components, and the best preservation of labile components in plasma is obtained when you freeze it within 6 hours after donation, and you lose some Factor VIII activity during storage between 16 and 24 hours, and additional loss is observed for longer storage.

I think the Factor VIII was at that time an important factor for the collection of blood and, therefore, it was chosen as the lead factor for this. But it should always depend on your need or what you like to manufacture from the plasma, whether you need storage--time to freezing, which is according--it depends always whether this is a labile--whether the product of your intention is labile in plasma or the factor is labile in plasma or not.

So the freezing temperature itself, in the third edition I'm referring to here, we had the wording, "Any plasma intended for the manufacture of coagulation

factors or other labile components is processed shortly after separation or collection of it is frozen by cooling rapidly to a temperature of minus 30 degrees or below." That is important to note because we changed that already in the next year, and from the minutes of the meetings, I read that it was never the intention of Group 6B to fix it as it was the first time, to a temperature of minus 30 degrees. On the other hand, because--I will show you later or in the next slide--there were no data from industry who supported storage at minus 20. I think the Group 6B decided to do it similar to the conditions for plasma for transfusion in order to preserve the integrity of the proteins in plasma.

Nevertheless, we have then changed that again and divided that in the sections for factors that are labile in plasma and when obtained by plasmapheresis from whole blood, plasma intended for recovery of proteins that are labile in plasma is frozen by cooling rapidly at minus 30 degree. And for the non-labile, it is frozen at minus 20.

We have heard that rapid freezing is essential for the preservation of proteins or Factor VIII in plasma, and so the plasma for transfusion requires that, to reach a core temperature of minus 30 within 60 minutes. But for the plasma for fractionation, this time is not specified, and it means rapidly at minus 30.

Rapidly at minus 30 can mean that you have storage which is capable of holding the temperature at minus 30 when you put in your blood banks or the plasma banks, but it does not go below minus 30, and you have evaluated your process that it is rapidly--that it is a rapid process and it means that you don't spend too much time from donation to the freezing process.

At that time industry asked for freezing at minus 20, but Group 6B decided not to set the minus 20 because industry couldn't provide any data which were in favor of the minus 20 freezing. And we don't--even today we don't have the data, but meanwhile industry is satisfied with the current regulation in the EU.

Then let's come to the storage temperature. In the second version of the monograph, it was mentioned storage should be done at minus 25 degrees. We heard about the eutectic point. Probably there is no--I learned today, but at that time it was discussed that the storage should be below the eutectic point, and it was a very controversial discussion whether repeated passage across eutectic point might lead to a degradation of proteins, and it was well recognized that this was in contrast to the U.S. and WHO documents. But later, when Group 6B again changed the storage conditions to minus 20, and it was recognized and we heard today that you can store plasma at or below minus 20. The scientific

evidence for the storage temperature was shown, and, therefore, the monograph was changed.

Now we come to the famous storage and transport conditions, and that really has been discussed a long time. And in the beginning, in the third edition, you remember the plasma should be stored frozen at or colder than minus 25. Therefore, there was a time restriction to the shipping condition at or below minus 20, and the time restriction was 4 weeks, and there was also the ability that there was an excursion of the time for not more than 72 hours and if the plasma at all times maintained below minus 5 degrees.

When there was a change in the storage condition for the plasma, the time restriction for the shipment was removed, and the transport condition was still there. When the storage temperature is exceeded on at most one occasion for not more than 72 hours and if the plasma is at all times maintained at a temperature of minus 5 degrees.

Again, with the current edition there is a change to this. It was recognized that maybe this restriction is not adequate and that industry may lose a lot of plasma when that excursion occurs not only once but two times or several times. And, therefore, we mention now that the temperature is between minus 20 and minus 15 for not more than a total of 72 hours without

exceeding minus 15 on more than one occasion, as long as the temperature is at all times minus 5 or lower.

We have given some information of industry and examples of industry that when the temperature in the storage goes down to minus 15, it takes about 12 hours--it takes about 12 hours that it goes down to minus 15, and that it takes again about 12 hours to come up to minus--come down to minus 20. So for us it was convincing that this could be at more than one occasion, and we changed it according to the need of industry.

So excursions are allowed which guarantee that the plasma is still in its frozen state and suitable for fractionation, and it complies with the requirements of industry.

Then expiration. The monograph does not mention an expiration for plasma for fractionation. And is this really a matter of concern? I think in practice not. According to the marketing authorization, we have that fixed to two or three years, depending on the application, and our data from batch release show that plasma is almost manufactured 6 to 12 months after collection. And all concerns which have been discussed were safety concerns, for example, state-of-the-art screening of the donations, and that the marketing authorization holders, I think also the safety concerns

and economical reasons, though there is no need for them to store plasma longer than two or three years.

This is the complete text which deals with the issue of storage transport of plasma for fractionation, and it reads, "When obtained by plasmapheresis, plasma intended for the recovery of proteins that are labile in plasma is frozen by cooling rapidly at minus 30 or below as soon as possible and at the latest within 24 hours. When obtained from whole blood, plasma intended for the recovery of proteins that are labile in plasma is separated from cellular elements and is frozen by cooling rapidly at minus 30 or below as soon as possible and at the latest within 24 hours of collection. When obtained from whole blood, plasma intended solely for the recovery of proteins that are not labile in plasma is separated from cellular elements and frozen at minus 20 or below as soon as possible and at the latest within 72 hours of collection."

I have put the wording together to this table to make that clear. The excursions are given at the bottom, and you see there is a question mark, plasma obtained from plasmapheresis. It's not mentioned there. There's a current discussion on this, what should the time to freezing be for plasma obtained by plasmapheresis when it is intended for proteins which are labile--not labile in plasma. But that is under current discussion whether

there should be a time limit or whether it is common practice that it is frozen in a short period of time, let me say, 6 hours after donation at the latest.

So there are still open issues which are not discussed. For example, the conditions depend on the factors which are labile or non-labile, but there is no definition given in the monograph. That is for me a little bit strange, and I would prefer to have at least some examples what the monograph means with labile and non-labile and so on, and that could be reason for further discussion of the monograph.

When we heard about the current intended revision of the plasma storage and transport conditions, or when that was published by FDA, Professor Seitz, who is head of Group 6B, wrote a letter or a comment on this revision, and he very much pointed out that we are interested in harmonization of these conditions, and at least this would allow an exchange of plasma for fractionation or an exchange of intermediates according to the need of manufacturers and according to the need of people in different parts of the world.

So I think it would be very good to have the same quality standards for plasma for fractionation in the countries where plasma is fractionated. To harmonize the standards in the U.S. and Europe would be a first starting point for this. And I think industry would also

appreciate harmonization of these standards because they are globally operating. For them, the logistics would be easier, and they would have maximum flexibility and availability of plasma and intermediates.

And what I'd like to say is that industry is satisfied with the EU regulations at this time because they are evidence based and, we feel, well balanced. I think not everything is scientifically--for each of the parameters we are discussing, there is a clear scientific decision, but I think it is the practice and everybody is well satisfied with these practices at this time.

The last point is: How do we maintain harmonized regulations? That is another issue for the next meeting perhaps, but at this time we should start perhaps with the harmonization of regulations regarding plasma for fractionation.

So let me summarize what I wanted to--the information I wanted to give you. There is one standard for plasma for fractionation in the EU. The collection and testing of plasma is regulated by Directive 2002/98, and the production and the manufacture of plasma for fractionation is regulated by the European Pharmacopoeia monograph. And the EU would highly appreciate harmonization of standard for plasma for fractionation, and it would be an advantage for regulators and industry.

Thank you very much for your attention.

[Applause.]

DR. HOLNESS: Questions for Dr. Dodt?

MS. CARR-GREER: Allene Carr-Greer with AABB. You spoke briefly to current discussions about whether there should be a different set of freezing standards for product collected for non-labile final product by apheresis. Can you say more about why you would consider that an apheresis collected product needs a standard separate from the whole blood? It was your Slide 27. You had the question mark there.

DR. DODT: That was non-labile.

MS. CARR-GREER: Non-labile.

DR. DODT: And for the non-labile from recovered plasma there is a restriction to the time for freezing, that is 72 hours, and at this time there is no time fixed for the time to freezing for the plasmapheresis-obtained plasma because Group 6B--I can say here briefly what we discussed. We wanted to fix that at 24 hours for the non-labile because we thought it was common practice in a plasmapheresis center to do the freezing immediately. But there have been--some member states are opposed to this because they have national laws which require a 72-hour time to freezing for the plasmapheresis plasma when intended for the production of non-labiles. So we have probably to take into account the national law of some of the member states.

MS. CARR-GREER: So you are looking at some pre-existing--

DR. DODT: Pardon me?

MS. CARR-GREER: You are looking at pre-existing conditions in some of the member states, not necessarily a science or evidence based--

DR. DODT: In this case, we have to because the Pharmacopoeia Commission didn't agree to this draft where we said that plasmapheresis plasma has to be frozen in a time below 24 hours. But this will be discussed at the next meeting. My personal point of view is that a time of 24 hours to freezing does not--is not opposite to the national laws. They can still have their national law requiring a 72-hour time to freezing, whereas the monograph says when it is used for fractionation, it is 24 hours. But that's my personal point of view.

MS. CARR-GREER: And if I could just ask one more question, would this be plasma collected by apheresis at the same time a red cell is collected? Or is this purely plasmapheresis?

DR. DODT: This I don't know. And this is out of the scope of the monograph. But maybe some of the plasmapheresis centers can give you an answer, and I believe there are some people around here.

MS. CARR-GREER: Thank you.

DR. EPSTEIN: Thank you, Dr. Dodt. Could you comment for me how the product labeling works? You've suggested that the conditions of freezing are linked to whether you're making labile or non-labile plasma proteins. But how is that determined when the product is actually placed in commerce? Does the label say that it's intended only to make labile products or non-labile products? Or does the label simply state the conditions of time to freezing and freezing temperature? In other words, how is the message communicated?

DR. DODT: This I don't know. This is, I think, the part of our GMP inspectors to take care about the labeling of the products. This is not described in the monograph, and this is not described in the marketing authorization.

So I think in general, plasma is frozen at minus 30 because then you have the better flexibility whether you--either you make non-labile or labile products from it. So I don't know whether there are any donation centers which do the freezing at minus 20. As far as I know, at the time of the development of the first plasma for fractionation monograph, there was only one manufacturer who did the fractionation of one product only, which was a non-labile one, and for that reason maybe this was included in the monograph. But I don't

know that correctly, probably. But there could be somebody who knows it better.

DR. EPSTEIN: I'm hearing you state that, in fact, the common practice is minus 30 freezing in less than 24 hours.

DR. DODT: Yes.

DR. EPSTEIN: For fractionation.

DR. DODT: Yes.

DR. FARRUGIA: I've got some comments, and they might pre-empt what I was going to say later, but it doesn't matter.

The first one is, particularly in Europe, a large amount of plasma for fractionation is recovered plasma.

DR. DODT: Right.

DR. FARRUGIA: Particularly in the (?) type environment. Now, you have shown us that there are differences between the standards for plasma for transfusion versus those for fractionation. I mean, this creates a substantial problem for people who generate plasma and after the requirements for transfusion are met, the rest is shipped for fractionation. So I just wanted to know if you wanted to comment on that.

The second one, and I'm a bit hesitant because there's a large man behind me here--

[Laughter.]

DR. FARRUGIA: But you made the interesting comment that the industry is satisfied. My understanding is that the industry in this country is not satisfied. And my understanding also is that it's the same industry. So I just wondering whether you wanted to comment on that.

DR. DODT: You're right that most of the plasma for fractionation is obtained from plasma from whole blood, and here are the conditions. And I think time from collection to freezing you have more stringent conditions, and the freezing temperature is more stringent. So most of the donation centers are doing the freezing to minus 30, and they do the freezing--time from collection to freezing is 6 hours, but not more than 18 hours. So that perfectly fits with the monograph, and there is no reason why plasma which was originally collected under these conditions cannot be used for plasma for fractionation.

DR. BULT: Dr. Dodt, Jan Bult, PPTA. You mentioned the desire from the European perspective for harmonization. The good thing of the workshop today is we'll gather a lot of information that will give us a picture whether that's achievable or not. But one of the things that you mentioned is that the difference between the minus 20 and the minus 30 is based on science, and you explained that the reason why the 30 degrees was

chosen for plasma for fractionation is because you did it for transfusion. I'm not so sure that that is science.

The question that I have for you is: If you talk about the need and the desire for harmonization, do you believe that the Expert Group 6B will be willing to reconsider the minus 30 degrees and, for example, take the U.S. example?

DR. DODT: Yes, I can think about a revision of the monograph, but it will be based on scientific data. And at this time we do not have scientific data for the freezing at minus 20. At the time the monograph was developed, industry was asked to provide data, and they didn't. And, therefore, as I explained, initially the temperature was fixed to that for the plasma for transfusion in order to avoid--or in order to guarantee the quality of the plasma.

So it is up to industry to provide data that plasma frozen at minus 20 has the same quality and is good enough to assure the quality of the finished product. And then Group 6B will be convinced and can change the monograph. I can't see any reason why we shouldn't do that.

DR. FITZPATRICK: Mike Fitzpatrick from ABC. I was curious about the difference in the expiration dates between plasma for transfusion and plasma for fractionation and the rationale behind three months at

minus 18 to minus 25 and a year at less than minus 25, but no expiration period at all for plasma for fractionation.

DR. DODT: I haven't been involved in the discussion about plasma for transfusion, but there was heavy discussion about this expiration date for plasma for fractionation. That was also before my time. But, nevertheless, in one of the last minutes, I read that this should be again discussed. But as I told you, I think there's at present no need to set an expiration date. It's not in the interest of industry to have plasma collected and stored for years, and it is not in the interest of industry, for example, to retest all the donations or maybe single donations or plasma--yes, single donations when there are some emerging diseases which are coming up during the time of storage and which could make it necessary to have special tests which we are knowing now on these plasma units. So I think it is in the interest of industry to use the plasma as soon as possible.

And, on the other hand, I said that it is mostly fixed in the marketing authorization. And there is it two to three years.

PARTICIPANT: I just would like to make a comment on Jay's statement, current practice is minus 30. I think this really depends, especially in the recovered

plasma sector, so if the blood banks know that the product will not be used for factors, it's clearly minus 20. We cannot say the current practice is minus 30. It really depends on the use. I think if we have, let's say, smaller blood banks, then they tend to assign the plasma for fresh frozen, and then they redesign it to plasma for fractionation. But especially bigger blood banks, they have a constant overflow of plasma they do not use for fresh frozen, and clearly this plasma is only frozen at minus 20.

DR. DODT: Thank you.

DR. HOLNESS: Now we'll have a discussion of the current Canadian standards for fresh frozen plasma, cryo, and recovered plasma. And for that we'll have Dr. Thomas Walker, and he's the Director of Regulatory Affairs of Canadian Blood Services in Ottawa, Canada.

DR. WALKER: Good morning, ladies and gentlemen. First of all, I'd like to thank the FDA for inviting CBS to come and, we hope, contribute to what promises to be a very important meeting.

Secondly, I'd like to declare that although I'm speaking about government regulatory requirements, I'm doing so not as the regulator. I'm doing so as a regulatee. There might be a slight difference of perspective or maybe even a conflict of interest there.

That said, what I want to do is, first of all, list the plasma products that we make in Canada, the indications for their use, the freezing methods we use, the storage conditions, quality control requirements, shipping methods, and then I'd like to summarize some challenges that we encounter because of the current requirements.

I would also like to point out that if you go hunting for any of these standards in documents published by Health Canada or by other standards organizations in Canada, you won't find them. They are interpretations of language like "freeze immediately" that we, CBS, have written into our standard operating procedures which have been approved by Health Canada. So what I'm going to present is not necessarily something issued by Health Canada. It is approved by Health Canada.

So what do we make? This should be very familiar to those of you from the U.S. From whole blood collections, we make fresh frozen plasma, or FFP; frozen plasma, which we call FP24; cryosupernatant plasma; and recovered plasma. From apheresis collections, we make either fresh frozen plasma, apheresis, AFFP, or source plasma. I'll use the acronym SP as I go forward.

The decision as to what we make from a donation is made by CBS. There is no difference in the consent process on behalf of the donor. In fact, the donor does

not know what we're going to make from the plasma or from their whole blood donation at the time they donate. This may reflect the fact that in Canada there's only ourselves and Hema Quebec, and both of us, when we make plasma for fractionation, do not sell it. We send it for contract fractionation, and we bring back all of the products for treatment of Canadian patients. So the donation is going maybe not directly, but it is going to the same target patient population, regardless of how we treat the product.

As I said, that's very familiar to those of you from the U.S. The product names and specifications were actually copied from the CFR and AABB standards by Health Canada back in the early '90s. Now, at that time the operator of the blood program, the Canadian Red Cross Society, had proposed something a little simpler. What we had proposed was that the product be called plasma, regardless of how it is made; that the volume should be stated on the label; that the anticoagulant should be stated on the label. If the freezing method was not sufficient to maintain the Factor VIII level for FFP, the 0.7 IU per mL limit, the product would be identified as Factor VIII-depleted. And the only restrictions on the use, i.e., for transfusion or for fractionation, would be in cases such as a donor with a malaria risk history where the product was only suitable for manufacturing.

I believe there are a couple of other instances where we would only use a product for transfusion because it would be unsuitable for fractionation. But the statement would be made only in those cases.

Moving on to indications, again, very similar to the U.S. situation. FFP and AFFP, note the indication for patients on Coumadin is only in an emergency where there is no sufficient time to bring back the coagulation function through administration of Vitamin K.

The FP24, as indicated, is not intended as a source of Factor VIII. However, we're finding it has about 75 percent of the level of Factor VIII that FFP has.

One thing to emphasize, when we send plasma for fractionation currently, we are only bringing back albumin and IgIV, no coagulation factors.

Freezing methods, FFP within 8 hours after collection is quick frozen, and we define "quick freeze" as dropping the temperature to minus 20 within 90 minutes. FP24, quick frozen within 24 hours. Cryosupernatant, now that is made concurrent with cryoprecipitate from a product we call first-stage cryoprecipitate, but essentially it's FFP, within 4 hours after thawing the FFP, if you like, to make the cryo. The CSP is frozen or stored at minus 20 or colder. The cryoprecipitate is quick frozen.

Recovered plasma, 72 hours after collection, but 6 hours after separation from whole blood, we place it at minus 20.

AFFP and source plasma, there are two alternatives allowed: one, within 8 hours after collection, we quick freeze; or, two, within 2 hours after collection, we store in what we term "a qualified freezer," and that is a walk-in freezer that's been demonstrated through validation to lower the plasma core temperature to minus 20 degrees C. within 6 hours. Typically they are running at minus 40 or minus 50 degrees C.

Storage conditions are interesting. The current Health Canada guidance document, which was issued in 1992, requires minus 30 degrees storage of products for transfusion and allows minus 20 degrees C. storage for products for fractionation. The Canadian Standards Association--and just for those of you who aren't familiar with CSA, it's an organization not unlike Underwriters Laboratories or the ASTM. They publish--they convene standards committees that generate consensus standards which CSA then published. CSA is actually more like UL than ASTM in that they also offer certification services against many of their standards.

Now that I've done the commercial for my former employer, CSA has published what is a national standard

in Canada, and it allows minus 20 degrees C. storage for all products. Health Canada has accepted SOPs based on the CSA standard, although they have not yet modified their guidance document. They're in the process of writing a regulatory instrument that will adopt all or parts of the CSA standard.

We understand that the rationale for the CSA position was to align with the AABB standard, again, harmonization, and also to recognize the capability, or lack thereof, of Canadian hospitals. They have long used the minus 20 degrees C. standard, and they're not in a position to refit, readjust, rebuild, replace their freezers in the short term to comply with the minus 30 degrees, which was Health Canada's position.

Now, we haven't yet reset our freezers, so what I'm going to talk about in terms of what we're achieving doesn't reflect the minus-20-degree storage temperature. It takes a while to validate one of these boxes, as you know. Currently the set points that we use in various centers range from minus 25 to minus 60, and I'll come back to the impact of that in a few minutes.

Part of storage conditions are shelf life. The approved shelf lives are 12 months for the products for transfusion, 10 years for the products for fractionation. Do we need 10 years? Probably not. Plasma is usually fractionated within 6 months. We've had some instances

arising out of contingency plans around West Nile virus, stockpiling plasma in the winter to support areas where we stop collecting plasma for transfusion during a West Nile virus epidemic in the summer, where we would need the 2- to 3-year shelf life for recovered plasma in order to avoid wasting the stockpile that we didn't use. But we certainly have not had an instance where we've needed a 10-year shelf life.

Quality control requirements: not less than 0.7 in 75 percent for FFP or AFFP; not less than 0.52 IU of Factor VIII in not less than 75 percent of units tested for FP24. The only parameter we check for CSP, RP, and SP is volume, and we do check volume for the other products as well, of course.

We're awaiting FDA's promised guidance document on QC sampling to overhaul this plan. We don't think it's optimal, but certainly we've seen some interesting proposals from the FDA in recent months. The reason that we're not checking the Factor VIII in CSP, of course, is it's not indicated for that use, and we're not checking it in RP and SP because we're not currently fractionating for Factor VIII or any coagulation factor.

When we were deriving Factor VIII from our plasma, our fractionator tested pools--or actually sampled the product, did the Factor VIII determination, told us what levels we were achieving, and then

negotiated the contract on the basis of that. In our case, it wasn't negotiating a price for the plasma. It was negotiating a yield in return for our fractionation fee.

Shipping methods. Products going to hospitals for transfusion we ship in insulated containers with dry ice and a protective barrier between the units and the dry ice. The products for fractionation we put into corrugated boxes with corrugated dividers to keep the units from rattling together. And we put them in a refrigerated vehicle maintained at nominally minus 20 or in accordance with the CFR requirements.

Now, what are our challenges? One is temperature excursions occur. Defrost cycles in the freezer boxes, even staff picking up--or entering the freezer to put product in, take product out drive the temperature up. The USP concept of a mean kinetic temperature, which is essentially an effective average temperature, is not recognized by our regulator. They do recognize 21 CFR 640.76 which allows temperature excursions for source plasma, but they only recognize it for source plasma. That provision is not extended to any other product.

One point to note, a glimmer of hope for us, the CSA standard states only that the product must be

maintained frozen during transport. That only applies to products for transfusion.

Because we've got to watch out for these excursions, we have to bring the set point down so that the peak temperature doesn't go above the limit. This increases operating cost because the heat flow into the box is proportional to the temperature differential. You either have to invest money in thicker walls or in running the heat pump harder to get the heat back out of the box.

The other thing that this does is that it creates a problem with container breakage. Why? Because plastic films have what's called a "glass transition temperature," and Dr. Farrugia referred to that sort of parameter in reference to plasma this morning. The term is very descriptive because at the glass transition temperature that nice flexible film becomes a very thin piece of glass and very brittle and very weak.

For PVC, which is what is normally used in blood bags or plasma bags, that glass transition temperature is somewhere between minus 20 and minus 25 degrees C. If you get colder, you've got the plasma in a glass bottle, effectively. We've seen breakage rates as high as 6 percent on the products for transfusion. The breakage occurs during transport. The breakage occurs in our own

freezers. Plasma for fractionation, the rate is only about 0.34 percent.

We're trying some solutions to our breakage problems. One is bubble wrap around the plasma when we're shipping it--or when we're storing it, as well as shipping it. Also, we've seen some correlation with the use of slab dry ice instead of pellets. Slabs cause more breakage. Those measures are being tested. And we have the nagging thought that fractionation experience suggests that maybe minus-20-degree storage and shipping would solve the container breakage problem.

Now, I'm going to go out into left field a bit here, but I was invited to comment on the manufacturing process, and I'll take a little bit of an extension that labeling is part of the manufacturing process.

CBS collects plasma in Canada. We have it fractionated in Clayton, North Carolina. We move the plasma under what's called an import for export exemption agreed with the FDA and to which both ourselves and Bayer are parties. That means we've got a fair bit of legalese to include on the label that most of you don't. Because we collect in Canada, we also have to list every test we perform on the label, not just the FDA required tests. And we've run out of space. We looked at just going to a smaller font size. Well, we're already using Arial Narrow 6 point, and I don't know about you, but my arms

are barely long enough to let me read that. If we go any smaller, forget it.

We were trying to find a wording that would be acceptable to two regulators and fit in the space required, and we hit upon the question: Why don't we just do what we do with the products for transfusion where there is a statement, "This product may transmit infectious agents. See Circular of Information." We know that our fractionator requires a certificate that lists the units and exactly what tests were performed and is signed off two or three times. They require that for their records. We require it for our records. As far as we know, that's the only document the fractionator checks. I've never in numerous visits to fractionation plants seen an operator read the label, except perhaps to check the number against the list. And we're wondering why a label statement like "This plasma is negative or non-reactive by FDA requires tests. Consult testing certification for lists of tests performed" couldn't be used. It's short, it's concise, and it doesn't have to be changed every time you add a new test. And who knows when the next occasion for that will be?

And, to close, it seems very little these days gets done by one person alone. Everything is a team effort, and this presentation is no exception. I'd like to credit my teammates: Dr. Heather Hume, who's also

here today and has promised to help me with any medical questions that come up; also Mr. David Howe, back home in Ottawa; and Ms. Yanick Charles.

And that, Mr. Chairman, we'll do our best to answer any questions the group may have, time permitting.

DR. FARRUGIA: You made a lot of interesting points, and I guess you're in a kind of unique situation because your relationship is per force to two regulators. You've got Health Canada and the FDA. But, I mean, I'm going to resist asking many questions. I think this is probably for your medical director because I was very, very intrigued with the statement that the apheresis FFP has different indications than the whole blood-generated FFP. And I just wondered what's the logic of that.

DR. WALKER: I'm sorry if I gave that impression. That's not the case.

DR. FARRUGIA: Slide 5.

DR. WALKER: Both FFP and AFFP have the same indications.

DR. FARRUGIA: So those are considered equivalent indications, they're considered the same. Why is the AFFP list much more specified?

DR. WALKER: Sorry. Both products--

DR. FARRUGIA: Oh, they are the same indications. Sorry.

DR. WALKER: All the same.

DR. FARRUGIA: I do apologize.

DR. WALKER: I think I used something--I don't think I used a different convention. If I created confusion, I'm sorry.

MR. GIROUD: My name is Yvan Giroud from ZLB Behring. If I understand you correctly, a sharp peak that would reflect a defrost cycle, let's say, goes up to minus 10 or maybe even to 0 degrees, and then rapidly goes down within less than one hour to the base temperature, such a peak would be considered as a deviation, as a temperature deviation.

DR. WALKER: That's correct.

MR. GIROUD: I'm not sure that this is current practice by the industry or not, but in our procedures, we have clearly defined that such a peak would not be considered as a deviation. We accept defrost peaks because such a sharp and rapid temperature change cannot reflect the temperature of plasma.

DR. WALKER: Our logic is more or less the same, but I was just describing the way the rules are currently enforced in Canada. Perhaps if we wrote up an SOP for dealing with such deviations and submitted that to Health Canada, they might approve that. But we haven't tried that yet.

MR. GIROUD: I have a second comment. This is regarding labeling. I understand that test results are

important on the labels for blood products to be used for transfusion. But with regards to plasma for fractionation, in fact, much more important than the label are the plasma paperwork or the test certificate we get either in paper form based or in electronic delivery notes. And I wonder whether this is an important aspect with regard to labeling of plasma for fractionation.

DR. WALKER: Well, thank you, that's certainly our question.

MR. FRANKLIN: Ian Franklin. I work in Scotland. I'm here representing the European Blood Alliance. You're the first speaker to actually talk about indications for these products and components. And you're also the first person who's come out with a general 20-degree sort of consensus temperature.

I guess the patients are interested in the quality of what they get. Is it going to correct their blood clotting defect and not give them a virus, not give them an inhibitor?

In Canada, do you have hemovigilance that can actually provide data to show that your FFP stored in this way is efficacious and, similarly, that all the plasma products that are made in this way are also efficacious? I'm guessing the answer might be yes, but I'd be interested to know.

DR. WALKER: I think I'll lateral that one to Dr. Hume.

DR. HUME: Dr. Heather Hume. I think I can only say I wish that the answer were yes. But I think in the recent publications from Britain about the studies around FFP that we haven't done any better in North America than the data that was published in that study. So, you know, we know that we fulfilled the requirements, as Tom has showed them there, but the outcomes in clinical use, the literature is pretty sparse.

As you know, in Canada, we use for the treatment hemophilia A almost uniquely recombinant factors, very few or just a handful, literally, of hemophilia A patients who will be on plasma-derived factors. And the same thing with hemophilia B, and even for von Willebrand's disease, it would be very rare now that we would use cryoprecipitate. So we don't use them for Factor VIII other than in the multiple coagulation deficiency setting.

MR. FRANKLIN: Just to clarify, that would mean that FFP hemovigilance would be based on clinicians' complaining that it didn't work, or is that--

DR. HUME: Well, we do think that we're building a fairly good hemovigilance network in Canada. But our hemovigilance is targeted to adverse effects of transfusion, transfusion reactions, transfusion

complications, and not to an inadequate outcome for the use of FFP. But I can't say that I--I've heard those complaints, but I think you'd have to look at it in a proper study to really be able to answer the question properly, and we haven't done that.

PARTICIPANT: I was noticing in your talk about the breakage of the bags, which is kind of a stunning number, 6 to 8 percent I think I recall. PVC is the bag with the glass transition point, as you mentioned, right around minus 20 degrees C. But that's a useful thing for fractionators in that they put them in nitrogen so they can disengage the frozen--but there are plastics that are colder--that have glass transition points colder, but still much higher than nitrogen. And I can't imagine that there isn't a better plastic that would entirely avoid this problem. If used in volume, the cost couldn't be that great.

DR. WALKER: We haven't found one that's licensed for the purpose yet. There are definitely polymers that, as you say, can withstand lower temperatures. They haven't been pursued by bag manufacturers, to the best of our knowledge.

PARTICIPANT: I know that Jim Drago at Bayer a while ago was working on a bag, I think it was EVA or whatever, and I thought that that had been adopted. But

I'm sure there are people from Bayer who can speak better about it than I.

DR. GILCHER: Ron Gilcher, Oklahoma Blood Institute. For the record, Dr. Farrugia, there is a difference between fresh frozen plasma whole blood-derived and fresh frozen plasma apheresis-derived. And at the Oklahoma Blood Institute, when we're doing massive transfusion therapy, which I'll call therapeutic plasma exchange, that is only done with apheresis-derived. It is 90-percent absolute plasma with essentially one-half to two-thirds the citrate content compared to fresh frozen plasma whole blood-derived, which is only 80 percent absolute plasma by volume and 20 percent is the anticoagulant and has significantly more citrate.

DR. ROCK: Gail Rock from Canada. If I could just comment that recently we've had our residents running some studies that they're doing, and they have pulled a lot of fresh frozen plasma and done assays on them. And I've been kind of struggling with the fact that our Factor VIII assays are running anywhere between 54 and 77 rather than 100 percent per unit. And I don't know if there's any relationship whatsoever, but I do know that the cryos we're making out of those FFPs are, in fact, also very, very low in Factor VIII. And so I'm wondering if some of these other alterations may, in

fact, account for it, and I think it's something we can talk about when we get back home.

DR. WALKER: I look forward to seeing your data.

DR. FARRUGIA: Can you comment on that aspect then? Perhaps the fact that you're not in the disciplined framework of having to generate Factor VIII-rich plasma for fractionation because your country made, I think, the appropriate decision to go recombinant so you don't get Factor VIII. Do you think that that kind of situation is impacting on the Factor VIII quality of the clinical FFP?

DR. WALKER: I'd say it should not be. We have some control as to--well, back in the days when we were fractionating for Factor VIII, we diverted plasma frozen within 8 hours for fractionation. The potency of our fractionation pools have gone down because we've taken the early plasma to make FFP. Now, to hear that the potency is not what it should be is a bit of a surprise, and it's definitely something that we'll want to follow up. Our data aren't telling us that, so what's the difference?

DR. HOLMBERG: I'm Jerry Holmberg with Health and Human Services. Two issues I wanted to address, primarily the breakage of the PVC and also the labeling issue.

In a previous life that I've had, that being the U.S. military, the U.S. military routinely freezes their PVC plasma at minus 65 or colder and has a 7-year approval on the clearance on their FFP. The breakage is primarily associated with, like you said, I think, laying it maybe on a slab of dry ice versus pellets or not using a blast freezer, and also in the shipment of it. And I think we've learned lessons in clinical practice. When I first got into the business, it was you always took out four FFPs if there was an order for two because of the breakage. But I think a lot of the breakage was with PVC.

Now, I think EVA may be a little bit better as far as the breakage, less breakage on that. But I think Dr. Valeri has done a lot of research, I think most recently published in Transfusion, on the breakage rate with the PVC.

The other issue that you mentioned, and I think if you have a definite challenge in Canada, is with the labeling and the languages. Again, in a former life, I was very much involved with the ISBT 128 in which there was a standardization, worldwide standardization of the data elements. And although one of the key guidelines to that document is to be able to have eye-readable below the bar code, what it does is it enables a lot of the languages to be quickly interpreted by the computer

because the data elements only knows the computer language.

However, I think that there's a real issue here on the plasma fractionation side, and that is that I don't think the plasma fractionators have really moved to do international labeling in identifying the data elements so that there's standardization of the data elements.

DR. HUME: Not to belabor the point of how much Factor VIII is in CBS' products, but we actually also looked at this when we were having to move to FP24 for reasons related to West Nile virus and wondering if our clinicians would accept the use of FP24. And so we found rather better labels than Gail did in her study at the hospital--and mind you, this was for plasma that was frozen only for short periods of time, but either at 8 hours or at 24 hours. We were actually surprised at the levels, and if anybody is interested in them, I can share that work with you.

But a good number of the units of FP24 would have passed the requirements for FFP, and particularly if those units came from people who were of Group A because, you know, they have higher Factor VIII levels than those in Group O. In the Group A units, in fact, most of the FP24 Group A's were as good as the FFP Group O's.

We are also looking, because we are thinking very seriously of changing to the buffy coat method of production in Canada, so we're looking at the Factor VIII levels that we would see at 24 hours if we were freezing our plasma at 24 hours, but after rapidly cooling it to 20 to 24 degrees, which is not what we currently do in Canada. And, again, almost all the units would pass the quality control currently required for FFP under those conditions. And, again, we will likely be publishing that data later.

DR. HOLNESS: Dr. Farrugia will update us on the Australian standards for plasma.

DR. FARRUGIA: This will be mercifully brief. I'm acutely conscious that I'm standing between you and lunch, and I apologize for not having the handout. But I only put the thing together yesterday, and it's available for anybody who wants it, and it's available to the conference organizers.

Okay. So this is Australia, its position in the world, and we are, like the United States, a federation of states and territories, and this is a very important political situation and constraint on everything in Australia, including the blood system. We are a social market economy, what used to be called--nowadays it's not so fashionable--a welfare state, and the Government of Australia is the primary deliverer of health care,

although actual services such as hospitals and so on are delivered by the states.

The national blood agency is the Australian Red Cross Blood Service, and it is funded by all the governments of Australia. Until relatively recently in time, this was basically a fragmented system, and each state and territory had their own blood bank pretty much under their own oversight. Over the past years, this has consolidated into a national service. A couple of years ago we established under a legislative framework a National Blood Authority to oversee the whole system in terms of funding and policy, and I think I can safely say that regulation which has been in place in terms of all aspects of the blood system for some five years now has proven to be a major driver for uniformity and consolidation.

Now, this is a big country. Australia is basically geographically the size of the mainland United States and of continental Europe outside the former Soviet Union. So this is a big country, and there's not many folks who live in it. There's only about 20 million of us, and most of us are concentrated here on the eastern seaboard. But the fact of the matter is that there are people all over the place, and, therefore, the blood transfusion needs are all over the place, and there are blood banks all over the place. And blood banks are

actually like they are in any other country, a major focus of societal and community cohesion. I would say that. So, you know, we have the same challenges that anybody has in a big country like this with a relatively low population density, although most of the people is centered in the major metropolitan centers.

Now, what are the standards? (?) this morning to the European Pharmacopoeia and the standards for Human Plasma for Fractionation. Now, in Australia, the regulator, which is my agency, has as the default standard for all medicines the--actually, not the European Pharmacopoeia. It's the British Pharmacopoeia. And one can speculate as to the exact reason for this in relation to our undoubted relationship to the mother country, but, of course, nowadays this has tended to become subservient and entirely covered by the European Pharmacopoeia. So for all intents and purposes, we're under the EP, and Dr. Dodt has explained to you the European framework, and he has mentioned repeatedly Group 6B, and we're actually honored to be observer members of Group 6B because we obviously have a stake in it.

This is just the extract from the Human Plasma for Fractionation monograph which deals with the issues of interest to this meeting, and these have been covered very adequately by Dr. Dodt.

In addition to that, from the European environment for plasma for fractionation, we also extract as a mandatory requirement--and this is kind of interesting because this is a guideline which in Europe is still in the form of a guideline rather than a strict mandatory requirement, the European Medicines Agency's guideline for so-called Plasma Master Files. And the very first draft of this document is embedded in our regulatory law as a mandatory requirement for any manufacturer of plasma derivatives wanting to market in Australia. And I personally think that this guideline is an enormously useful regulatory document and captures within it all the real issues in relation to plasma for fractionation. It does have resonance to the issues we're discussing today, but there's much more detailed information requested in terms of issues such as the epidemiology of infectious disease markers and supply and selection of donors than is found in the other documents.

This is just an extract from the guideline summarizing the contents and the issues which are of importance. I don't want to go too much into this.

Now, in addition to that, we have a separate, although somewhat parallel and sometimes convergent, regulatory framework for blood components outside the plasma derivative environment. And in 2000, we adopted as the universal Australian standard for these the

Council of Europe Guide, which has also been referred to here. And this guide is overseen by the Council of Europe, and there is a special committee, Special Committee SPRGS, on which we are also honored, as is the FDA, to sit as observer members, and this has the job of maintaining and developing what I think has proven to be a very resilient and excellent document over the years. So it's kind of curious because whereas this in the outside environment has been a guideline and in Europe has been simply a guide for the Council of Europe member states and anybody who wants to pick it up, in Australia it is a mandatory regulatory instrument.

It's also interesting to note that as a result of the Blood Directive over the years, aspects of this Council of Europe recommendations and the guide are being slowly assimilated into annexes of the Blood Directive and, therefore, as part of mandatory European law, but that's something which is still under development.

Now, I'll just spend some time--and these parts of this talk are in your handout because the slides which were in the first talk which I took out because I thought it would be better in the second talk I didn't have all that much to say. And just, you know, to sort of outline some of the differences between the two European standards which we use in terms of plasma for transfusion and plasma for fractionation. These have also been

overseen by Dr. Dodt, so I don't want to belabor them too much except to say that there are some differences.

They tend on the first instance to cause some problems. For example, if you look at other aspects such as storage, the storage requirements are a bit different in terms of the absolute temperatures mandated in real terms, although, as usual, the industry initially made some substantial recommendations. I mean, you know, this is all part of the debate. And we find that these are not really insurmountable, and if you look at the fact that, you know, the transfusion plasma, for reasons which I think are still to be explained, has a stricter requirement than the fractionation plasma, then we simply adopt the position and the industry adopts the position that, in terms of the range of equipment which they have, they will use the stuff which can generate minus 25 for the transfusion plasma and the freezers which can generate minus 20 for the fractionation plasma, and everybody's happy.

Of course, they would be happier if they had the ability to have a totally uniform situation, and we would never dissuade anybody from adopting what is putatively a higher standard and putting the fractionation plasma at minus 25 or below. But we will not mandate this because we'd like to stay popular with the people who will

ultimately have to pay for it, apart from anything else, unless there is a very big requirement.

Now, there's this other issue of the Factor VIII level quality control procedures, our plasma suppliers undergo this kind of guide--well, not guide. It's a requirement of the two standards. It's an equivalent requirement.

As I've indicated before, I find this requirement to be easily the least justifiable, although I think it is important to monitor the amount of Factor VIII in plasma, and I thought the discussion--the issue raised by Dr. Rock just now was particularly interesting, and I think that this particular requirement adds relatively little value to the system. And I'd be interested in thoughts on how this can be made better and more relevant.

But I think what I'd like to share with you now is some actual figures on the Australian plasma production system. This is data for the financial year--our financial year is '03--July to June, '03-'04. So over that period of time, we collected something like 910,000 units of whole blood.

Now, there's a bit of a mistake here in terms of units of recovered plasma less than 24 hours post-donation. I believe that the number is actually a little less than that because I think that captures all the

recovered plasma. However, I can tell you that the vast bulk of the plasma generated from recovered sources in Australia is frozen within 24 hours. We know this. And this is the result of an enormous effort and investment by the relevant governments and the Australian Red Cross Blood Service.

And so I would say that this is not unachievable. Obviously you have to put the resources on the ground, and obviously you have to assess whether this is something which is actually going to yield you benefit. And I think that every blood environment has to make those decisions pretty much on its own because every environment is substantially different. What I would point out, though, is that the logistics for us are no less easy than for anybody. But the system is able to absorb them.

What is actually quite interesting in terms of our enormous effort, given that we are in a situation that we're generating plasma both for clinical use and for fractionation is the amount which is actually diverted into clinical use. And you've got the numbers there, and I've put some exclamation marks next to them because it's a subject on which I hold strong views. And it is definitely the case that we are currently pushing into the clinical transfusion environment something like 49 metric tons of plasma production. And recently we

have worked very hard in developing guidelines for the optimal use of blood and blood components in Australia on the basis of what evidence is available in the literature and in clinical opinion. And we have as a government published these for use by prescribers. And I can tell you that about 40 to 60 percent, depending on what time of the year you look at it, of the clinical fresh frozen plasma is transfused outside these guidelines, and this is not a subject for this meeting, but a very substantial issue for us, as I believe it is worldwide.

You will notice that we are generating quite a bit of apheresis plasma now and that this is an encouraging thing. Again, it is the result of substantial investment by the governments, and we are now looking at about 35 percent of the pool being in the form of apheresis plasma. And over the past year, we pushed into the system something like 270 tons of plasma for fractionation, and about 190 tons of this--and this is a personal approximation, these two figures, because I haven't got them firmed up yet because the data is very recent--was manufactured to plasma-derived Factor VIII concentrate.

So, to conclude, we align to European requirements for both types of plasma. It has tended to cause the occasional tension, but it is not really an insurmountable problem. But we would still like to see

these European requirements come to some level of reconciliation and to have any differences more explicable on the basis of science. Considering that we are observer members on the committees which oversee these, I guess we are as responsible as anybody else to push for this outcome.

And as I said before, despite logistical challenges, the majority of our plasma from whole blood is able to be recovered within 24 hours, for whatever benefit might be accruable from that.

And I think that's about all I have to say. Thank you very much.

[Applause.]

DR. HOLNESS: I'm afraid we're running a little over time, so probably the best thing to do is now to go to lunch for one hour and come back at quarter after 1:00.

[Luncheon recess at 12:15 p.m.]

A F T E R N O O N S E S S I O N

[1:15 p.m.]

DR. HOLNESS: I just want to announce that there will be a question and answer period at the end of the meeting for at least an hour or so. Unless you have a really burning question, you can hold your questions till the end of the meeting.

Our next presenter will be Mary Gustafson. She's a senior regulatory policy manager for the Plasma Protein Therapeutics Association, and she'll give us an overview of the industry.

MS. GUSTAFSON: Thank you, Les.

Plasma has been used as a source material for plasma therapy since the discovery by Cohn of cold ethanol fractionation precipitation in the 1940s, and at the time these products were licensed, the manufacturers of licensed biologicals had to do soup to nuts processing. They were responsible for everything from the source material through the final product.

The only relaxation at that time was a provision in the regulations called short supply, and that enabled the director of biologics to periodically announce final products that were deemed to be in short supply, which then allowed those manufacturers to use some unlicensed materials in the manufacture of the products. And through the years many of the fractionated products,

starting with albumin, were listed on the short supply list by the biologics directors, and therefore, they were able to enter into what we're called short supply agreements, which are basically contracts, but they have a special meaning with suppliers of plasma.

And up until the mid 1970s that's how all plasma was used in fractionation. In the mid 1970s source plasma was licensed as an independent product not as a final dosage form product, but a for-manufacturing use product, and of course, safety and quality of plasma has always been important, but the primary impetus was donor protection because donors were being entered into serial plasma pheresis programs, and it was through that they needed to have more oversight over their health and well-being. And as we know, recovered plasma is still supplied under short supply, and that's really the reason why we're here today.

As I mentioned, source plasma was licensed in the 1970s, and there's a huge set of regulations that control the manufacture of source plasma dealing with, as I said, donor safety, donor quality, going through labeling and disposition of the products. But some of the regulations which have been hit on today that address the reason for the workshop today, which is primarily the collection and storage conditions, is the requirement that plasma is frozen immediately after filling and

stored at a temperature not warmer than minus 20, shipped at minus 5 or colder. And then there's an allowance for temperature excursions, so that plasma that inadvertently is warmed above minus 20 can be used in fractionation, and even one that goes further, which is a relabeling provision that allows the relabeling of plasma that goes up to a plus 10 to be labeled as source plasma salvaged, and it's suitable for use in fractionation.

And also through the alternative procedures request provision in the regulations, I think it's fairly common, what I've heard from the industry, that if they request that plasma that maybe goes a little bit above the excursion allowance, the request that it not be relabeled as source plasma salvaged is usually approved. The important thing is that the fractionater know the history of the plasma that they're buying to know if it's suitable for the products. Then there are additional criteria that's specified by the fractionater even for the license source plasma product.

For recovered plasma there's very few specific regulations. As I said, it's controlled primarily through the short supply agreements between the fractionater and the supplier, but there are some labeling provisions, and that is, instead of an expiry date, there's a collection date required, and there's labeling as to whether it's being shipped under short

supply, which means that it can be used for manufacturing use in fractionated products, or if it's not being shipped under short supply, a labeling statement that it has to be used for non-injectable products and products that are not subject to license under Section 351 of the Public Health Service Act.

Other requirements, as have been discussed earlier today, are extrapolated from the whole blood and plasma requirements for transfusion, and then the specific criteria that are specified by the fractionater.

I won't go through the list of European requirements. They were covered very, very aptly by Dr. Dodt. There are some high points though, and that is that there's one standard specified in the European pharmacopeia monograph for plasma for fractionation regardless of how that plasma is derived. And what's been discussed extensively is the requirement when labile proteins are being recovered for cooling rapidly at minus 30 degrees centigrade or below, then the requirements for non-labile proteins, the storage which is the same as U.S. at minus 20 or below, but then the shipping is considered storage in Europe, and so it's the very same temperature. It has a slightly more flexible excursion allowance than the U.S. requirements, but on the flip side of that there's no ability to relabel a salvage plasma if you exceed that excursion.

I will talk a little bit about harmonization because as an association we've been waving the banner for harmonization. Plasma therapies are manufactured and marketed in a global environment and PPTA supports and highly recommends harmonization. However, there's a few caveats there, and that is that harmonization, in our understanding, is not conformance to the most stringent regional standard. If we did that then harmonization would be easy. It also would be less flexible and less desirable.

We support harmonization that's based on scientific principles, and in the absence of agreement on science the industry appreciates flexibility.

I stole a couple of slides from Jan Bult and didn't realize that Dr. DiMichele was going to steal the same slides, and she presented them--the format of the slides were beautiful, the way she put them together and presented them this morning.

But these slides have to deal with recent developments in the plasma industry, concerns about consolidations of the plasma industry companies that have decided to get out of the business. It's resulted in plasma center closures and some fractionation facility closures. All of this has resulted in a reduced volume of fractionated plasma, but another down side is staffing reductions. Companies have had layoffs. People have

been losing jobs, trying to do more with less, and perhaps that is one reason why issues such as subtle differences in freezing and storage has not been a major priority in this environment.

There have been some very positive developments also. New companies have entered the U.S. market. If you look at the CBER approvals for 2003 and to the present, there have been numerous new product approval advancements in the plasma area. There have also been facilities upgrades and build-outs, and we continue to see enhanced technologies that result in higher yields, and I think you'll find that the fractionaters view some of these downstream processing enhancements as more beneficial or more useful in optimizing products than concerns about some of the differences in the handling of the plasma initially.

There's utilization of both source plasma and recovered plasma in fractionation. In fact, looking at data from the Marketing Research Bureau for 2003 in the U.S., out of nearly 13 million leaders of plasma collected for fractionation, a little over 10 million liters were source plasma and about 2-1/2 were recovered plasma. These are U.S. data alone. You'll see a higher proportion of recovered plasma being used globally.

Another slide that I stole from Jan is the differences in the drivers for plasma collection over the

years. In the early years the market was driven by albumin, and then that has switched to immunoglobulins with the Factors falling in the middle.

Again, a slide from the Marketing Research Bureau, data from the Marketing Research Bureau, the slide has a graphic representation showing the shift over the years from primarily albumin production and sales to IGIV with the factors falling somewhere in between.

This next is a pictorial of a leader of plasma showing the five major products that are derived from the liter of plasma. The take-home message here is that all of the products are important in a portfolio. The fractionaters cannot stay in business making one product alone. There has to be marketing viability for a broad range of products within the portfolio.

Besides the issues that are being discussed today, I think it's important that we can't look at the freezing, storage conditions in isolation. There's many variables that go into the fractionation process and these include the source material, the donor issues, just general biologic variability of human beings, the frequency of collection, methods of collection, even bleed time, time to separation, freezing, the things that we've discussed today, but then also the manufacturing issues.

The fractionation process alone by itself reduces yield, and we know that the all-important viral clearance steps that we couldn't do without, they're not terribly friendly to the proteins. But then we have other enhancements then to make up some of the protein loss in terms of purification and concentration, and all of these are extremely important in the fractionation process, and are considered by the manufacturers of the plasma-derived products.

In summary, there have been changes in the industry, in product demand, in business practices, and these impact manufacturing more than the volume of plasma that's collected right now. Both source and recovered are considered to be suitable starting materials for fractionated products, and that the final product outcomes are dependent on a variety of factors, and it's very hard to look at a couple of them in isolation. Manufacturers validate their processes based on the influence of various factors throughout the collection and manufacture of the products.

Thank you.

[Applause.]

DR. HOLNESS: Next we'll have a discussion of plasma for fractionation, and the presenter will be Daniel Albrecht. He's a Senior Vice President for Global Quality Safety and Compliance at ZLB Behring.

MR. ALBRECHT: It's a pleasure to be here today and to have the possibility to share some thoughts with you about plasma standards from a fractionated point of view.

I want to thank FDA for taking the initiative in organizing this workshop. It is definitely very important that regulators, patient groups and industry have such information exchanges. This helps understanding the potential concerns the different stakeholders have.

In my talk I will not go into the details of current fractionated practice since this will be done by the following speakers. Rather, I will try to highlight some general principles that apply to our starting material, plasma. Nevertheless, I made kind of literature search about temperature and I found some interesting hits. This is one of them, and I will share some more of them during my talk.

So initially I thought our life is tough, but when I look at this servicing guy I still think we should not complain too much.

[Laughter.]

MR. ALBRECHT: Having joined this industry five years ago from a traditional pharmaceutical industry I was really fascinated by the unique nature of our starting material. In conventional pharmaceutical

operations you mostly talk about manufacturing of finished products. Starting material is somewhat less important. In our industry the main starting material, plasma, is really everything. It is a unique starting material insofar that it is donated by people and used for people. Truly each unit is different. This becomes very evident to you when you spend a day down in manufacturing and have a look at the units when they are pooled. The most obvious difference of course is just the color. Due to this uniqueness it is of course very important that our manufacturing processes are very robust and are able to cope with this variety.

However, our starting material is also the major concern of potential safety issues due to the potential of transmitting diseases, and hence, also requires sophisticated quality control measure and manufacturing processes that are able to inactivate or eliminate such potential infectious agents.

Our starting material is also the major cost driver of this industry. Taken the long cycle time of manufacturing into consideration, fractionaters have on a permanent basis a huge amount of bound working capital.

Last but not least, I am also convinced that we have a responsibility towards the donors who provide this starting material. We have to make sure that we can make appropriate use of their donations.

So if you assume that all relevant quality measures, as for example, donor selection, plasma testing, but of course also the appropriate freezing conditions are in place, one could assume that all plasma is equal, meaning all plasma categories and all plasma sources could be used for all products and in all markets. This assumption is even more justifiable if you think about the processing of the starting material. The processing steps of the fractionaters and the overall quality systems maintain and assure the quality of the starting material and of course also the run of the final products. However, plasma business follows a little bit the same principles as the master pig, Napoleon, in George Orwell's book, Animal Farm, namely, while all plasma is equal, some plasma is more equal than others, meaning that perceived quality of the plasma varies greatly from market to market, and not all plasma categories, as example, apheresis or whole blood, can be used for all markets.

The same is true with the different plasma origins. Not all plasma from all countries can be used in all markets. Sometimes the evaluation criteria even includes political considerations. So as a matter of fact, fractionaters need very sophisticated systems to make sure that plasma is used according to these different requirements.

The plasma industry consists today of a global and complex network of supply. Fractionaters tend to be integrated with plasma collection facilities. Quite often they also have contracts to external blood banks or competitive collection facilities. Fractionaters also tend to have several plants and it is common that plasma intermediates are shaped within these plants, depending on the core competency of the individual plant. Intermediates are also shaped between different companies. In national tenders it is furthermore sometimes practiced that the final products go back to the plasma providing organization since such countries often have a self-sufficiency program. Based on this situation, it is evident that this industry needs very solid quality systems that assure the quality of the starting material.

We think these quality systems are very important for not only final product but also intermediates that good quality is assured. And what we say in our company sometimes, you want to assure, as we say, quality from vein to vein.

As you see in this slide our industry has indeed rather major quality systems in place starting with the regulation framework and the different pharmacopeias. Our understanding is that these documents should set the basic framework and define minimal standards. Further

down the pyramid of documents we then have many guidelines and other quality papers.

Last but not least, so-called quality agreements between involved parties, as example, a plasma supply and a fractionater play a crucial role in today's environment. In the recovered sector such agreements are governed by short supply agreements. What we see today is that short supply agreements are quite often just the governing framework for an extensive set of paperwork, as an example, commercial contracts, quality and delivery requirements, and then furthermore, special agreements.

It is quite standard practice that companies establish quality and delivery requirements on their short supply agreement umbrella. As you see from the table of contents of ZLB Behring's quality and delivery requirements for plasma, these are already comprehensive documents that cover in general all aspects of quality, as for example, donor cell action, collection, processing, freezing, storage and so on and so on. I think it is important to mention here that these types of papers have nothing to do with the fact that recovered plasma is not a licensed product. It is a basic GMP requirement that you have to define responsibilities between different parties, so you also need such agreements with source plasma suppliers.

Having made introduction to the existing quality framework of plasma for fractionation, we can now of course ask ourselves if there's a need for additional standards in order to assure the safety, purity and potency of these products. To answer this question from a fractionater's point of view, I tried to follow a risk-based approach as also represented in the FDA's initiative, cGMPs for the 21st century, where the goal is to implement approaches that are focusing both industry and agency attention on critical areas.

So this is my checklist. I think basic regulations and standards are in place to ensure quality of the final products. As we have seen this morning, the standards are not really the same all over the world. These differences are most probably not due to scientific evidence but rather to the fact the they were developed without really scientific evidence. So for sure harmonization is something that would make my life much more easier.

We really have to keep in mind that these are not new products. They have been around for decades and there is a huge amount of experience around in the manufacturing of these products including of course collection, freezing and shipping of plasma. From a fractionater's point of view and in terms of final therapeutic product, I think for albumin and

immunoglobulin the specific freezing, storage and transport temperatures are somewhat less important for the safety and quality of the final products.

Just this last month ZLB Behring had a ceremony where we could hand over the 100 millionth gram of IVIG manufactured in the Berne plant to a patient. A considerable amount of this IVIG, and this is also a FDA-licensed product. It was created out of liquid plasma in the years before '92. And if I say liquid, I really mean liquid product, liquid plasma. In terms of quality of safety, there was no difference to the two-day produced IVIG. I fully agree with one of my speaker colleagues from this morning that a microbiological baseline control is needed for the starting material, and in these terms freezing of plasma is of course the right thing to do.

Our experience with Factor products is also the time to freezing is the most relevant factor for minimizing yield loss. Transportation temperatures afterwards are somewhat not very relevant as long as the plasma is frozen. Also we did not make extensive studies--ZLB had different factor products lines with different national temperature requirements for the plasma. I can say that in the past 24 hours minus 18--and I'm very proud that I can introduce here a new number, minus 18. So this also worked for our plant in the past in terms of safety and quality. Just to put

this into context, you probably could say, if it's frozen, just keep it nice and cool.

So I think it's very important that we are taking--because if you are talking about quality and safety of products, we have to keep the totality of all quality measures in mind and cannot look at one measure in isolation. Quality contracts or agreements are a good tool to define all these measures. I'm a great believer in quality contracts since if these papers are written appropriately, there is no ambiguity left as to responsibilities of the different stakeholders involved in the game. Again, this is not something special to recover plasma. You also need these kinds of things for source supplies, including of course regular audits done by the fractionaters. Last, but not least, in these times of scarce resources we truly have to focus on critical areas and areas of concern.

If I look at the recalls and withdrawals from the last four years published on the CBER home page, I was not able to find any issue that was due to the fact of inappropriate plasma temperature standards. Of course this is a very personal assessment and different people might read different things out of this data.

To summarize, my answer to the question whether we need additional standards for plasma, I think that this is not an area where we should focus our today's

resources. Today's standards are appropriate to ensure the safety and quality of this starting material for fractionaters.

There is also an additional thing I want to mention. All the quality professionals, including myself, tend to look for additional standards. You also all know that in general new standards do not make it easier to manufacture product. In general costs increase. Furthermore it is really difficult to get rid of a standard once it is established. ALT is such an example, if it takes you years to eliminate this ALT testing from the specifications on a global basis.

So I think we as the people who are driving these standards have to ask ourselves the crucial question in everything about implementing a new standard. Do the patients profit from this new standard from a safety or quality point of view? If we cannot answer this question with a clear yes, I think we should forget it and move on.

So from a very personal point of view, plasma freezing, storage and transport does not keep me sleepless in bed during the night. However, there are many issues that make me uncomfortable these days. For example, harmonization. Working in a global company with being present in more than 50 markets, you don't believe me how many headaches I already had if you have to

allocate products to different markets than initially foreseen. Almost never the national requirements are the same, and you always need a lot of time, a lot of energy to prepare the scientific expert reports that show to the importing market that although the requirements do not meet national standards, this product is safe to use. As it has been mentioned before, harmonization has to be driven by scientific data, and to establish minimal standards and not to use the most stringent requirements. In the absence of scientific agreement, industry needs flexibility.

Another really hot topic in my eyes is the economics of our industry. As it was explained earlier in this workshop, our industry is undergoing significant change: consolidation of fractionaters, closing of centers, but on the other hand, also entry of new players to major markets. From a fractionater's point of view, we have seen in the last couple of years a tremendous pressure on costs, and it is our job to make sure that we do not add additional operating costs unless a patient see a real benefit.

So to conclude this talk, my very personal opinion is that today's standards are adequate to ensure the safety and quality of plasma-derived products. And again, from my personal point of view, I would like to encourage everybody to focus on more critical areas.

The last slide I have for you is just a reminder, just if the presentations go too long and there's just cold coffee left, don't worry, it could be even worse.

[Laughter.]

MR. ALBRECHT: Thanks.

[Applause.]

DR. HOLNESS: Now we'll have several presentations on current practices, and our first presenter will be--

DR. FARRUGIA: I have a question. Are we going to have questions?

DR. HOLNESS: Yes.

DR. FARRUGIA: The question for the FDA is in relation to this business of short supply agreements, which I understand is what underpins the minimum regulatory oversight of recovered plasma. We keep hearing that this is an industry which is actually over producing at the moment, has substantial inventory and that there's in fact a glut and we can see the consolidations leading to the closure of plasma collection centers. So how can you oversee under the presumption that the product is in short supply?

DR. EPSTEIN: I think de facto we've allowed the manufacturers to define their own need, and we've allowed the shipments of the recovered plasma as long as they

conform to a suitable contractual agreement, so we've really not focused on asking whether there's a global shortage or a global glut. We've left it to the parties themselves.

MR. ALBRECHT: I understand the regulator side because I was also working for an inspector for the Swiss Health Authority for many years. But on the other hand, if you compare to the pharmaceutical industry, I think--and I am convinced you are light years ahead in terms of GMPs and in the end everything should be governed by GMPs, and you don't need exact wording for everything because in the end it's still the responsibility of the fractionater. I have to release a product. I have to be happy that safety and quality's okay, and from this point of view I think we have a whole bunch of documents that govern this plasma.

DR. HOLNESS: Mary?

MS. GUSTAFSON: Albert, just to answer your question, I didn't really go into this in detail because it's not really my life any more, but it's kind of a moot point because in the late 1980s the regulations were changed and it opened up licensing, it changed the definition of manufacturer and the licensing provision to include the term "applicant," which can be someone who controls product manufacturing but doesn't do every single step, and it opened the door to all kinds of

contract manufacturing. And during those discussions, also what was discussed was, is it time for us to remove 601.22, which was the short supply provision, from the regulations, and it was left in primarily because it was a very special relationship between the fractionaters and the collectors of recovered plasma. However, there's really no concept any more about whether a product's in short supply or not because the regulations are more open.

DR. HOLNESS: Jay?

DR. EPSTEIN: Well, I just wanted to add a remark that the point has been made that the short supply agreements govern the quality of the starting material by specifying many conditions, and that's certainly true. But I think that the point that gets overlooked is that that occurs outside of the regulatory framework. The FDA does not review the short supply agreement, only the fact that it exists and is in place. And so the question that we're really asking ourselves is whether there ought to be minimum standards established through regulations and/or guidance that govern that starting material or whether it should be left entirely to the discretion of the contractual agreement, and that's really the heart of the matter is whether there ought to be any minimal standards. And of course there are such standards for source plasma. That's the chief difference.

DR. HOLNESS: Our next speaker will be Barbara Glantschnig. She's the head of Plasma Quality Assurance at Octapharma in Vienna, Austria.

MS. GLANTSCHNIG: Thank you. Good afternoon, everybody.

As I followed the presentations, the most important general aspects concerning quality of plasma for fractionation have been very well pointed out already, especially the previous presentation of my colleague from ZLB, so I will really focus on the very specific specifications that Octapharma has established over the years for the manufacture of its very products. Our manufacturing process might differ from that of others, so it's really tailored to our experience and our needs, and I will show some of the details as we go along.

We basically use--we came to using different plasma types for three product groups. One group would be the production of SD-plasma for transfusion. This product has been on the market here in the U.S. for a while, manufactured from a different supplier. Our product is not on the market in the U.S., but in Europe and other parts of the world, and we have been selling many million units of this product, and this has a defined starting material that differs a little from the rest of the fractionation products we have. The second

group would be fractionation of coagulation factors and coagulation factor complexes. As it is a question of yield, of course, what starting material you use for these products, we have defined our own specification for this group, and then the third would be fractionation of the IVIG and albumin. That is of course the most stable products and that we do not have such specific requirements as for especially the first group, SD-plasma.

This table gives you an overview on what plasma starting material we use for which products. I name the types of plasma according to the current understanding of these qualities here in the U.S. So I use recovered plasma for plasma derived from whole blood, and source plasma is plasma derived from automated plasmapheresis.

As you can see here, the recovered plasma 8 hour, which would be fresh frozen plasma 8 hour, can be used and is used at Octapharma for all product types because it is complying with all our specifications. For SD-plasma we also can use source plasma that was frozen within that timeframe adequately, and we do not, however, produce SD-plasma from 24-hour material or of course not 72-hour material. The Factor IX complex and Factor IX, we found the best suitable material is also the FFP 8 hour and the source plasma. We do at this time not produce these factors from 24-hour material. For Factor

VIII, however, recovered plasma 24-hour is perfectly suitable, and we find the yields satisfactory, and so we have been using this material for at least 10 years now to produce this factor. For IVIG and albumin we use all the product groups including 72-hour recovered plasma that we obtained from blood banks here in the U.S.

Now, the details of these specifications for the plasma are given here. For the FFP derived from whole blood, the 8-hour material, we require that the whole blood is stored at room temperature and then separated in a high spin centrifugation process so that we have optimal separation of blood cells from the plasma part. This is a very important quality aspect for us when we produce the SD-plasma. It has to be frozen within one hour to record temperature of minus 30, and this is basically what we took from the current Council of Europe recommendation for transfusion plasma, and we find it gives us a very good preservation of all the coagulation factors that we need to have in this SD plasma in a certain mix and at a minimum level. This is not fractionation. The plasma is basically untreated except for the virus inactivation, and so we need to make sure that we have an appropriate level of coagulation factors in the final product.

The storage, however, can be and is at minus 20. This works perfectly well for this fresh frozen plasma.

Expiry date is one year and that is again based more or less on our turnover time and on the logistics we have. It is not based on any scientific decision. The apheresis plasma that we can also use for SD plasma is not necessarily shock frozen. It is in many cases but it is not required for our specification. The important thing is that it is as quickly as possible after collection put in a solid minus 30 environment, and that the plasma is allowed to freeze with sufficient air circulation. So shock freezing is not necessarily such a quality factor for the source plasma according to our experience. Storage and shipping temperature would be the same at minus 20, and the expiry date, if we use it for fractionation, is two years, and that is again based simply on a logistical and production planning schedule that we have.

The recovered plasma, 24-hour, that we would use for the production of Factor VIII and the immunoglobulins, we also require to be spun down from whole blood with a high-spin centrifugation process. The freezing is minus 30, but not necessarily shock freezing. The practice in many of our suppliers is however that they do shock freeze but it would not be required from our specification.

Finally, the 72-hour material is processed in the same way as the 24-hour because it's the same blood

bank supplying this for the sole production of immunoglobulins and albumin. The parameters for freezing and spinning would not be that critical as if you want to recover the labile factors, but it's simply the practice, so we have for simplification the same specification for this type of material. Again, expiry date, two years, and this works well for our turnover.

Now, according to what we saw when we developed our products, when we started defining what starting materials we need to use for what product, we found that the most valid in criteria in obtaining good plasma quality is really the time between collection of blood and plasma separation, and according to this we set our preferred specification at fresh frozen plasma 8-hour and source plasma to use for labile products. If prepared correctly, 24-hour material is still a good starting material for Factor VIII.

The method of plasma separation is also of relevance because if you can prevent cell contamination in the plasma and hemolysis, it will also give you a better starting material for fractionation. The behavior during fractionation is different, and you have less problems with filters and so on. So this is more of, not so much the final product quality that is affected but the behavior during fractionation.

And finally, the method of freezing we find very relevant for recovered plasma. There you really see a difference if you freeze it slowly or to shock freeze it, but for source plasma, we find that the normal minus 30 environment, as we use it here, for example, in plasma centers in the U.S., is sufficient to give you very good yield and very good material for fractionation. We see no difference there to shock frozen source plasma that is produced, for instance, in Germany, and that we purchase as well. So in our experience, minus 30 at least will do it in a normal environment.

So as a conclusion, Octapharma based to plasma specifications in general on the current pharm euro regulations as we are an international company and we are selling in many countries, the same as ZLB does. So we have to comply with the regulations that most countries ask for. That's also why I did not specifically mention the CFR regulations here. Of course they are fulfilled when we purchase plasma from the U.S.

For the SD plasma we have to apply some stricter requirements according to our experience with the material and the final product requirements. That's why we have the shock freezing implemented. And for storage and transport of plasma, we find the minus 20 a very practicable and also easy to maintain temperature, and we

would not suggest to change these requirements for the time being.

So that would be the information I had for you today, and I thank you for your attention.

[Applause.]

DR. HOLNESS: Questions?

DR. WEINSTEIN: Mark Weinstein from Office of Blood. You had mentioned a little bit about your experience in developing products, and say in the solvent detergent arena here, you found, I gather, that freezing was important. Why did you think that was important for that particular product? What happened when it wasn't prepared in this particular way?

MS. GLANTSCHNIG: As you know, when we develop products our R&D Department is doing small scale trials before they really set up a production process, and by using different starting materials it was found that the level of coagulation factors that remain in the product after our SD treatment, with the pool size we use, is really depending on the type of starting material. So the FFP, frozen within 8 hours and shock frozen, gave us the best and most stable level of Factor V and Factor VIII in a final product. And in order to meet our specification, we had to go to that starting material.

DR. WEINSTEIN: Did you look at these proteins before you applied the solvent detergent manufacturing

and activation procedure? In other words, was there an effect--you know, one of the questions that we have before us is of course the integrity of proteins that we are looking at, and the potential that as you wait for a longer period of time, before freezing or perhaps the effect of freezing itself, can cause alterations, unanticipated alterations in protein integrity, which may be reflected in yield. So that's the sort of framework that I'm asking this question.

MS. GLANTSCHNIG: To my knowledge we had not looked simply at plasma or different plasma types before we did the small-scale development trials, but we saw that with different starting materials we achieved different results, so we only can go from the final product and say by using this material it was fine, it worked in all of the cases very well, and by using, let's say, 24-hour material, it did not work that well, or we had more variances in the final product coagulation levels. But SD plasma is really special because there is no fractionation involved, no concentration. It's just you go through just some viral inactivation then, and therefore we think here it's really critical to have a very good starting material as you cannot correct things or concentrate the factors you need afterwards.

DR. HOLNESS: Our next presenter is Jonathan Knowles, Senior Director, Regulatory Affairs and Quality Assurance, ZLB Plasma Services in Boca Raton, Florida.

DR. KNOWLES: Good afternoon, and I hope after this weekend we'll still be based in Boca Raton, Florida, for those of you who haven't seen Hurricane Frances.

I have just a few slides to show you to talk about the plasma used by ZLB Behring and the specifications that we have, and I'll draw a few summary comments.

We use source plasma and recovered plasma. Unlike Octapharma, we're using the recovered solely for further manufacturing, so for Factor VIII and von Willebrand's Factor and for IVIG and albumin, we're using source plasma, and that's source plasma collected in this country for FDA licensed products. And the recovered plasma, frozen within 24 hours, is used both for Factor VIII, von Willebrand's IVIG and albumin. And the recovered 5-day material is used only for IVIG and albumin.

And the specifications, the source plasma from apheresis, and I have two temperatures there. For product that is destined for EU markets it's frozen at minus 30, typically placed in the freezer within 30 minutes of collection. And for centers that do not have

to supply product to Europe, minus 20, the CFR standard, is used.

For the recovered plasma, 24-hour plasma, we require that as part of our short supply agreement to be frozen at minus 18 C and stored at that same temperature. Shipping is only required technically to be minus 5 C, but in practice, all the shippers will use minus 20 C, so that's what I put up there. Three year expiration for the recovered plasma in Europe that we use, and I put this in just to make that point. The specification for European recovered less than three days to the freezer, and freezing at minus 5 C, and again, that product shipped at minus 20 and expiration is three years.

In summary--and these points have been made before--the ZLB source plasma specs are based on CFR and EP requirements. Our recovered plasma specs are part of the short supply agreement that ZLB has with blood centers. And as Daniel pointed out, they're very detailed specifications based on our quality and delivery agreements with those centers. We've determined that both recovered and source are suitable raw materials for fractionation, and the conditions in which we currently freeze and store have shown to be adequate for the products that we are currently producing. And to make a point that hasn't really been made before, that ZLB Behring is one of the larger users of flash freezing, had

been through Aventis, and we've determined that that process does not necessarily add to the quality or safety of the product, and we do not see that as a necessary requirement for source plasma, and in the future we'll probably not use that process.

That's it. Any questions?

[Applause.]

DR. WEINSTEIN: Just another question about the definition of flash freezing. I know we've heard that freezing it to a core temperature, I guess, of minus 30 degrees within an hour, I guess is one of the specifications. Again, what is the definition of flash freezing?

DR. KNOWLES: I think there are a lot of definitions and a lot of different names for that same process: blast freezing, flash freezing, snap freezing, I've heard quite a few. I'm certainly not an expert to decide that, but in this context, it's placing the plasma in a--I believe it's minus 55 environment for 90 minutes.

DR. WEINSTEIN: But there isn't this core freezing business, in other words, ensuring that the--

DR. KNOWLES: That's the intent, but it's not defined.

DR. EPSTEIN: Dr. Knowles, my question is probably as much for Dr. Glantschnig as for you, but I'm interested in your comment that flash freezing does not

add to quality and safety, whereas I think by implication Dr. Glantschnig said the same thing, although she further said that it didn't affect, as it were, the levels yielded in the source plasma. I would just like to focus on that, because if I understood Dr. Farrugia's data correctly, rapid freezing should produce better yield, and it shouldn't matter whether you're starting with recovered plasma or source plasma. Putting aside the question of whether you need higher yield and putting aside entirely the question of whether it's a regulatory issue, I'm just concerned over a disparate scientific finding. So I wondered if you could comment specifically on what experiment you're talking about when you claim that there was no benefit with rapid freezing for source plasma.

DR. KNOWLES: Was that directed to Barbara?

DR. EPSTEIN: It really is, yes, but I guess the question for you is whether your statement is based on the same kind of observation, or are you simply saying--

DR. KNOWLES: It's based on empirical data at fractionation plant, that adequate supplies--adequate yield can be obtained without flash freezing, and partly that's due to improvements in yield through the manufacturing process over the years, and that can improve the yield in a significant and sustainable way, and be less costly than the up front freezing.

DR. EPSTEIN: Right. You're saying you can achieve your benchmark yields in other ways.

DR. KNOWLES: That's right.

DR. EPSTEIN: But that's a different statement than saying that rapid freezing in itself would not improve yield. So I'm just wondering if we could get that clarified.

MS. GLANTSCHNIG: Okay. So where the data or the experience comes from in our case is that we have been using source plasma as it is produced in the U.S. pheresis centers for I think eight or ten years now in extensive volumes. And this plasma we required freezing at minus 30, but not flash freezing. So it was the big walk-in freezing boxes operated at minus 35, 38, and the plasma was put in throughout the day, and the temperature of minus 30 was maintained during the whole-day operation.

So we take this plasma and we process it in non-mix production, meaning just this plasma, and we produce with our standardized manufacturing method, have different filling sizes for the different products, and obtain a certain yield per liter of plasma.

Now, when we did the same with German source plasma produced in centers that use flash freezing methods, meaning minus 30 core temperature reached within one hour, the time the plasma was put in these freezers

was normally within 30 minutes after collection, and when we compare the fractionation data on the same filling sizes, yield per liter, with this material to that obtained from U.S. centers, we see no significant yield differences. That is what I meant. We did not analyze the plasma itself prior to going through the fractionation process.

DR. FARRUGIA: I think it's important to compare like with like, because they're not, because the source plasma--this was a point made by Dr. Glantschnig here--it's different even in composition. It's got more Factor VIII inside it de novo. See? I think the Octapharma observation actually supports one of the points I made which is that up to a certain level of manufacture, the freezing rate has a strong influence, and in the fractionation data I showed was that when you're looking at the cryo stage and the intermediate purity stage in the old concentrates, sometimes these temperature differences come out quite strongly, and they come out in Octapharma for the SD plasma, where the level of purification is such, or level of manufacture is such that if you like the viciousness of the manufacturing process, it is not wiping out, it is not obviating any benefit to get through the initial being careful with the plasma.

DR. HOLNESS: Our next speaker will be James Sesic, Director of Regulatory Affairs at Grifols in Los Angeles, California.

MR. SESIC: I expect this will be one of your shortest presentations, and probably less controversial.

Grifols Biologicals uses source plasma for nearly all of its production, and currently that's what we're using. I put up on the slide that we use the source plasma salvage that has been defined by the FDA for the occasions when the equipment does break down and we feel that it's still sufficient. And we use it for our whole product mix.

About 10 years ago we started phasing out our recovered plasma program, not because we had any safety or efficacy issues, but because the management at that time felt it was easier to ensure compliance by having our own centers and our own laboratory testing. So currently everything is source plasma, and our experience with recovered plasma is quite dated.

The specifications that we've used for the source plasma is, as you would expect, minus 20 degrees. I did let you know that we also use the minus 30 because we are marketing in Europe, but that minus 20 is our standard, and minus 30 is what we try to make sure we have enough of so we can meet our European goals. We start everything at minus 20, and while I listed as a

minus 5 as a shipping temperature, I think you heard before that most of the carriers are now shipping at minus 20, so that's in practice what's going on out there.

We haven't done any changes to the expiration date other than what's in the CFRs, and when we did do the recovered plasma we didn't specify freezing times. We asked them to keep it at minus 18, and unfortunately we didn't have an expiration date those years ago for that plasma.

That's pretty much it.

DR. HOLNESS: Questions?

DR. WEINSTEIN: Do you find that there's a problem with inventory management? In other words you have, you know, here's a pool here at minus 20, here's a pool at minus 30. But maybe this isn't really a very difficult or costly concern, but is that a problem or isn't it, or would you like to eliminate that problem, I guess, is one of the questions?

MR. SESIC: Virtually we have eliminated it by trying to go to the minus 30 standard. It's much easier for a fractionater such as ourselves, who makes one set of product lines and sells it throughout the world, to keep a single standard. You're right, it's much easier for us to go to a single standard than to have two standards, because not only do you have to keep track of

the different pools, but also the different fractions that we make product into, and after a while that can become complicated and it takes extra resources.

DR. HOLNESS: Our next speaker will be Roger Brinser. He's a Senior Director of Regulatory Affairs at BioLife Plasma Services in Deerfield, Illinois.

MR. BRINSER: Can everybody hear me? I've been sitting in the back and I've been having trouble hearing, so I promised myself I'd talk very loud here.

As Les mentioned, I am the Senior Director of Regulatory Affairs for BioLife Plasma Services, and we are the source plasma collection branch of Baxter Health Care Corporation, and it's our intended purpose to collect source plasma for further manufacture by our Baxter BioScience Division for their product line. We also supply source plasma to other third-party manufacturers. And it's the intent of this talk to discuss the issues mentioned at the Federal Register notice specific to source plasma, and the discussion won't be on any of our contract manufacturing that Baxter performs.

As an overview for source plasma, just trying to address the issues mentioned in the Federal Register notice, time held before freezing, freezing temperature, plasma storage temperature and shipping temperature.

Talking about time held before freezing, what we had to do from a BioLife perspective is we look at the two standards that we have to comply with, the U.S. CFR requirements, which talks about storage immediately after filling, and we've seen this slide numerous times. The area of course that I wanted to highlight was the statement "immediately after filling." The European pharmacopeia requirement talks about freezing as soon as possible, so from a BioLife perspective what we try to do is interpret what's the best way to meet those requirements. Initially in our initial SOPs and formatted instructions to the donor centers, we tried to use the terminology "as soon as possible," or "immediately after filling," and from a quality perspective we continued to be cited. So we ended up putting a timeframe in there of 30 minutes, and then we started getting cited for the fact that we couldn't freeze plasma within 30 minutes.

So ultimately our current standard is to place plasma units in freezer within 30 minutes of receipt of processing, and we also put a caveat in there that says it's used as a guide because we really don't see any effect if we put the plasma in the freezer within 31 minutes versus 30 minutes, and we still feel we're trying to meet the intent of the requirements.

For freezing temperature the CFR and EP requirements are consistent with the previous slide, and what we do from a BioLife requirement as source plasma for further manufacturing of U.S. products, we meet the CFR requirements, and are placed in a freezer operating at minus or colder. If the source material is for further manufacture of European non-labile proteins, then we meet the EP requirements, and are placed in a freezer operating at minus 20 or colder. And if it's for labile proteins, we place it in a freezer operating at minus 30 or colder. We manage that process by each collection facility has certain standards that they have to meet, and we manage our inventory based on the freezing and storage abilities of those facilities.

For the plasma storage temperature, the CFR requirement talks about storing immediately after filling at a temperature not warmer than minus 20. The pharmacopeia--here's where they're consistent--store in transport at or below minus 20, and for BioLife, we do store all product at minus 20 or colder.

For shipping temperatures the CFR talks about exposures warmer than 5 degrees Centigrade, maintain shipping temperature colder than 5 degrees Centigrade. The pharmacopeia talks about transporting at minus 20 or below, the same consistency for storage and transport, and from BioLife, we do transport at or below minus 20.

That is somewhat of an industry standard right now because the transport services provide that to us, but the acceptance of the source material is based on the U.S. or the EP requirements.

Just a few other points to consider that I wanted to bring up during this conversation, and I think a couple may have already been mentioned before, and particularly some reference to some of the ambiguity of the languages. The current CFR definition of "inadvertent exposure," currently is "an unforeseen occurrence in spite of compliance with good manufacturing practices," and from our perspective that's not quite clear. At one time we thought we had a clear definition of that, but unfortunately the current thinking had changed, so from an industry perspective we're at somewhat of a loss as to what exactly inadvertent exposure is.

And in reference to the European Pharmacopeia requirements--oops, sorry. Also the current CFR allows for one episode warmer than minus 20 for up to 72 hours, but does not allow for multiple episodes of shorter duration. So we have situations where the freezer might reach minus 19 for 15 minutes, a day later it reaches minus 19 for 15 minutes. Based on the CFR requirements that would be classified as source plasma salvage,

whereas if the freezer met a temperature of minus 6 for 72 hours, it's still good as normal source.

I don't want to leave the monograph out. The European Pharmacopeia monograph doesn't allow any definitions for source plasma salvage, and that's probably one of the most significant issues we have, particularly from a transportation standpoint because it is quite difficult from a U.S. perspective to transfer source plasma overseas and continue to maintain that storage requirement in transit.

So in conclusion, Baxter BioScience and BioLife specifications are based on the CFR and European Pharmacopeia requirements or regulations--regulations, requirements, excuse me. Freezing and storage conditions of minus 20 or colder appear suitable for source plasma. There appears to be no safety or quality-related issues for finished products.

That's it.

[Applause.]

DR. HOLNESS: Any questions?

Our last speaker for current practices will be MaryAnn Lamb, Senior Director of Regulatory Affairs at Bayer Health Care.

DR. LAMB: First, I'd like to thank the organizers of the meeting for the opportunity to present

this afternoon. What I will do is briefly review the current practices at Bayer.

At Bayer, we manufacture our portfolio of plasma-derived products from source plasma. We do not currently fractionate from recovered plasma. However, we do produce our alpha-1 proteinase inhibitor product from intermediates that we purchase from other manufacturers that we obtain through contracts and quality agreements. We manufacture that from intermediates prepared either from source plasma or from recovered plasma.

The specifications that we have for the source plasma: We freeze, store, and ship at minus 20 degrees C. or colder. Our current expiration period for the plasma, for the source plasma, is three years. This is based predominantly on logistics, inventory control, and related to testing requirements for source plasma, not driven by the product quality, protein quality of the product.

With regard to the plasma that is used to produce the IV-1 paste, the intermediate that we purchase, if it is produced from source plasma, we have the same specifications that we do for the source plasma that we fractionate. If it's produced from recovered plasma, it is frozen and stored at minus 18 degrees or colder and shipped at minus 20 or colder. And as far as

an expiration period, that is as specified by the fractionator.

The basis upon which we've established these specifications are primarily driven by the current regulatory requirements, in the U.S. the CFR requirements, which I think have been reviewed extensively in the other presentations today. For products that are manufactured for the European market, we adhere to the EP Monograph or Human Plasma for Fractionation for non-labile proteins, for the recovery of non-labile proteins. We do not currently license and market coagulation products in Europe, so we do not have a requirement to freeze at minus 30.

And as I mentioned, we do purchase paste from other manufacturers, and this can be from either source or from recovered plasma. And we have specifications for final product quality. The same specifications apply whether the material is fractionated at Bayer or whether it's from intermediates from source or recovered plasma. And so there is no difference in product quality or stability.

We do have an ongoing stability study. To date, we have data for three years. The principal stability indicating parameters that we have monitored are Factor VIII potency and antibody to hepatitis B. We collected source plasma from a number of random donors. This was

thawed, pooled, and transferred to plasma collection bottles that we currently receive plasma in. The plasma at the appropriate time points was removed, thawed at 5 degrees C. for 19 hours prior to testing. And our evaluation of the pooled data trend for the parameters monitored indicate that there is no significant change at storage at minus 20 or colder for Factor VIII potency or for the hepatitis B antibody. And I'd like to add that the set point for the study is minus 25 C.

I think in conclusion, we at Bayer feel that the existing U.S. regulations regarding the freezing, storage, and transport of plasma for fractionation that have been in place for decades have served the consumers and the industry well. We feel that the decreased demand for plasma-derived Factor VIII products brings into question the need for investing significant resources into increasing Factor VIII yield through plasma collection activities. And we feel that in the absence of a demonstrated improvement in quality of the derivatives that are manufactured from plasma frozen rapidly after collection, that the manufacturers should be permitted to have the flexibility to improve yield through other avenues, such as process innovation and optimization.

Thank you.

[Applause.]

DR. HOLNESS: Questions for Dr. Lamb?

DR. WEINSTEIN: One of our concerns, theoretical concerns, I guess, has been the notion that perhaps plasma that is held maybe for 120 hours might have a different profile of degradation, products aggregation, different elements compared to something that might have been held for a shorter period of time. And there is a potential then in the manufacturing process that you could be isolating purifying fragments or other impurities that were not recognized or not thought of to be in the product using a different kind of--or plasma collected at a different time.

And there is also the issue that we occasionally are asked from a company asking can we use this paste from another--manufactured by another company here, and the requirements that we have may only specify, say, freezing to minus 18 degrees, or whatever. But, in fact, there is a question here of whether the manufacturing process is robust enough to eliminate these fragments, or has there been testing to determine whether this product made out of recovered plasma collected under, you know, differing conditions might, in fact, affect the final product, but in rather subtle ways.

We have also heard, of course, that we don't have strong indications from clinical experience, that we see a safety element here, but I'd just like your

comments on this notion of potential variation dependent--and unexamined consequences of what might occur.

DR. LAMB: I think that we, as part of our process development, do characterize the intermediate material in the manufacturing process. We have in-process controls and specifications, and we also do some additional what we call non-routine characterization to address some of those very issues that we raise.

We do feel that our processes are robust, and we validate the processes to be able to use, you know, other source materials such as intermediate fractions. And I agree with you that those types of things should be addressed, and we do attempt to address those as part of our process and product development work.

DR. GOLDSMITH: My name is Jonathan Goldsmith from the Immune Deficiency Foundation. I just want to extend the question that Dr. Weinstein asked. Have any of the manufacturers who have used both recovered plasma or source plasma at different times to manufacture products, such as immunoglobulins, have they gone back and looked at their safety records for those products over time? Have they done some kind of careful analysis such as events that occur with IGG, such as urticaria? Are they related to perhaps some of the source material that was different for some of these different manufactured lots? Some of you may have data where

you've used a certain kind of recovered material or source material to make the same product at the end of the day, and then what's happened with the safety database? That's one other question.

DR. EPSTEIN: Well, I just want to make known that FDA has asked that question of manufacturers that have produced products using the same manufacturing procedures, but with segregated starting materials, either source plasma or recovered plasma, whether that was at different times or concurrently for different customers. And at the same time, FDA is actively interested in the question of exploring our own adverse event databases to see if we can shed any light on this. And I think that, unfortunately, you know, today at the time of this workshop, we're not in a position to report analyzable data. But this is a question that is of central concern to the agency, and it comports with the idea that when we see differences in yield of starting material, that may be unimportant in its own right since we don't see yield as a regulatory issue, but that the deeper question is whether it's a marker for protein integrity, and that the losses may relate to degradation, but they could also relate to denaturation or aggregation, as has been suggested.

So this is one of the big unknowns at the moment, but it's part of what drives conservatism on the part of the regulators.

MS. GLANTSCHNIG: I maybe also would like to answer part of the question of the Immune Deficiency Foundation concerning the immunoglobulin that we manufacture. We do it from both recovered plasma and source plasma. For the U.S. market, it's only recovered plasma because this is the only material we have so far licensed here for this product in the U.S. But for the European market and other markets, we have been using source plasma as well in about--well, at least equal volumes, if not a little bit more source than recovered, but substantial volumes of both starting materials. And the ten-year safety record of the IVIG product that we have does not suggest any difference in safety, adverse events whatsoever, no matter on the starting material, if it's recovered or source. So this is basically the experience we have. I could not say that there is any concern in this regard.

MR. ALBRECHT: I can mainly comment on recovered plasma, IVIG manufactured out of recovered plasma, and I don't know if this helps, but our system is a little bit different. In this case, we analyze every adverse event report, and we always trace this back to the lot, if possible. And so this is a very specific analysis, and

what we see, we don't see any difference between recovered and source, but also from the safety history of our IVIG, there's an excellent track and adverse events are really very low.

So what I want to say, if there would be, let's say, a peak in adverse events, we would see this immediately.

DR. ROCK: Gail Rock, Ottawa. My comment doesn't particularly pertain to the immunoglobulins, but just a little historical note in terms of the comments about protein denaturation.

About 20 years ago, we did studies following the antigen as well as the biological activity of a number of proteins and certainly found, for instance, that while the von Willebrand factor, ristocetin co-factor activity dropped off, the antigen recovery, as most people would measure it today, remained completely constant and consistent for at least 48 hours. And we found that same dissociation as well between the VIII:CAg antibody and the biological activity of Factor VIII. So there definitely is a dissociation and a reorganization of proteins.

DR. HOLNESS: Next we will have a presentation on issues related to frozen storage, and for that we have Jim Viane from ZLB Plasma Services in Boca Raton.

MR. VIANE: Good afternoon, everybody. I'd like to thank the PPTA and the FDA for the workshop and for the invitation.

As mentioned, I am Director of Engineering Services, which is a fancier title for Director of Facilities. I'm responsible to maintain and upgrade the plasma collection centers for the ZLB Plasma Services Group, which currently has about 65 locations across the U.S. As such, I'm responsible for the design and the real-world implementation and the knowledge in fulfilling all the industry regulations that we are challenged to meet.

The topics that I'd like to cover today include the following: the requirements for freezing and storage, factors affecting the freezing, current industry practice, typical equipment needed, cost implications, and the safety concerns involved.

Basically I don't have a lot to add to the these requirements for freezing and storage. I think they've been covered by all the previous people, so I will just skip over this. And this is the CFR requirements. I also have the EU requirements here for everyone's reference, and we'll move on to basically the factors that are affecting the freezing environments for the plasma.

Obviously, first and foremost is the freezer configuration and size. Specifically the volume of the freezer box has a lot to do with the capability of the box.

The next bullet point, the environment. When we design a box, we have to take into consideration its ambient temperature. A box that is going to perform at minus 20 or minus 30 in Tempe, Arizona, has to be designed considerably different from a box that operates in Duluth, Minnesota, as you would expect.

Another obviously important factor is the loan of the product, how much product goes into the freezer, and the time interval in which it does. Then, in addition to that, the center production volume, the higher the production volume, the more infiltration goes into the box, which is caused through the loading and unloading or shipping process and the defrost cycles that are involved in keeping a box in good condition.

Then, finally, the last item affecting freezing is the heat exchange or the time interval in which we're charged to draw down the product to its core temperature.

Moving on from here, this slide, I hope I don't get anyone too confused. I want to talk here briefly about the set point of the box being minus 20 for the current U.S. regulations and minus 30 for the GHA regulations or the EU regulation. The alarm set points

that we have to maintain in our centers typically are at least 8 degrees colder than the set point of the box. And in the next slide, you'll see the reason that we have to design that way.

Obviously, the plasma placed in a freezing chamber immediately after collection, usually within 30 minutes, EP requires placement in minus 30 or colder within 24 hours for recovery of labile proteins. This is obviously the freezing requirements.

The storage is the minus 20 that we've been discussing, and then transport temperatures are industry practiced at minus 20.

This slide, I want to basically point out that in order to maintain a minus 20 degree box as well as to have time to react to an alarm situation where a box is warming up, the engineer has to design the box at a minus 35 environment, and that provides enough of a buffer that if a box hits a minus 28 temperature, the alarm company is notified, and it provides time obviously for the alarm firm to contact us, for us to get to the center, ascertain what the problem is, determine if we need to move product, relocate the product to a secure location, and call and have repairs made. And then obviously the same scenario occurs if we are going to establish a minus 30 freezing box. We would have to have a minus 38 alarm set point and a design set point at minus 45. Really,

the point of this slide is this minus 45 design set point. The current equipment that we use in the industry, that's widely used, is single-stage equipment. Single-stage equipment, the condenser motors come from the factory. The lowest rating is minus 40, what they call saturated suction. And if we're going to use the minus 30 for a freezing temperature, we're going to need a design set point at minus 45, which would then indicate that we would need to go from a single-stage equipment to a two-stage equipment. And two-stage has a saturated suction temperature of minus 60. These things, the two-stage equipment, we just want to point out, is very expensive to own it, to operate it, to maintain it. It's basically akin to moving from a Chevrolet to a Ferrari. And the people needed to work on that equipment, there's a difference in knowledge, and we want to make sure that that's understood.

The next thing I'd like to point out, again, are some of the requirements in the difference between the minus 20 freezer and the minus 30 freezer that we would foresee needing to happen in the industry. If we consider the minus 20 at this stage to be our base model, these boxes exist throughout the industry, and they're typically four-inch urethane boxes. As I stated, they run on a single-stage compressor, six-horsepower compressor. The evaporator size is mentioned here only

in the sense that it's a base or standard to what's needed. And the operating expense is, you know, nominal. It's widely understood and is not a major concern.

And, finally, the system, one of these systems would typically cost in the range of about $30,000 to install and operate.

In comparison to that, if we were to create a freezing temperature set point at minus 30, these boxes would need to be removed, these four-inch boxes, and replaced with five-inch urethane boxes at a minimum. There are people in the industry that have six-inch boxes. We would have to move to the two-stage condenser equipment and in the 15-horsepower range to pull the temperature, maintain that temperature. Evaporator size would probably be bigger to create more turnover in air flow.

Operating expense would be at least one and a half times the base expense, and the system cost would approach $100,000 per freezer. That's been our experience.

This next slide, I'd like to point out again the difference between the proposed minus 30 freezing, storage box, and then what's been discussed here briefly today is flash freezing. As Dr. Knowles mentioned, we have a number of these flash freezers in our centers, and we are familiar with them. And what we're defining to be

a flash freezer is a minus 55 or colder environment. Currently, in our centers we have three of these units per facility. Two are in operation. One is typically a back-up unit. One of them at least has to be set up to run overnight to pull down product at the end of the day. This equipment is obviously two-stage equipment. There is a 15-horsepower compressor in each unit.

The operating expense here, when you have three of these units, is going to be at least three times your base cost. Basically these systems cost on an individual basis about $90,000 a unit to own and to validate, which is equivalent to $270,000 worth of equipment in most of our facilities. And then we'd like to point out that you still need to have storage freezers or freezer boxes set at a minus 20 or minus 30, beyond just the flash freezing equipment. And obviously we have, you know, more costs associated with that.

The other thing we'd like to point out are some safety concerns. This slide was presented previously by the PPTA to the FDA in the October 28 letter to the FDA. Essentially, if we look at the freezer temp, the existing conditions minus 30, set point with approximate wind speeds of 20 miles per hour for the evaporators. You have an equivalent working condition temperature of minus 55 C. in those environments. And this is categorized, the risk category of increasing danger, danger from

freezing of exposed flesh in one minute. So the people that work in these environments must wear personal protective equipment, and it's recommended that in terms of maximum work periods that they work no more than 30 minutes within breaks in between.

Under the proposed rule for freezing, if we had a minus 30 freezing box, we would have to maintain, as I pointed out, probably minus 45. We're doing minus 45 design temperature. With wind speeds being the same, we would be working in an approximate equivalent temperature of minus 71 Centigrade, and this is categorized as a great danger in terms of the risk category. And as such, all non-emergency work should cease. So there are definitely safety considerations that need to be considered in this environment for our people.

With that, in summary, I'd like to say that we believe the current freezing requirements are sufficient for the manufacturer of derivative products. Decreasing the freezer or storage temperature by 10 degrees Centigrade will require significant equipment upgrades, replacing single-stage with two-stage equipment. As stated, they're mechanically much more complex and expensive to operate, own and operate. They require specialized training for maintenance and repair, the mechanics. Again, they're a Ferrari mechanic. Parts are not readily available for two-stage, and we would have to

replace our existing four-inch boxes with five-inch boxes.

There is a significant increase in cost to install, maintain, and operate this ultra-low-temp equipment, and obviously associated with that, increased costs to validate the upgraded equipment. And last, but not least, I'd like to reiterate the increased safety considerations, risks to the personnel.

That's it.

[Applause.]

DR. HOLNESS: Questions?

DR. WEINSTEIN: I'd just like a little clarification about the design versus alarm set point, one of your slides here talking about the minus 20 degrees Centigrade, the alarm is set at minus 28 degrees and design set at minus 35. Does that mean that for minus 20 degree--the current setup here for a minus-20-degree freezer, that most people have their alarms set at minus--the set point is minus 28--is that correct?--and design set at minus 35? Could you give sort of a context of what that actually means?

MR. VIANE: I can't speak for, obviously, the entire industry, but from our standpoint the answer is yes, that we do have some variation in the alarm set point, but we try to give ourselves as much of a buffer as possible to prevent a deviation or an exposure of the

product. So we do try to maintain our freezers. I think probably the lowest we have as a set point is minus 26. So we do try to maintain as close as possible to the minus 28.

DR. WEINSTEIN: So, in fact, it's not all that distant from minus 30? Is that what we're to think? Or that maybe isn't what other folks are--

MR. VIANE: Yes, I can't speak for the industry.

DR. WEINSTEIN: But we'll be interested in knowing, again--one of the issues that we do hope to learn about is what the real practice is rather than--we know that you're following the CFR, and we acknowledge that. But this may not be the forum to get that information precisely. But we have asked companies about that, and we hope to get that further information. That could be helpful.

DR. FARRUGIA: I'm very interested in this point you've just made about occupational health and safety, and I'd just comment that your company in Australia has freezers in the fractionation plant which are set at minus 40. And we have a very rigid and extremely tough occupational health and safety law in Australia. You know, people grumble about it, and I don't know that it is an issue.

So I appreciate the nuances of what you've said in relation to different set points and so on, but I think it's a little bit overdramatic.

DR. KNOWLES: Let me make a point back to your question, Dr. Weinstein. I could tell you were getting ready to go to, well, if you're already at 28, then why not go to 30. I think the point we were trying to make here, the difference between the single- and dual-stage, and also the difference between being at minus 20 or minus 30 is you can't take a minus 18 or minus 20 box and turn that knob down. You can't do it. You need a new set of equipment. It's like tires. You've got tired rated for 150 miles an hour. You're not going to go more than 80, hopefully, you know, on your Ferrari that he was talking about. But the point is the design spec of that freezer, you know, we have that--that mark set in that CFR is very golden to everyone in this room. That minus 20 is an important number. We don't want to miss it. So we're going to set that set point at minus 28. In order to do that, the design of that box has to be for that minus 35. That doesn't mean you can comfortably at minus 30 with that. In fact, it means exactly the opposite. But you don't want to run that close up to the performance tolerate of that equipment. So we've overbuilt that system so that it will comfortably run at 28 given the other variations in the system, as it ages

or as the temperature changes outside. You mentioned the Duluth versus Tempe, different times of year. You have to spec this equipment to hit the average. If we're all in Southern California with a moderate consistent climate, it would be different. But we have to spec these things to really be tougher than they need to be in order just to maintain that minus 20 with that comfortable buffer. So to go to minus 30, then you've got to go to 45.

DR. FARRUGIA: The other point I'd make is, you know, this morning I said that as far as the data shows in terms of at least Factor VIII, minus 20 and minus 40 storage are pretty equivalent. But remember this, that if you're storing--and I've seen this happen. If you're storing at minus 40 and the damn thing breaks down, the chances that then you will move into the temperature and time zone covered by the incursion type provisions are lower than if you are storing at minus 40. You've got a considerably bigger buffer there.

DR. WEINSTEIN: Just a further question about that. To reach the minus 28 degree temperature, core temperature, does that occur within, you know, a relatively short period of time, like an hour, two hours? Or is that measured, is that known? In other words, we may not be reaching a core temperature of minus 30

degrees within 60 minutes, but are we reaching minus 28 within 60 minutes?

DR. KNOWLES: Well, I was addressing the FDA requirements, which are silent on the time issue.

DR. WEINSTEIN: Yes, that's right. But we're trying to see whether there's some--

DR. KNOWLES: I don't know that we know that for sure, what the answer to that is. The goal is to maintain a minus-20 environment. And I did not address the time to get down--I don't think you did either, the time to get down to--and that depends a little bit on the various equipment.

DR. WEINSTEIN: Right, but again, I guess the question is: If we tried to head toward harmonization, if harmonization would help the industry in trying to alleviate some of the problems of organization of, you know, maintaining two different inventories and so forth, is there a possibility of having some reasonable temperature and temperature to--the final core temperature that could be realized and accepted by both parties.

DR. KNOWLES: Yes, I understand your point.

MR. VIANE: I'd like to make one more point as well about Albert's comment with regard to the CSL freezer in Australia. I've been in that freezer, and that's an ammonia-based system. So you are, again,

stepping into a whole different level of equipment, and it's a 24/7 plant with people on-site that are able to maintain and operate that type of equipment. We don't have that luxury in the individual plasma collection centers.

MR. PENROD: Josh Penrod from PPTA. I wanted to help Dr. Farrugia out for his edification and clarification as to how we derived the figures in the temperature table. Those figures were derived from the American Conference of Governmental Industrial Hygienists, which sets threshold limit values and standards. It's a voluntary organization, and they don't set the standards that are force of law under the Occupational Safety and Health Administration. However, frequently the ACGIH does have standards that are emulated by NIOSH, which is a division of CDC, which in turn is then picked up by OSHA. And having consulted for and litigated against OSHA, I can assure you that they take their standards very seriously.

DR. HOLNESS: We will now have a presentation on the impact of change, Roger Brinser from Biolife.

MR. BRINSER: Thanks, Dr. Holness. Jay had mentioned this morning about a straw man, and, well, unfortunately, PPTA had a straw man last night, and I believe I drew the short straw so that is why I'm up here again.

[Laughter.]

MR. BRINSER: I'm here to talk about the impact of change to existing regulations. I think we've already had some discussion here prior to this. I'm just going to try to summarize a little bit here what we've talked about up to this point.

Why change? Obviously, you've heard from industry that the manufacturing methods designed to incorporate current FDA requirements for storage and shipping of source plasma for manufacture. Using existing requirements outlined, the manufacturers feel pretty comfortable with that, and they feel that the products are safe and high quality, and I think, to Mark's point, I think we do--I don't necessarily know if we're asking for help to manage that inventory process because we've all figure out ways to do that up to this point, and I think we're doing it fairly successfully.

And final products, manufacturing, the current storage and shipping requirements are safe and effective. The increased yield of plasma-derived Factor VIII is not a drive for manufacturing at this point from a manufacturing standpoint. And we also are somewhat concerned about whether or not yield is truly a regulatory issue and whether it's an issue that needs to be addressed between the manufacturer and the collector

themselves based on the finished product that they're manufacturing.

We've also heard earlier about different considerations for change. I think Jim gave a good presentation on obviously the cost of new equipment. I know our organization has been going through this ourselves as we add new facilities. It is an extremely costly venture for the newer types of freezers. It is a significant upgrade in terms of cost. Obviously, the operating aspect of it is better in terms of maintaining a higher rate of temperature, but it is a significant cost.

Validation costs for that freezer, that is something that was touched on, too. That is a fairly high cost for us as well.

Maintenance, we tend to--I think we personally have paid for several cigarette boats from different gentlemen who claim to have performed freezing maintenance for us.

Ultimately this translates to the increased cost of the source material, and then ultimately it affects finished product because the source material is the largest component of the finished product.

There are employee safety considerations. I know from our company we have a very active environmental health and safety organization, and they do have some

concerns regarding--as we approach colder and colder freezing temperatures, making sure that we have appropriate attire for personnel to protect them.

Also, any changes, anytime you have a change, obviously introduce new compliance challenges, and that to us from a regulator's standpoint, the person who is responsible for compliance of our organization, that is where I tend to start getting a little skittish because we are starting to--different challenges with compliance, trying to maintain additional temperatures, obviously there's additional opportunities.

The cost of change. PPTA did provide written comments to the proposed rule on labeling and storage, and those included results of an industry survey from last year. And that survey was based on minus 30 degrees storage temperature, and I believe the freezing temperature wasn't necessarily addressed in the proposed rule at that time. And we tried to capture in the survey the need or cost of equipment upgrades, validation costs, SOP and training updates, maintenance costs, compliance, and excursion costs. And our estimate at that time was about $70 million that it would cost industry to perform this type of upgrade or to meet these requirements.

So now we are at the question whether or not storage temperature in the proposed rule is not currently under consideration. We had a little bit of a debate

about that last night, whether it is or isn't. But it appears that there is somewhat of a focus towards harmonization with the European Pharmacopoeia Monograph, and as Mary had mentioned earlier, obviously harmonization is fairly critical to the industry because we do want to reduce barriers and open markets, but we also want to harmonize based on science, and what we've heard earlier, obviously we don't necessarily want to say we'll use this practice because it's the most stringent.

Obviously, some of the things we talked about earlier, too, issues for freezing, definitional issues, what is meant by cooling rapidly. That was a target of conversation as well, whether it's air freezing, flash freezing, blast freezing. This was a new one to me, snap freezing. I've never heard that one before. Or shock freezing. So, you know, part of that is just trying to define which are the same, what is different, and what do we really want when we say we want something cooled rapidly. What should these parameters be that we want to try to focus our attention on?

The estimates that actually PPTA prepared in our comments were based on air temperature freezers. So obviously if there's a different thought process, if we're looking at freezing to minus 55 or colder, obviously there's other added costs that we haven't

really talked about, and Jim already discussed those in terms of what those might be.

In terms of compliance and cost, obviously the current regulations for temperature excursions--these are the U.S. regulations--and salvage provisions do provide needed flexibility. We are appreciative of that because we do have the opportunity, if we have excursions, the FDA works with us to determine whether or not we can release that plasma, source plasma, based on information we have at hand regarding the nature of the freezer, et cetera, in terms of the operating conditions at the time the plasma was stored there.

However, if that flexibility goes away or if we possibly harmonize with the European Pharmacopoeia requirements, potentially the change in freezing temperature would increase costs of plasma production, as I mentioned before. And we do have information from one company that had estimated that that might be as much as $2.73 a unit based on freezing at minus 30.

And the other thing that we're concerned about, obviously, is if there's changes in allowances for temperature excursions. It could actually reduce the volume of plasma for use in manufacture and add compliance challenges. So if we do change the freezing temperature, we may actually increase yield. But if the plasma was collected--or in storage for an interim

freezing period of time, if it was out of compliance, it may not be used for further manufacture. So at that point the diagnostic manufacturers would be very happy because they would be getting plasma very cheap.

Trade-offs. We think the resources spent on changing the freezer and storage conditions would be better utilized in today's economic environment. We talked about this earlier, that we're all getting squeezed. We're all trying to best utilize our dollars that we have available. And obviously we would like to continue to make sure that those are all pushed towards these four issues: obviously, infectious agent clearance research, new product R&D, facility upgrades and build-outs, which is fairly important as well, and the enhanced manufacturing technologies, what do we think that we could actually get more bang for our buck in these types of--if we focus our attention on these issues.

In conclusion, the changing temperatures for freezing and storage would increase costs. That's a given. We're not necessarily certain there's an appreciable added value for the final products. And obviously it would redirect resources that could be used for advancements and improvements in other areas. And, finally, I guess a statement that if it isn't broken, don't fix it.

Any questions?

[Applause.]

DR. HOLNESS: We'll take an afternoon break now. We'll come back at--

DR. EPSTEIN: Les, could I make one comment?

DR. HOLNESS: Oh, I'm sorry. Sorry, Jay.

DR. EPSTEIN: That's all right. Just because the question was raised, FDA's current thinking is that in finalizing the proposed rule on product labeling, that we would not finalize the requirement for lowering the freezing temperature. We see that still as a matter of open discussion. It's partly why we're having the workshop and, you know, reviewing practices, practicality, and the underlying science. So that's just to allay anxiety.

I should mention that other aspects of the proposed rule really were not at all controversial, and we're hopeful that we'll be able to move those forward.

DR. HOLNESS: Thanks, Jay.

Now we can go to coffee. Come back at 20 minutes to 4:00.

[Recess.]

DR. HOLNESS: I hear, "Start talking and they will come."

We now have a presentation on current practices. Our next speaker is Peter Page. Dr. Page is a senior medical officer at the American Red Cross.

DR. PAGE: Thank you very much for the opportunity to speak. As was said, I will just talk about our current practices related particularly to plasma.

The American Red Cross' blood donor recruitment and collection goals are developed with the intent of meeting patients' needs for single-donor blood products--red cells, plasma for transfusion, and platelets. And the whole blood collection goal is essentially driven by our attempt to meet patients' red cell needs.

Our plasmapheresis is very limited and is focused on patients' needs for single unit component transfusion, particularly to help make up for the chronic shortage of Group AB plasma, the universal donor, and also to have plasma in larger bags so that where massive transfusions, exchange transfusions in liver transplant, the hospital has fewer bags to handle at a time.

The number of red cell units needed by patients far exceeds the number needed for single-donor plasma, and I'll show you those numbers in a minute. So plasma for fractionation for us is a byproduct. Utilizing this byproduct for plasma derivatives optimizes the utilization of the voluntarily donated blood resource and helps contain our prices for other blood components, primarily red cells.

An addition bullet to put on this slide for the Red Cross is similar to the Canadian situation. Our recovered plasma, we contract with fractionators to them fractionating the various derivatives and then return those derivatives to us for us to distribute to customers for patient use. So we likewise do not sell our recovered plasma and lose control of it.

What are the options for plasma? The collection method is listed in the first column, and then whether it can be used as a transfusable unit, recovered, or source plasma.

Whole blood, the plasma can be either for transfusion or recovered plasma for frac, but not source by definition.

The plasmapheresis we do is not source plasma. It's infrequent plasmapheresis. The donor does not donate any more often than every 28 days, meets the requirements for whole blood donation, but does not meet the annual physical exam and quarterly protein monitoring of source plasma donors. We do that to meet AB needs and for jumbo units, and it is transfused. We do not--it can't be used--have it intentioned for recovered plasma and fractionation until it's outdated a year later, and we don't follow that option. And we do not use it as source, although that is permissible.

We do a lot of plateletpheresis to help meet the increasing need of patients for platelets, and when we're unable to get two platelet products per single pheresis procedure, which we do about 50 percent of the time, we try and get an extra unit of plasma off the same procedure, and that's called concurrent plasma, and we use that for transfusion.

The bottom column just shows you the number of different product codes that there are for transfusable, recovered, and source plasma, which are listed here. This is the number of different plasma codes for plasma for transfusion. Many of them are divided for pediatric use, which we also provide on the bottom half, but it's basically FFP and 24-hour frozen plasma. There are two codes for source plasma, and there's a number of recovered plasma for various uses as well.

Now, the numbers in this and following tables are rounded, and ignore the plasma that is discarded from all autologous whole blood donations and the plasma that's included with whole blood distributed as whole blood, and does not include cryo and cryo-reduced plasma. So those are some of the reasons that the numbers won't add.

We collect about 6.3 million units of whole blood, and 1.5 million of those end up as being single-unit plasmas for transfusion, 4.1 million for recovered

plasma; and the difference is due to the exclusions I mentioned at the beginning.

We do 60,000 plasmapheresis (infrequent) procedures per year, all for transfusable plasma. And of the 400,000 plateletpheresis procedures we do, generating about 600,000 plateletpheresis products, the ones that don't generate a second product, we try to get concurrent plasma, which we do for about 70,000 units per year.

We collect whole blood every day of the year, including Christmas and all holidays, to meet patients' needs, particularly platelets drives. Of the whole blood we collect, 22 percent of it is collected at a fixed site where we have control of the facility and the furniture stays there every day. We have 277 fixed sites throughout the U.S., the Red Cross does. The other 78 percent of the whole blood is collected at mobile sites. Mostly commonly we drive a truck to a school or a company and offload the furniture and equipment, collect blood, and then take the blood and the equipment back home. On average, we go to 600 different sites every weekday. We go to a smaller number every weekend day. In the year before last, we went to 970 sites on one day. That was our max for the year.

At these mobile sites, or actually at most of our sites, the average time that we're there collecting blood is five hours. Then after we stop taking the last

donor, we have to clean up, collect our equipment, shut down, and drive home. So if you're looking at time to freeze after collection, you've lost five hours in the beginning.

4.3 million of our whole blood collections are available for time-sensitive component manufacture, for example, FFP, cryo, platelet concentrate, which require processing within 8 hours. But this requires us to go to these mobile sites and distance fixed sites with a driver and a truck or a car for an extra pickup before the five-hour drive is completed to get it back in time, adding to our expense. We clearly do that most for our nearby mobiles and fixed sites.

2.2 million of our whole blood unit collected is more than 120 miles away from our lab or where our freezer is. So you've got travel time there at least, plus the time of the mobile, making it impossible for us to separate and freeze all our blood within 8 hours, and actually not all of it within 24 hours, as you'll see.

I say here that--I'll show you later that we have 48 laboratory sites where we have freezers, and our future plans going off a number of years are looking to consolidate into a smaller number of sites, those laboratories, but still freeze as much plasma as we can. But it will make freezing fresh or freezing quickly more expensive and more difficult.

Group AB plasma is what drives our plasma production needs. It's the universal donor type for plasma recipients. It's used routinely in neonates. Only 4 percent of the U.S. general population is Group AB. And AB FFP is chronically in short supply. That's why we focus our plasmapheresis recruitment on Group ABs, and 40 percent of them are Group AB. And this is what drives our plasmapheresis recruitment, not an interest in making more plasma for frac.

I talked about concurrent plasma units in some of our plateletpheresis collections. Here again plasma is a byproduct, not the reason for the intent, and we have filed for that and we freeze it within six hours of collection. I mentioned the reasons we do that before. I had left out that it may take a bit longer for the hospital to thaw it, but this is usually for massive transfusion where they can have that time before they're done.

Now, the time interval to freezing after collection, the first two bullets are for transfusable plasma. More than 1 million of our units get made into FFP, and then there's also first-stage cryo that gets frozen within 8 hours, and we store it at less than minus 18 and a dating period of a year.

Also for transfusion we have frozen plasma 24 hours. We have greater than 400,000 units that are

distributed for transfusion. It's frozen within 24 hours and also stored at minus 18 and has a year dating.

We have done this in order to improve the availability of Group AB plasma, which you'll see shortly it has, and also decreases our costs by not having to have so many mobile component pickup runs, and extra drivers pick up blood before the Bloodmobile is over.

We have just over 4 million units of recovered plasma, and the time interval to freezing after collection is specified in the contracts that we have with the fractionators. For 3.3 million units, it's less than 24 hours, and for 800,000 units--well, we make it within 24 hours for 3.3 million units, which is acceptable for some products, and we can't in 800,000 units which are frozen only 24 hours after. So it would be a shame in my mind to lose availability for patient use of those 800,000 units for plasma derivatives. So the recovered plasma we store at either minus 18 or minus 20 or lower per the contract with the fractionator, and there is no outdate, but the fractionators have specifications operationally.

How quickly do we freeze? We have 135 blast freezers--or whatever other term you want to call them; I don't know the distinction either--at 35 of our 40-some laboratory sites. So we don't have them everywhere. I don't know the percentage of our plasma that is blast

frozen. Two people in our organization, in separate parts of it, off the top of their heads in the last few days guessed maybe 50 percent. As we look to upgrade and consolidate our manufacturing sites, we're looking to increase that percentage over a number of years.

The rationale for us using blast freezers is to meet the time requirements of 6 or 8 or 24 hours after collection, since much of the blood is collected at the beginning of a mobile that runs five or six hours and then could be an hour drive away. So it may arrive at the center on the eve of the deadline to get the freezing done, and we want to get it in the freezer and frozen as quickly as we can.

Of all the collection sites that we have, the fixed sites, we have 142 of them without blast freezers. So the plasma by plasmapheresis, the concurrent plasma, is not available to be frozen immediately there, and we do not have centrifuges for separating whole blood at those collection sites. So all that blood needs to come back to the center prior to it being frozen.

Our estimates, which are recent and crude, are that those freezers would cost at least $35,000 for the freezer itself, require a fair amount of floor space. Because of backup and peak volumes, we'd need more than one or two per site. We'd need, as was pointed out more specifically and elegantly earlier, electrical

infrastructure upgrades, and we have concern but no data about the brittleness of having it much colder.

For our storage, we have 900 freezers, of which 125 are walk-ins, and they are at 48 different sites. We set the alarm set points 5 or 10 degrees colder than the upper limit of permitted storage range, and I was interested to see 8 degrees in an earlier presentation. At most of our sites--not all, but most of our sites where we have freezers, we have staff on-site 24/7, so they're there to immediately react, and we don't need to wait for an alarm company to be notified and then find us, which I think gives us a bit of a head start in dealing with a drifting temperature. And as was pointed out earlier, the concern is door openings when you're entering the freezer to put more in or take more out frequently, and then the defrost cycles on top of that do put us at risk for temperature excursions, which we do experience inasmuch as many of our freezers are quite old at this point.

So to maintain minus 25, we have set the alarm set point at less than minus 30. As was mentioned, we'd have to change all of our 900 freezers from one-stage to two-stage, and details of that were presented better earlier. Our electrical capacity, as was stated by another, would have to increase. We'd have to increase our emergency generator capacity to handle this in case

our regular power went out. And we'd have to develop procedures, training, validation, et cetera.

If the shipping requirements were to be colder, our shipping costs for a number of our units would double inasmuch as we'd put half as many units in the box probably, in each box.

This slide should be titled "Transfusion Plasma," which I'm looking at two different ways. Of the plasma for transfusion, 91.6 percent of it comes from whole blood and 8.4 percent from plasma, either pheresis or concurrent from platelet. From whole blood, we get 5.6 percent of those 91 percent units as AB, which is more than the 4 percent of the general population. When a repeat donor is known to be AB, we make a particular effort to make sure that plasma gets to be an FFP for transfusion, not recovered.

When a first-time donor comes in and we don't know their prior blood type yet, we're not as able to do that promptly but can do it later. So if it happened to come in and get frozen within 8 hours, we'll make every effort to make it an FFP if it's AB.

And for pheresis, because we target our plasmapheresis on ABs, 23 percent of those 8.4 units are AB. So AB needs and shortage are what drive us.

Looking at it a different way, of the plasma we distribute for transfusion, 70 percent is FFP frozen

within 8 hours, and almost 30 percent is frozen within 24 hours. A number of the medical advisory committees and a number of our regions have accepted 24-hour plasma clinically as equivalent to 8-hour FFP. Not all, but many have based upon data of clotting factor assays. This helps our costs a little bit and improves their availability of AB plasma for transfusion. There are different product codes. Some hospitals can only accept one product code for transfusable plasma, so some regions have gone entirely to 24-hour plasma, and some have stayed entirely with FFP. A few regions do a bit of each.

This is a complicated slide that I don't know that I need to dwell on too much. It just points out our efforts in getting AB plasma for transfusion, and we do better from pheresis than we do whole blood. And that points out that we get 24-hour plasma from transfusion from whole blood and plateletpheresis but not from plasmapheresis because we freeze that more promptly. But it's a million and a half units of plasma for transfusion.

Oops, that was supposed to have been deleted.

I think as someone else said, plasma derivatives have proved effectiveness for helping many patients for half a century, and the historic problems that there have been have not been related to plasma freezing or storage

temperature. And with that, I'll end these remarks. If there's any questions, I'll try.

MS. SCOTT: For those 800,000 units of recovered plasma for which freezing occurred greater than 24 hours after collection, do you have an average and a range of freezing times for those?

DR. PAGE: No, I don't, but I think that most of them are over 8 hours and not by too much. I think they don't--the mode is not 23.9 hours. When we needed to freezer within 15 hours when we were making solvent detergent plasma, we didn't have much difficulty in meeting that 15-hour requirement. Getting an exact frequency histogram for that I think would take us a while to do. But my general sense is it's closer to 8 than 24. And clotting factor concentrates are not made from those.

MS. SCOTT: Thanks.

DR. PAGE: Thank you.

[Applause.]

DR. HOLNESS: Moving ahead with current practices, we now have a presentation from Susan Wilkinson. She's the Associate Director and Associate Professor at Hoxworth Medical Center in Cincinnati.

DR. WILKINSON: Thank you very much. Good afternoon, everyone. It's a pleasure to be here. And I

should say that I'm speaking on behalf of the American Association of Blood Banks this afternoon.

I will be addressing the AABB's--not only their plasma standard-setting activities, but also their standard-setting activities in general.

First, I think as many of you know, the American Association of Blood Banks is the professional society for over 8,000 individuals and 1,800 institutional members involved in blood banking, transfusion medicine, and cellular therapies. The AABB membership is responsible for virtually all of the volunteer blood collection and more than 80 percent of all the blood transfused here in the United States.

Founded in 1947, AABB's highest priority has been to maintain and enhance the safety and availability of the nation's blood supply. And I might add that the cornerstone of this priority continues to be the association's standard-setting and its subsequent accreditation activities.

A little bit about standard setting. Again, the AABB published its first edition of standards for Blood Banks and Transfusion Services, also referred to here as the BB/TS standards, in 1958 and began its accreditation program in the same year. And, again, this was to assure that members were in compliance with the standards that had been set.

The BB/TS standards are the ones that would apply and do apply to recovered plasma, although the association is involved in a number of other standard-setting activities as well.

The group that actually formulates the Blood Bank/Transfusion Service standards is referred to as a program unit, and this program unit is comprised of volunteer professionals who are leaders in the fields of blood banking and transfusion medicine.

The AABB standards are scientifically based, clinical practices. They obviously include cGMPs and quality assurance principles, a theme that we've heard here many times today.

The AABB standards are reviewed and updated on a regular basis, and, again, updates are based on changing practices and technologies.

During the standard development, broad input is sought and includes not only AABB members, but it includes input from external agencies and the general public. External representatives to the BB/TS Program Unit include the American Red Cross, the American College of Obstetrics and Gynecology, the Department of Defense, the College of American Pathologists, the Food and Drug Administration, and the State of California, who has adopted the AABB standards as its state law relative to blood banking.

Well, what is a standard? Well, first of all, it's an imperative statement that includes quality and operational requirements. I'll come to this in the next slide, but the AABB standards revolve around a quality system, and this encompasses all the activities that we set standards for. Standards are required goals. They're not methods. And, again, as I said, they're scientifically based and clinically sound. They are to be unambiguous. I'm not sure always our members would agree with us in terms of that statement, but they are intended to be unambiguous requirements that provide the basis for the AABB's accreditation program.

Now, again, the accreditation program's goal is to assure that the AABB institutional members are in compliance with the standards.

Again, standards are minimal requirements that may be, in fact, exceeded in practice.

I mentioned our quality system and how it is centric to the standards that we set. This revolves around what we call ten quality system essentials, and these include organization, resources, equipment, supplier and customer issues, process control, which obviously includes many of the technical requirements, documents and records, deviations and nonconformances, assessments, process improvement, and facilities and safety. And, again, the plasma requirements really

revolve around each of these ten quality system essentials.

Now, the AABB standards have specifically addressed recovered plasma since the 21st edition of its standards, and we're now ready to publish the 23rd edition. I would champion, though, that while recovered plasma has not been specifically mentioned in editions prior to the 21st, those requirements did apply to the collection, manufacture, storage, and shipment of recovered plasma.

Based on the outcomes of this workshop, again, the proposed rule for the revision of labeling and storage requirements for blood and blood components, including source plasma, and other scientifically based, clinically sound practices, additional requirements for recovered plasma can be generated through the association's process. And tomorrow I will review the AABB Task Force on Recovered Plasma proposed requirements for a new product, and this would be, again, a product for further manufacturing that we are called Plasma for Manufacture.

I'd like to end my brief comments with you this afternoon with some comparison of selected plasma requirements, and I want to acknowledge Laura McDonald of BCA America for putting together the following two charts. I'm not going to belabor these charts because

we've really talked about, well, at least the EU chart previously. But I do want to make a comment, and that is that it has two requirements for not-labile products--let me restate that. There is a requirement for products that are not labile in nature and those that are produced from whole blood. And, again, I think as you'll hear from my other colleagues in the voluntary sector, most of the products that are manufactured from recovered plasma are, in fact, those that are not labile.

Again, we have an issue here with apheresis and products from concurrent--the collection of concurrent plasma as we do apheresis. And I think this template that is looking at what the final product is, as opposed to either intent or the method of manufacturing, is far more reasonable than what we currently have in place.

The final slide just captures the various AABB requirements, and I think as has been stated, the current temperatures for freezing and storage are minus 18 degrees or lower. And you'll hear some data later on about what percentage of manufacturers, in fact, are at minus 18 and how those that are less than that actually fall out.

I do want to end my comments with you this afternoon just to re-emphasize what the AABB stated in its October 2003 response to the proposed rule on

revisions to labeling and storage requirements for blood and blood components.

First of all, I want to re-emphasize that we believe that freezing and storage at minus 18 degrees C. for one year for licensed FFP and cryoprecipitate for transfusion should be maintained.

Secondly, we would support, though, additional product storage requirements of minus 20 degrees, that is, for products for further manufacturing, with a corresponding shelf life of 24 to 36 months.

Thank you very much.

[Applause.]

DR. HOLNESS: Questions?

DR. WEINSTEIN: I just wanted to clarify. Did I hear right that you would support this minus 20 degrees versus minus 18 degrees? Maybe elaborate on that a little bit.

DR. WILKINSON: In our written response to the docket based on the proposed rule, we talked about supporting additional products that might be discussed at a temperature of minus 20 degrees if the storage length might be extended to 24 to 36 months.

DR. WEINSTEIN: What do you see--what are the impediments of having everything at minus 20 degrees? You know, this is a little differentiation because there isn't--you know, I would think there could be a problem

here, again, inventory, and shipping and, you know, minus 20 degrees seem to be a nice round number. So what might be the problems?

DR. WILKINSON: Well, I think Mike Fitzpatrick will actually share some of the problems, and I think a lot depends on whether you're looking at a hospital transfusion service or whether you're looking at a blood center. I think there are some differences that I think Mike will be sharing with you along those lines that I do think, you know, make the distinction potentially problematic.

Thank you.

DR. HOLNESS: Our final speaker for this afternoon before the panel discussion will be Mike Fitzpatrick. He's the chief policy officer for America's Blood Centers.

DR. FITZPATRICK: Thank you. Good afternoon, and I want to thank FDA for allowing us to be here. I want to thank all the previous speakers for making my worst nightmare not be true, which is to be the last speaker of the day running well over in time. But we're actually on time, and I intend to keep us that way. I'm going to talk about current practices in freezing and storage as conducted by our member centers and also by hospitals.

ABC is a network of community-based blood centers. We collect about half the blood in the U.S. The other half is collected by the Red Cross and some by some independent centers. We have 76 members in 45 states, and we have the Hema Quebec as a member now. We collect about 7.6 million donations and ship about 1 million liters of plasma for manufacture into therapeutics.

When the proposed rule came out, we responded in October of 2003, stating to FDA that the proposed rule, we felt, would have a negative impact on many members and other blood centers. This was going to be borne despite an absence of known complaints regarding the efficacy of these products, which has been discussed previously today. As a result of our response and questions, we surveyed our members to find out specifically what the current practices were.

We asked them to identify what plasma products they produce and store, to describe the time frames, equipment, and the temperatures at which they freeze and store the products, and for the first time, we asked them to further send out a smaller survey to the hospitals that they served, and we received responses from 168 hospitals that are included that you'll see later.

We asked the hospitals what products they have on hand and their storage temperatures, and then we asked

both facilities if they would need to modify current settings or purchase new freezers if the rule becomes effective and to estimate the cost of those changes. And I wanted to thank Jim Viane for his very well detailed information about set points and engineering and those things that go into freezers that aren't addressed in the survey but all go into the costs that are associated with making changes.

We received responses from 52 centers, about 68 percent of the membership, and that 68 percent is responsible for collecting about 75 percent of the blood, or 5.7 million units. We received specific responses from 168 hospitals. Our members serve about 3,300 facilities. I just want to give you some perspective there.

If we look at blood products manufactured--and this is from our centers--you can see that most of them manufacture fresh frozen plasma. PF is plasma frozen or frozen plasma. That would be the 24-hour product that the Red Cross referred to. Cryo and then recovered plasma. "Other" would be probably autologous plasma, plasma for fibrin glue, that sort of thing. So most of the centers produce primarily recovered plasma and FFP.

When we look at the time placed in freezers after collection, we look at 13 percent at 12 hours or less; 40 percent at 24 hours or less; and then a few at

72 hours; and some N/A, meaning that they provided us other responses outside of those areas.

When we look at their storage practices and we look at the blood centers, I've given you the percentage and the number of respondents in parentheses there: minus 18, about half, 52 percent; minus 25, the other half. The numbers don't add up to 100 percent either across or down because some facilities do both, and they have freezers that can maintain either temperature. And we see that about 40 percent of the centers are using blast freezers at minus 50.

The hospitals--and you'll see two differentiations here, hospitals as reported by blood centers. So we have 35 of our blood centers that reported on what they believed their hospital practices are, and then we have the hospitals replying directly, the 168 hospitals. So you'll see a difference here in the practices. Don't take that as a discrepancy but take that as a fact that those sets of respondents probably don't overlap, that we have received individual hospital responses, 168 hospitals, and when we looked at 35 of our centers serving well over two or three thousand hospitals, responding with what they believe their hospitals do.

So you can see our centers that responded, most of the hospitals had minus-18-degree freezers; a few,

minus 25. In the direct survey we see a difference there, though, which is fairly significant. We see 22 percent at minus 18; 68 percent or 113 of the hospitals have minus 25-capable freezers; and then a few at minus 80; and others reporting, some at minus 60, some at minus 55, different temperatures.

When we asked them about the impact of resetting the alarms--and just to expand a little bit on what Mr. Viane talked about, keep in mind that when you're setting a freezer at minus 20 or minus 25 or minus 18 and everyone sets their alarm lower because you want the alarm to warn you so you can interdict and fix the problem before you get out of control, the temperatures in a freezer cycle up and down. They cycle when you open the door; they cycle when you put warm product in to freezer; they cycle when the compressors go on and off. So besides setting the freezer alarm at minus 25, you're trying to set it at a point where, as the temperature cycles up and down, you don't constantly get alarms.

When the centers responded, 69 percent said that the alarm would be to be reset by the manufacturer. You'd have to call in the technician to have them reset the alarm. Twenty-seven percent said, no, they wouldn't have to. A few weren't sure. When you looked at the hospitals--and these are the direct hospital respondents, those 168 hospitals--69 said that the manufacturer would

have to; 48 percent said no; and 11 percent weren't sure. The cost estimates ranged from $500 to $1,000--now this is per facility, not per freezer--at each center and $200 to $5,000 at each hospital, with the average--oops, I'm sorry. That's a typo there. That should be $500 to--I believe it was about $19,000. But the average for the centers was $16,744 and for the hospitals was about $1,000 per hospital.

When we looked at purchasing new freezers, you can see the respondents were split on their purchase of new freezers: from the blood centers, 40 percent yes, 40 percent no, 20 percent sort of undecided; the hospitals, only 19 percent said yes and 67 percent said no, and that matches--if you remember the storage temperatures, about 68 percent said they were storing at minus 25 already. Cost was $2,000 to $280,000 per facility, depending on how many. The high there is New York Blood Center. And for the hospitals, $3,000 to $30,000, with an average as you can see, not an insurmountable cost but a cost nonetheless.

We asked them about the impact of the reduced shelf life as the proposed rule did discuss a 3-month shelf life for fresh frozen plasma that was stored at minus 18, and a 1-year shelf life if it was stored below minus 25. Of the centers, 86 percent said they would rather replace their refrigeration equipment than reduce

the shelf life to 3 months. That is not exactly an unexpected answer, but it would be an expense. Of the hospitals, 75 percent said no, they wouldn't accept a 3-month shelf life; 13 percent said yes; and 6 percent just skipped the question.

When we look at the summary, we can see that we have centers that are capable of minus 18 to minus 25, and I'll address the minus 20 question mark at the end, if that's okay. Most respondents freeze recovered plasma between minus 20 and minus 24. They would have to have the contractor change the settings. Cost estimates range from a low of $500 to a high of $100,000. And for the hospital, the cost would have to--about 40 percent would have to replace the freezers. So there would be a fair amount of work and cost involved in implementing the new proposed rule.

You can see that 68 percent store FFP in a minus-25-capable freezer already in the 168 hospitals that replied, and keep in mind 168 is a very small subset of 3,300. The cost estimates were an average of $1,000. Sixty-seven percent wouldn't need new freezers, and then the 41 that estimated the costs looked like about $8,800 each.

So from the results of the survey, we proposed that the practice as proposed in the proposed rule is not really the current practice. It's only 40 to 50 percent

of the practices going on at the blood centers. We think there needs to be a clear reason for changing the current practices when you see that there is a difference in what's going on. As discussed earlier, we still are curious to know what's wrong with the efficacy of the current product. And how would the proposed changes improve product safety and efficacy? Which our members felt should be the main goal of such a change.

Before I end, just a couple comments from today. FDA and the other international organizations are faced with a good goal, which is harmonization. If we all store products and treat products the same way when we ship them to the manufacturer, then the manufacturer can treat them in the same way and hopefully have the reliable end product at the end of the manufacturing process. But the goal should ultimately be for the patient and the safety and efficacy of the product that's provided to the patient.

As Dr. Farrugia has said in his talk, the low-yield products and even the intermediate-yield products, there's very little difference between the Factor VIII concentrate in the end products, depending on the source material. And Barbara Glantschnig mentioned the same thing from ZLB. With their products, with different source materials, they don't see a difference in the

Factor VIII levels in the concentrates that they produce from those products.

And as Dr. Farrugia also has said, most of the things discussed are doable, and that's would probably--that's a true statement. Most of these things are doable. The reason for doing them should be apparent and for the benefit of the patient.

I just brought to mind that at the Health and Human Services meeting last week there was a discussion about hepatitis B virus NAT testing, and the question presented to the committee was: Is there a perceived public health benefit from doing hepatitis B virus NAT testing and spending the money to do that? Or is there a more worthwhile use of that money? And the committee responded that vaccination programs would probably be a more worthwhile use than the few window cases of hepatitis B that would be picked up by mini-pool NAT testing. And as we consider things like changing storage temperatures and replacing freezers and going to dual-cascade systems that require a lot more maintenance and are more trouble-prone--and I have a great deal of experience with those from 28 years with the frozen blood program in the military where we store frozen red cells at minus 80 degrees Centigrade--we need to consider the best efforts that we put our resources to. And as was discussed earlier by the PPTA, perhaps we should look at

better research into Factor VIII concentrate and what is the impact of a change in the source material to the end product. Is there an inhibitor formation that is being prevented or formed by different storage temperatures? And as Dr. DiMichele has said, maybe we should maintain the ability to produce plasma Factor VIII in the best way possible for those areas of the world that can't afford recombinant Factor VIII. And our resources should probably be geared to answer that whole question as opposed to the single question of should we change our temperature of storage and freezing. And for the minus 20 question mark, the impact of shifting from minus 18 to minus 20 for most freezers, except for the hospitals that have very small chest freezers, is probably minimal. With the set points that are being used for alarms and temperatures now, minus 20 at most facilities is probably achievable and doable. There would be some hospital sites that don't use large freezers that would probably have more trouble.

Thank you.

[Applause.]

DR. HOLNESS: Questions?

DR. FARRUGIA: I just want to preface my remarks by saying that what I'm about to say is not meant as a criticism or in any sense offensive. But I was very intrigued by your figure that you're extracting 1 million

liters of plasma for fractionation from 7.6 million donations. This is actually very modest.

DR. FITZPATRICK: That's true.

DR. FARRUGIA: And I estimate that you are, in fact, extracting at about two-thirds of the rate of the Australian Red Cross Blood Service, just, you know, one of my few bases for comparison. And this is in a relatively, at the moment, unregulated environment. So to what do you attribute this low efficiency rate? Because I don't think it is the stringency of the regulatory requirements, and I just want to make the point, and maybe we can take this up in the discussion. It seems to me the organization doesn't really have a plasma culture, and it could well be the case that having a bit more seriousness and stringency in the requirements might stimulate a bit more of a plasma culture.

DR. FITZPATRICK: Just to respond to that, I wouldn't use that figure as an efficiency because those are ABC members who have decided to meet the contract requirements that we have negotiated with Octapharma. So we have a specific contract with Octapharma that requires a specific number of liters per year to meet that contract. And we have other members who have a contract through BCA Heme America, which are not accounted for in that figure. So that's--

[Inaudible comment.]

DR. FITZPATRICK: For the million? Sure? Okay. And we have some members that have independent contract with plasma for manufacture. So that's not a total efficiency.

The other response I would have to that is, as far as I know, we have been able to meet the need of any supplier that has come to us and requested plasma. So we are meeting the supply demands that are being placed upon us. If the demand was increased, I think we would be able to meet that demand.

DR. WEINSTEIN: Another question about the very nice cost analysis that you've provided here. I guess one of the issues that has been brought up is this idea of labile products and non-labile products and freezing under different conditions of minus 30 for a quick--well, relatively quick freeze, and then storing at minus 20 versus minus 20 freeze and storage for the non-labile products. How would that--and you have certain, you know, contracts to make products, the labile products and the non-labile products, and a certain proportion of material is segregated for each of those uses, intended or final product uses. What would be the cost impact of having the blood collectors who are making products with the intent of making labile products have a minus-30-degree freezer to freeze their plasma initially and then

to store it at minus 20 versus perhaps the larger market, which would be the minus-20-degree market?

So we are not talking about storage at minus 30, right? We are talking just about this idea of freezing--

DR. FITZGERALD: A rapid freeze method of some sort, whether it's a blast freezer or a walk-in or whatever.

DR. WEINSTEIN: Has that analysis been done, I guess is what--

DR. FITZGERALD: As you can see by the data, there are sites that have blast freezers. Those that don't would have to purchase one at a price of anywhere from $35,000 to $50,000 apiece. And then if that were a requirement, as Dr. Page has said, once you make that commitment, you have to buy a back-up. So you have twice the cost and the maintenance involved with that. So there's a significant cost to that if you're going to freeze at a more rapid rate and then store at the lower--at the higher temperature.

You know, one thing, if we move forward--and as Dr. Epstein has said, it sounds like FDA wants to look at the temperature issue in more depth before the rule comes out. But there's a group of cryobiologists in the Society of Cryobiology that I worked with rather extensively when I did my doctoral dissertation, and those folks have a lot of information on freezing rate

and protein denaturation and stabilization at different temperatures.

If the goal is a product that provides a stable protein versus a fresh frozen plasma product for transfusion, those are two different goals. We meet the requirements of Octapharma and ZLB with specific contracts. Those sites that need to freeze an 8-hour-or-less product at minus 30 have made the commitment to purchase the equipment and meet those specifications in that contract to provide the manufacturer the raw product they need to produce the protein they want to transfuse. So if we're going to regulate all products for a requirement of a single protein to get the best protein possible, I think that is a debate that we need to--as we're doing these two days--discuss. If we're talking about freezing products that can then be converted and used by the manufacturer in the manufacturing process, then I think it's--we need to make sure that we freeze FFP and have it prepared and stored in a way that it meets the requirements of the patient that requires FFP.

When we sell it to the manufacturer, it's our responsibility to tell the manufacturer how it was frozen, how it was stored, so that they put it into the right manufacturing stream for the product they're producing. Those are different questions.

DR. GRIFFIN: Hi, Mike. Gary Griffin from M.D. Anderson Cancer Center. I have a couple comments and then a question.

First of all, it would concern me--and we have about 18 freezers. Unfortunately, we have bragging rights to--we're probably the largest transfusing hospital. We transfused about 180,000 last year. About 10 percent of that was fresh frozen plasma or cryoprecipitate. And so if we had to track products that we move in and out, the difference between minus 18 and minus 20, it would probably be impossible. I don't see how we would be able to do that from a transfusion service perspective. So I would vote to go ahead and make it 20 and make it easy for us.

And the question--and maybe Dr. Page could also comment on this--is: My perception is that as you preposition FFP oftentimes in transfusion services and then you rotate that inventory out, at least that's what I would expect of my suppliers, the blast freezer, we have one, and I think we collect about 30,000 units, and that wouldn't be a major impact on transfusion service. Expiration date would devastate us. Probably more than anything just the workload of continuously moving that inventory over would be a drastic impact on transfusion services.

DR. PAGE: In follow-up to Gary's comment about rotating FFP inventory, during the West Nile experience a couple years ago, we looked at the average age of FFP when transfused and when in our hospitals and when shipped. And we found that most of it had been used by three months. Now, it's nice to have the whole year for sure, but my sense is that many of our hospitals don't have freezer space to store many FFPs, so they keep a minimal inventory and just have a supplement. I don't believe that we take FFP back as the return.

MS. CARR-GREER: If I could clarify, AABB, in comments to the proposed rule, as Susan was saying, we don't see a need to move away from the current requirements of minus 18. Into the document we did see where if a move was felt to be the direction we were going, that based on some literature cited in the proposed rule, and based on what we believe members could do, minus 20 with a payback of the 24 to 36 months was doable and would have some payback to offset making that move. But we were not advocating two different temperatures. That was the main thing, Gary.

DR. HOLNESS: Okay. Next we'll have a panel discussion moderated by Dr. Mark Weinstein. Mark is the Associate Deputy Director of the Office of Blood at CBER. You can come up and take these respective chairs, if you'd like to.

DR. WEINSTEIN: We're going to have a dialogue amongst the panel members, the speakers, and I hope a good participation with the audience. If we can get the questions of major interest, there we go.

We'll discuss the first question here: What conditions of plasma collection, processing, shipping, and storage are necessary to ensure safety and efficacy of plasma derivatives? Should the same standards apply to all plasma independent of the end products? You can just leave it up there.

DR. BIANCO: Celso here. Let me try to say that those conditions that should be part of regulations should be cGMP and donor qualification.

DR. FARRUGIA: Well, you know, I agree. But the distinct impression I'm getting as a result of what I've heard today is that that's not exactly prevalent on the ground, because I've heard a whole raft of conditions and different shapes and sizes. And it seems to me that there's even a level of uncertainty, as I've heard resonate from some of the presentations from the industry, as to what they actually do.

I heard at least one speaker say our people think that, you know, half of our centers are collecting at about this temperature and so on. And this fills me with fear as a regulator because it is a GMP issue. How come they don't know? That's the first point.

The second point is, yes, I agree that it should be GMP and it should be a fairly uniform situation. And I think it is linked to the question of quality because I think there's two aspects to this quality issue. And I think it is true that we have to keep in mind that these are--that this is a raw material destined to be manufactured into final product. But there is a question of quality related to the material itself. And I think it comes back to that issue which I brought up, that you have to have something which is capable of delivering a uniform, consistent product. And I think that this vast range of temperatures proposed is very unlikely to do so.

I find myself mystified about people quibbling whether it should be minus 18 or minus 20, for example, but I do think that in relation to the vacuum of scientific knowledge--and, you know, it's up to the industry to generate the data. And I see that in the past 20 years there has been a lot of relaxation on this. There hasn't been much data generated.

But in relation to the vast vacuum of scientific knowledge, I don't think it's a bad idea to peg things to a protein which is exquisitely sensitive to those things which happen in plasma which would lead to proteolytic degradation, and that is Factor VIII. So apart from the issue of whether Factor VIII is going to be important or not--and I look to Donna DiMichele to make some

additional comments because I think she should be worried about the low status which Factor VIII has been given, particularly by the PPTA. I think there's the question that Factor VIII should be considered as a very good surrogate marker for quality in want of data indicating otherwise.

DR. WEINSTEIN: Maybe Donna would reply, and then, Celso, you can--

DR. DiMICHELE: Yes, thank you, Albert, and I would agree. We've certainly heard several people from industry basically say that the production of plasma-derived Factor VIII is certainly not a priority for the industry anymore, and that is concerning. I mean, based on the data and certainly the concerns of multiple organizations that I presented, and basically the views that I presented this morning.

To take the issue of quality, I mean, there's something I haven't heard today. We've talked a lot about process. We've talked a lot about current practices. One measure of quality was the amount of Factor VIII per mL in products, and there certainly is a standard that's been set. And one of the things I haven't heard--or maybe I did and I didn't get it, but maybe somebody could remind me--from the fractionators is, What is the average amount of Factor VIII per mL in your starting material for concentrate that you're

getting with the current, you know, collection and processing and shipping criteria? And how much does that vary? And at what point does low yield become a cost-ineffective measure and would really de-motivate you from being able to gear up production should, you know, the need materialize based on, you know, us being able to get developing countries to begin to buy this clotting factor?

DR. BIANCO: I want to try to address a few points from each point of view, first the challenge from Albert. I think cGMP means that it's well done, not that it's all the same. And if manufacturers--and I hope that the manufacturers will manifest themselves--have validated procedures using the materials that they get, with the quantities that they get, that at the end produce the products that they claim, I think, that they did the job and the internal things that they do to improve that, that's very good. If there is something that they want us to do, the collectors, to improve that, it's true. But even you showed in your slides that a lot of differences in the starting material did not end up as differences in the end product.

The second thing that I think is very important is the point that you raised, but also Donna raised, is: How does that affect the quality of the final product? Yes, you have a marker, let's say, you have a cannery in

the mind that is Factor VIII, and so--but does it mean that if Factor VIII is dead that the rest of the proteins are dead and that the product is not good anymore?

The second thing is that most of the plasma is not used for the production of Factor VIII. Yes, there is this desire to supply to the Third World, but the Third World doesn't buy it. It's all sitting on the shelves of the manufacturers.

And the last thing is--I don't see Dr. Rock, but she said that it's not degradation. It's a change in shape of the factor.

DR. FARRUGIA: She said it was degradation.

DR. BIANCO: Proteolytic degradation?

DR. FARRUGIA: A form of denaturation.

DR. BIANCO: A form of denaturation. So that doesn't mean that it's a very sensitive protein to denaturation, but there is no reason to think that the other proteins that survive wouldn't be in very good shape. And this will be decided by analyzing those proteins, not by just a surrogate marker.

DR. WEINSTEIN: Mary?

MS. GUSTAFSON: I guess I had wanted to talk before Celso and I would have said many of the things that Celso did, and that is that once again the fractionators validate the processes and feel that they are getting good quality product and that you can't take

one aspect or one variable and look at it in isolation, that it's the totality of the manufacturing process that's important.

DR. DODT: If we would have a solid scientific basis, it would be easy to come to a conclusion here and already today perhaps. But I think that is the problem. And for the non-labile products and for the labile products, a storage of months, 20, is, I feel, an accepted basis for harmonization of storage temperatures. But the questions which were not addressed today is the difference between the minus 30 freezing and the minus 20 freezing. And we have fixed it to minus 30, and our intention was the preservation of proteins which are labile in plasma. And industry today talked about yield. Yield is their measure of integrity or whatever, but they didn't show that byproducts, degradation products, other products from plasma are not changed in the products when they are manufactured from plasma, either frozen at minus 30 or at minus 20. And I'm missing these data, and as soon as such data would be available, there wouldn't be any reason not to change the freezing temperature in the European Monograph, for example. But we asked you and we are still missing the data, and as I told you this morning, we have set the temperature at minus 30 for freezing for the reason of the preservation of the labile components, and it is up to you to give us validation

data which show that you have the same quality of products when you freeze it at minus 20.

DR. FARRUGIA: Look, I really think one of the things we need to perhaps come out with today or in this event or as a result of this process is this question of ambiguity of language. To me, this statement of you freeze at minus 20 or you freeze at minus 30 doesn't make any sense. I don't understand what it means. You can freeze a block of plasma to minus 20 faster than you would if you place it in a minus 30 freezer--if you place it in a minus 20 freezer versus a minus 30 freezer, depending on the capacity of that freezer, how big it is, in other words. Okay? And all I tried to show was that in relation anyway to Factor VIII--and I said the statement is contentious that everything hinges around Factor VIII, but nothing I've seen has convinced me otherwise--that in relation to Factor VIII, the important thing is how fast it's done. And you can't much really more scientific than that, unfortunately. Not the temperature at which it's done but how fast it's done, and I arbitrarily said let's consider minus 30 and the rate at which it reaches minus 30.

Because, you know, to say something is frozen at minus 20 and something is frozen at minus 30 doesn't make any sense in terms of what is actually done on the ground. It doesn't make any sense.

DR. WEINSTEIN: So, Albert, just to clarify that, minus--it's frozen to minus 30 within 90 minutes--

DR. FARRUGIA: The freezing rate--the rate at which it is--

DR. WEINSTEIN: But what is kind of the rate that you would--

DR. FARRUGIA: I arbitrarily took minus 30 because there's a reasonable consensus in the literature that minus 30 is, A, desirable, B, achievable, and the rate of one hour going to that temperature as being something which you can fix. Otherwise, if all you say is freezer at minus 20 and freeze at minus 30, you can achieve that situation in a vast variety of ways, which would all be different. And I showed that graph showing, you know, basically similar temperature--similar media and similar temperature environment in terms of different media and the different ways in which those environments deal with the challenge.

DR. WILKINSON: Albert, can I just ask a quick question? Are you referring to all products for further manufacturing, or when you say minus 30, are you just thinking about those that result in labile products? Or you really don't care, you just take the Factor VIII perspective and that's all said and done?

DR. FARRUGIA: Well, I think one can have a discussion on that, and that's recognized in some

standards like the European Pharmacopoeia Monograph. But I think life would be much simpler if we just had one temperature, one rate of achieving it, and a consensus on how to store it afterwards after it is achieved.

DR. BIANCO: Simpler for whom?

DR. FARRUGIA: Simpler for everybody. I mean, the impression I'm getting from you folks is--and, you know, I have to be careful. I'm a guest here. You know, I'm a foreigner. I'm one of the coalition of the willing, mind you, so you need to take care of me. And we've just signed a free trade agreement between the countries, so, you know, we're your friends here. But it seems to me that you have an enormous heterogeneity in the industry, and you have to understand that we regulators do not like heterogeneity. We gravitate to uniformity. And you have to be a bit sympathetic to that stance, and I think that it is not a desirable situation to have this, what I perceive to be a very complex industry framework in terms of this issue. I think the sooner you start approaching a more uniform situation, the better for all concerned.

Thank God I don't have to regulate you.

[Laughter.]

DR. WEINSTEIN: Tom?

DR. WALKER: Picking up on that, however, being an organization that is doing a rapid freeze for at least

some of our products, but then storing at minus 20, questions: Why would you take the temperature down below your intended storage temperature? Why would you apply it to a product that you can't--when you can't get the plasma back within 24 hours in order to freeze it? Why would you apply a rapid freeze to cryosupernatant plasma?

The amount of plasma you're going to freeze determines the capacity you need. The capacity you need determines your cost. And here we have an issue which is cost versus the benefit of making more Factor VIII available. So it's a balancing act that we're trying to pull off here.

DR. WEINSTEIN: Do we have comments from the audience?

MS. GLANTSCHNIG: I still would like to answer your question on Factor VIII availability. We are a company that does not have yet recombinant Factor VIII, so one of our focuses is still on the plasma-derived Factor VIII. So we are interested in harvesting good quality and good yield of Factor VIII from all of our production pools. And I can say that with the current plasma sources and the supply and the qualities we have with our defined specifications, we get more than sufficient cryo and Factor VIII for the current needs in our markets and also to supply additional markets.

The problem is exactly what was addressed by Dr. Bianco before, that the need to purchase these products or the capacity to purchase them is at this time a little bit of a problem for many countries. And that's why we have a lot of intermediate sitting on the shelf, and it just waits there to get out. So I don't think we have a problem really with availability with the current practices that I described for our products.

DR. DiMICHELE: Do you have the kind of data with respect to--the data that Albert Farrugia actually presented earlier about the fact that in the oldest of concentrates, the starting material didn't seem to make a difference in terms of the final material, but said that, you know, this data was very old and didn't apply to any of the concentrates. Do you have data--or data with respect to the concentrates that you supply that suggest that the same is true? And I guess the question that I'm trying to understand is that when you have low yield--and there's some, you know--I mean, basically your requirements now are freezing less than 24 hours. Some of it is up to 8 hours, some of it 24 hours. The question is: If you're getting a lower yield, how much cost does that add to the manufacturing process? How much does that make you unable to offer clotting factor at a price where it could move maybe in certain markets where it can't move now? And at what percentage of

Factor VIII yield--let's say, you know, instead of getting 0.7, you get 0.4--do you start to worry about the quality of Factor VIII when you've had that much of a loss of protein?

I guess these are all of the questions that, you know, as a treater would still be--and someone who's interested in the global market, would still remain unanswered after all of the industry presentations. I'm wondering if you have any information on that.

MS. GLANTSCHNIG: Yes, okay. Well, the experience we have with an 8-hour flash-frozen, minus 30-frozen FFP 8 hours, and the 24-hour plasma, frozen under the same conditions but not before 24 hours, is that we lose approximately in our production process--again, with the defined suppliers we have--I would say roughly maybe 8 to 10 percent. However, this is compensated for a lower cost of the starting material. So you balance, of course, your plasma economics, and you say for this material, this quality, I get this yield, and this is what we pay for it. And in our opinion or experience, it is so that the 24-hour plasma, the decisive moment for losing this Factor VIII is not the freezing in this case, but it is the time of storage. And for a big part of the whole blood collection that is collected in mobiles, it is a logistical challenge to bring back all the collections within 8 hours and freeze them within 8

hours. So that's why this has been an accepted practice, and it works well if you compensate it by how you--well, what you pay for your raw materials.

DR. WEINSTEIN: A quick question about the temperature, about keeping plasma before its frozen at 22 degrees, or something like that. How do you handle that? What is the current practice? And does it make a difference?

MS. GLANTSCHNIG: It does make a difference. The Factor VIII yields, if you only talk about that, in 24-hour plasma can be maintained at a higher level if you store it at a 22-degree environment before you separate and freezer it versus refrigerate it. We still do allow both practices, and, again, it's a matter of compensation for the raw material. But the 22 environment is better suited to preserve the Factor VIII, in our opinion.

DR. WEINSTEIN: Do you produce any of the products for very rare diseases, you know, like fibrinogen deficiency or Factor XIII deficiency or VII, or whatever? And are your conditions affected--do they affect those products?

MS. GLANTSCHNIG: We do not produce any of these specialty or rare-disease products. Where we see a difference also is in the coagulation factor complex products that we make, which we produce at this time from source plasma only and not from recovered plasma. But I

don't have all the specifics behind this right in my head, and this question has to be addressed to our experts, really. So I basically know about the Factor VIII and immunoglobulin side.

MR. ALBRECHT: Just about these different conditions we heard, you know, that they are concerning you. As I assume all the different freezing, storage, transport conditions you hear, you use them for licensed products. Most of these licensed products are regulated by the toughest regulators, FDA, also TJA(?) for some products. So if I hear this, my message is obviously temperature does not matter. I mean, that's how I read these things, this variety. It does not concern me. For me that's also evidence that it does not really matter.

DR. FARRUGIA: I don't understand you. Anything we regulate anyway is conformance to the requirements of the European Pharmacopoeia, including the Plasma for Fractionation Monograph, and those are well defined and specified and understood by us.

My comments were in relation to what I see as the current regulatory vacuum involving recovered plasma, and the sense I get that the recovered plasma sector in this country, currently unregulated except through this eccentric arrangement of short supply agreements, wishes to be regulated but wishes to retain in that regulatory framework the ability to maintain its current somewhat

heterogeneous situation. And you can't have it both ways with this, Celso, you know, we will protect you, but you have to do what we say.

[Laughter.]

MR. ALBRECHT: I think we don't have a problem about the EU--about the current EU regulations, but I'm a little bit skeptical if you would have lower temperature or this blast freezing requirement. I'm concerned about this.

DR. FARRUGIA: Well, but, again, it comes to definition, because I share the confusion about all this terminology. I don't know what blast freezing means. I do know what freezers we have in our blood service in Australia which managed to achieve the parameter I suggest, which is minus 30 in hour. In fact, I can tell you that from my experience--and I showed this data--it's achievable in half an hour in a special piece of equipment, in fact, in which the actual refrigerant mixture is not very much below that temperature.

So I think it's a question of defining. I'm certainly not of the view that everybody should have minus 55 freezers which cost (?) and so on. I don't think, incidentally, that that is uniformly the case.

MR. ALBRECHT: Still, I mean, when I hear all these things, now I should go home and I should be

worried about releasing products because, obviously, something is wrong.

DR. FARRUGIA: I think you should always be worried about releasing products.

[Laughter.]

DR. FARRUGIA: It's a very responsible thing to do, releasing products.

MR. BULT: I have a fundamental question to Albert. You mentioned the confusion with the different temperatures, and you used as an example the minus 30/minus 20, the impact on yield, and that was for you the clarification why you would like to go to the one-size-fits-all concept. I don't think this is the right approach. Why? Because as we've heard in a clear explanation from Barbara Glantschnig, we're here talking about business models. Yield is not a regulatory issue. Yield is a component of a business model.

Is it the role of the regulator to get involved in business models?

DR. FARRUGIA: Certainly not.

DR. DODT: But as I told you, we heard only about yield, and we didn't get an answer to our question or the question which came up this afternoon by Mark. He asked whether there is a change in the quality of the product and that could mean in the byproducts and the degradation products and so on. And we didn't have an

answer up to now--or we don't have an answer up to now. It's not the business model we are talking about and yields. It's the quality.

DR. WEINSTEIN: Mike?

DR. FITZPATRICK: Mike Fitzpatrick. Just for Dr. Farrugia, it is a heterogeneous industry. And as far as efficiency, if we look at our million liters, that represents four to five million donations depending on how much plasma you harvest from each whole blood unit. So I think the efficiency of both us and the Red Cross is about the same to meet the demand.

What I would not want to see is the regulators impose a--I would love to see harmony. I think there's nothing wrong with trying to get us all to the AABB standards or something we all try to comply with. Changes in standards for good reasons are done, and we should all try and do things in a more refined way and a better way and a more uniform way.

But if you impose a regulation that says reaching minus 30 in 90 minutes, what do you do with the products that are at 92 minutes and 93 minutes and 94 minutes? And are you going to regulate us into a shortage situation by imposing too stringent a regulation?

So if you're going to regulate the time to freezing and rate of freezing, which are from a

cryobiology standpoint extremely important things, whether you're preserving cells or proteins, whatever you're doing in nature, rate of freezing is very important. Defining the rate is important. But making the rate too restrictive in a fairly robust system--and plasma proteins are fairly robust, because what came out to me in your data was the fact that you saw huge impacts on fibrinogen levels, depending on how the source material was treated, very little impact on Factor VIII. That tells me that while it's a labile protein, it's pretty robust.

DR. FARRUGIA: Well, that in our particular environment which I tried to describe, which is what happens when you get temperature fluctuations. It was just one aspect of that.

I think in relation to how tight the requirements are made, that can be discussed, and that discussion, if a consensus is reached, can be reflected in the actual requirements. I don't think there should be much bloodshed or angst generated as to, you know, if something were--I mean, limits need to be established, rules need to be set down, and then agreement adhered to. I mean, that's how all of blood banking regulation is established. This is one area where there's a bit of a vacuum, but there are some substantial requirements in relation to, for example, the storage temperatures and

times for platelets and red cells and so on. And we still manage to generate products.

So I just make the point, I think--I do not say that Factor VIII is the be-all and end-all. All I say is that if you want to have an indicator of something which definitely deteriorates under certain conditions, Factor VIII is a good candidate. I still haven't seen any data which indicates--and I agree with this--that other proteins are affected. I do think, though, that there is an argument to be had about the question of a quality product, definition of certain parameters leading to a quality product. And for want of anything else, I would suggest that Factor VIII measurement related to that is a better situation than the current heterogeneous confused environment that I see.

DR. WEINSTEIN: Jay?

DR. EPSTEIN: Thank you. Just a few comments to try to kind of stratify issues. I've stated and other people have stated that yield per se is not a regulatory issue, and I stand by that. But we are concerned about Factor VIII for the reasons that Dr. Farrugia articulated, which is that it may, in fact, be a marker of quality for other things we cannot test or have not tested for. And, you know, we did see some data that storage or at least time prior to freezing can relate to clotting factor activation, that there is evidence of

degradation. There were data presented that the time to freezing did correlate in a systematic way with the rate of failure of the 0.7 IU per mL standard or the 70-percent recovery standard, whichever.

So, you know, we do know that something goes on with the proteins. We're not exactly sure how much it matters, and we have this big uncertainty how much it may relate to certain adverse reactions to the products that do concern us, such as the development of inhibitors and allergic reactions, to cite the two most prominent concerns.

So I think that the first point is that the conditions of freezing as they may relate to preserving Factor VIII is a surrogate for a quality factor.

Now, a parenthetical comment. Why minus 30? It's never made a lot of sense to me why you should freeze to minus 30 if you store at minus 20. I think that's a little bit why we were thinking about storage at minus 30. But I think that perhaps another explanation had to do with sort of loose thinking that if you simply put it in a colder freezer, it will freezer faster, and that is true. In other words, the rate of, you know, heat loss does depend on the temperature difference of the two objects.

So, you know, I think that what really went on there was that it was a surrogate for a more accurate

scientific metric, which is rate of freezing, but that doesn't mean that it played no role. In other words, putting it into colder freezers did ensure faster freezing. It's just that we didn't quantitate by how much because the correct parameter was not specified, you know, nor were the systems evaluated.

Now, I want to just shift gears for a moment and talk about storage temperature and dating period. Of course, it has been said before we have no dating period for recovered plasma. One of the issues that concerns the FDA is that if we bring it under a regulatory framework where there are standards in the CFR, should it not have a dating period? What should that be? Shouldn't that be science-based?

Well, I think that what we encounter is that we don't have a good database on the storage temperature in relation to the dating. What we've heard said, on the one hand, is, well, it doesn't matter because mostly we don't keep the products that long. You know, they're in a pipeline and, you know, it's a shorter time, that people have generally been happy with being able to store out to two to three years. In some settings, you know, it facilitates inventory management and, you know, the West Nile example. Of course, we don't have that right now. We have one-year dating.

But the point that I would like to make is that there was thinking, perhaps incorrect, about the eutectic point, and that is the thinking that drove all the concern, because the idea was that you didn't want excursions above the eutectic point because the theory was that you then have crystals slicing up proteins and it makes proteins bad. And so all of the debate about how cold to keep it and how long to date it had to do with the risk of excursions.

I think that, on the one hand, we've heard data that, well, there is no eutectic point, it's really a continuum, stop worrying about this magic minus 23. And, on the other hand, we've heard some data that minus 20 is adequate for long-term storage, at least in the Bayer experiments they got out, if memory serves me, to 3 years. But I doubt that anybody has ever done the 10-year study, or at least if someone has done it, we haven't heard about it. And I see that as problematic because the current dating period for source plasma is 10 years. And are we prepared to give 10-year dating to recovered plasma? And do we think the 10-year data is sound even for source plasma? And, again, that's part of the thinking. And if you look at some of the practices, you might have noted that there are centers that specify minus 65 for extended storage.

So I think that the storage question has two dimensions. It has to do with whether there's an ideal temperature, and it has to do with what do we really know about the storage period. And maybe we can dispense with the issue of store colder if we just don't store longer.

I have one comment on another domain. Since I see you pausing to think, I'll give you a chance, which is that it's presumed that if we were to require product labeling according to the freezing condition--in other words, time to freezing, temperature of freezing--that, therefore, we would be precluding use of certain products for certain use in fractionation, that's not necessarily the case. In other words, we could still leave it open to the fractionators what plasma they wish to procure. It's just that we would be moving the domain of quality assurance from the short supply agreements, which are not FDA regulated, into a set of minimum labeling requirements, which we then would regulate.

So, for instance--and this will be discussed more tomorrow--let's just say we were to stratify the label that you have to label frozen in less than 8 hours, frozen in less than 24 hours, and frozen in less than, I'm not sure what to say, 72 or 120. We could then have those products, plus/minus, you know, rate of freezing, on the label. They would then all still be available on the marketplace and the fractionators could decide, as

they now do, which one they want to procure for their needs.

So we're not necessarily saying that by having minimum standards for production linked to labeling and we're precluding further use of the products. We're only saying that that would supplant the current mechanism or complement the current mechanism, which is governed by short supply agreements that are unregulated. So that it would just mean that the suppliers have to make more patent on the product what it is they're supplying. It would not necessarily change the use patterns.

Anyway, so those are my three comments.

DR. WILKINSON: Can I ask a question? One of the things that strikes me in all this is we're obviously focused on recovered plasma and the freezing temperature. We're also focused on an assay for Factor VIII which, at least is my understanding, can be very problematic in terms of doing that assay and, you know, does one number jibe with another.

For the non-labile products that the vast majority of recovered plasma is used to manufacture, are there other markers in terms of quality that we should be looking at other than Factor VIII?

DR. EPSTEIN: Well, I think the technical experts need to answer that question.

DR. FARRUGIA: Well, you can look at things like fibrinopeptide A and the other markers of activation which I and others have alluded to. But in terms of access to these assays, ease and availability in mainstream labs, Factor VIII is infinitely superior. And nowadays we have quite robust assays for Factor VIII, and I happen to think that with the advent of the chromogenic assay--and I think Andrew Chang is somewhere here. He's much more current on these things than I am these days. But I do not share your total pessimism about the ability to do Factor VIII assays in a way that can give us some sensible data.

I do think that the statement in the EP and the Council of Europe Guide needs substantial reassessment, though.

DR. WEINSTEIN: Tom?

DR. WALKER: As I started to say, of the massive list of about four items I'd like to comment on, the question was asked about the Factor VIII in 24-hour plasma. Now, as it happens, we did a validation of 24-hour plasma from PRP method, and we're currently doing a validation of 24-hour plasma from the buffy coat method.

The baseline would be 8-hour FFP, which has a Factor VIII level of about 1 IU per mL, if you measure immediately after production. The 24-hour PRP method plasma, it's around 0.75. The 24-hour buffy coat is

coming in around 0.9. So it isn't all timing, and as Dr. Farrugia pointed out, cooling to 4 degrees rapidly and then holding seems to knock out Factor VIII more than cooling to 22 degrees and holding, and our data are confirming that.

Dr. Farrugia made a comment about the industry apparently wanting it both ways. Well, we have several different situations to deal with. We have plasma that's coming back--that we're going to make from whole blood donations, coming back from clinics 120 or more miles from the lab. There's no way that we will get that back in time to make FFP. The product that we're going to generate is not going to have any Factor VIII. There's no point looking for it. We need another indicator of quality of that plasma, because that plasma is totally good for making IGIV and albumin, which the industry have told us are the drivers of their manufacturing process right now.

If we want to fulfill a contract with a fractionator for plasma that can generate Factor VIII, we're going to have to divert plasma from FFP, which means we're taking the high-potency product out of--we're taking product where Factor VIII is and efficacy parameter, a parameter of efficacy when it's used directly for transfusion, we're taking it away and using

it for fractionation. So where are we going to get the replacement for that product?

So we've got, again, a balancing act, and that's why it appears that the plasma manufacturing industry, if you want to call it that, wants it both ways.

The colder freezer comment, when I said why take it to minus 30, I know that putting it at minus 30 is going to freeze the product much quicker than putting it at minus 20. In fact, we're using freezing our plasma at around minus 40 or minus 50.

If I could just answer the question of what is a blast freezer that keeps coming up, it's a freezer that idles at minus 40 or minus 50 degrees, and then when you loaded it up, you punch a button and it starts to blow air across the product at a very high rate, creating a wind chill, and that means that the product freezes much faster. You not only have a cold temperature, you've got motion to take heat away. But you can still stop that cycle after a certain time, which brings the product down to minus 20. So that's what I was asking. Why take it to minus 30 if you're going to store it at minus 20?

The issue of excursions is possibly one of the biggest sticking points here because if we could use some sort of average temperature indication, like the USP's mean kinetic temperature, we get away from these add 8 degrees for this and add 8 degrees for this. And the

freezer unit needs to have a capacity much closer to the actual limit rather than something far in excess of it. And we heard the colder you want to go, the more it costs. Well, inversely, if you don't have to go as cold, it isn't going to cost as much.

DR. WEINSTEIN: Albert?

DR. FARRUGIA: Yes, I just want to make one comment about this business of freezing to minus 30, then going to minus 20. I think the point I tried to make this morning--and it was actually well recognized and much better articulated by a comment from the floor here. And this is mostly shown from the data of Carlebjork in Sweden. The crucial parameter appears to be the transition time for that phase change around zero degrees, and the quicker you achieve that transition time, the better in terms of, again, the Factor VIII in this plasma--okay?--as recoverable as well in the cryoprecipitate.

Therefore, freezing to minus 30 seems to me to be a good practical compromise in achieving this desired aim. I would suspect that you would perhaps get better results if you freeze to minus 50, if you freeze to minus 60, but I am fully aware that the costs increase astronomically when you do that.

What is the case, though--and this was, I think, appreciated as well in Jay's remarks just now--is that

when you then, so to speak, warm up this plasma from minus 30 to minus 20, the deleterious effects which you would expect if there was a eutectic phase change at minus 23 don't actually happen. It appears to be the case that if you keep it at minus 20 it's okay. And you folks have said it's much cheaper to keep stuff at minus 20, and we agree, I agree.

So given that nothing bad happens when you do put it at minus 20, put it at minus 20. It's as simple as that.

DR. GOLDING: I'm stepping into dangerous territory because I'm in plasma derivatives and look at the product and not so much at the plasma, but by sticking your neck out, you know, like I usually do, I've learned something usually.

When I look at the whole process of the plasma derivatives and the product that we're looking at and we're approving, there are many steps in the way when the product is held up as an intermediate and there are different storage temperatures. And there are also different viral inactivation steps involving heat and all kinds of other processes that can influence the denaturation and the stability of the product. And when we look at it--I don't think we go to each company and say, you know, you should all store this intermediate for this period of time at this temperature. So why are we

asking it about the plasma? If somebody around here can explain that to me better.

But the question that I would ask is that the critical thing is not what the different conditions are, but what you end up with in terms of the product. And what we typically do--and it's very simple-minded, I think--is somebody wants to change the holding temperature for a starting material or for an intermediate, we tell them provide us with the data. And providing the data is not usually so burdensome, and I'm sure the data's out there.

So, in other words, if all these different companies have been using plasma stored at different times and prepared in a different manner, they have stability data on product that was made that way, and they have that data in-house, and they can look at that data and see if there's a difference. If there's no difference, you know, as far as I know, we'll always approve that as being a reasonable process.

Now, in terms of--just to change--shift gears a little bit, in terms of the question what do you look at in terms of the quality of the other products besides Factor VIII--and everybody's talking about Factor VIII. What's critical with Factor VIII is to look at the function of Factor VIII, and the same applies to all the other proteins that we look at. So we don't have such

high-tech methods for looking at these proteins and determining very fine changes in the protein structure. But the most critical test across the board and simple way to look at this is in terms of function. So if you're talking about other proteins, the one that comes to my mind is alpha-1 PI because it is a complex protein, and it does fold in particular ways. But if you look at the function, if you messed up the protein, denatured the protein, you just do a simple functional test. And when it comes to immunoglobulins, you can look at titers against specific--its ability to neutralize viruses and bacteria, and that is the critical test for looking at that, and, therefore, what we ask for in terms of final container testing and stability testing.

So I think, again, that the data is out there, that all these proteins have been manufactured for years and stability data is available under different conditions, including different conditions of plasma freezing and storage and when was the plasma used in its storage cycle. Was it after a few months? Was it after a few years? And what we would like to see, I guess, in this context, the worst case is always the better set of data to look at. If plasma was stored for 5 years or 10 years, if 10 years is the dating period, do we have data of 10 years? And if the only data available is 3 years,

why are we even contemplating 10 years? Because what we are usually deciding is to approve based on the data.

DR. WEINSTEIN: Andrew?

DR. CHANG: Andrew Chang from CBER, FDA. I think Dr. Golding pointed out very critical issues, that whether or not we should ask the company to evaluate studying source material independently or--which we spent, you know, a whole day here to discuss whether or not we should have a generic--sort of a generic approach to handle studying source material.

Now, if we choose to use the generic approach to handle studying source material, then you ask: Can we come up with a set of risk factors that we can monitor for all the product? Or are we only able to identify the risk factors for a specific type of product, then we control that element for that type of product?

So in my view, if we discuss--come up with a generic approach for studying source material, that serves to--lifts the burden to the individual company, so they do not have to evaluate each individual product and look at the specific condition that they used for studying source material for their end product.

MS. SCOTT: I just wanted to add a little bit to what Doug said because I think what Dov said because I think what he was covering really in a sense was efficacy and protein function. But I think that one of the

concerns that I personally don't have answered is: What difference does the storage make when it comes to the presence of proteins that you don't want in your final product?

So, in other words, there's a paper from a couple years ago which showed that levels of activated Favor XI are elevated in some immunoglobulins more than in others. And that's the kind of thing that you wonder if that had to do, looking back, with the amount of time that the plasma was sitting with blood and with platelets. And I think that the data doesn't seem to be out there to tell us whether or not this makes a difference.

Now, when we hear from Octapharma or ZLB Behring that they don't see any differences in terms of product made from source and recovered plasma, what I haven't seen is that data. These are spontaneously reported adverse events in a database. What do we really know about how many times or whether there's a difference between the source and recovered plasma products in those.

I would just say that I personally don't know. There may be no difference. But when it comes to the amount of time that recovered plasma takes to be separated, I do wonder if there might be differences in

quality that would be reflected in the final product after all that manufacturing.

DR. WEINSTEIN: Just a point I think that should be made here, we have to look carefully at the conditions of what is being called recovered and source plasma in the case of Octapharma, that, in fact, the minus-30-degree quick freeze is one of their conditions for both of those products. So it's not quite equivalent to what we are calling the more general recovered plasma conditions.

MS. SCOTT: I agree, and actually all three of our immunoglobulin manufacturers that use recovered plasma appear to have somewhat different ranges and different controls on how that plasma is handled before freezing.

DR. WEINSTEIN: Celso? Maybe this will be the last question.

DR. BIANCO: This is a question for you to take home and think about it for tomorrow. What has changed, prompted this desire to change what we do? Do we have more adverse reactions? Do we have something that the Factor VIII is disappearing in the vials? Do we have any indication that something--what is different between last week or before the proposed reg came out and before that? Why are we looking for change? Why do we have to do something about it?

[Pause.]

DR. BIANCO: I know you have the answer.

[Laughter.]

DR. WEINSTEIN: We'll resume this conversation tomorrow. Thank you--oh, Johannes? We have an answer here.

[Laughter.]

DR. DODT: No, I don't have an answer to that. But I have a comment on expiration dating of plasma, which was not discussed yet. This morning I gave you my point of view that I think the testing of the donations may be the reason that we should restrict the expiration of plasma for manufacture and that test kit generations will change and that the requirement is there to test according to the state-of-the-art methods. And so when you have a 10-year-old plasma, today we have the third-generation test kits. You will probably in 10 years test them with sixth-generation test kits, and that is a requirement at that time to test with the sixth-generation test kit.

And, on the other hand, I think it's another regulatory issue to trace back any donation to the donor and to keep the records, and I don't know how long you are requested to keep the records on the shelf. And that is another aspect considering especially, for example, antithrombin 3 or albumin, which are used as excipients

for some of the plasma proteins, and for this you have also to trace back the donations to the donor and to keep the documentation on the shelf for a certain time. And that restricts itself the shelf life of a product--or the shelf life of the plasma because shelf life of the product may be, when you think about albumin, 5 years' shelf life. It can be used in a plasma product, for example, when it is 2 or 3 years old. Then an additional 2 or 3 years' shelf life of the products that are already 6 years, additional 10 years for the expiration of the plasma for fractionation. That means the donation is 16 years old, more or less, or a donation is in a product which is 16 years old, and that's not what we like to see, I believe.

DR. WEINSTEIN: Just in answer to Celso's question, of course, I'm a little puzzled because, of course, we're looking at trying to create standards or examine recovered plasma issues, and this is, of course, what was presented at the beginning of the meeting. So I'm puzzled--

DR. DODT: That is a question of recovered plasma and source plasma, independent of the source of the plasma.

DR. WEINSTEIN: Okay. We'll resume tomorrow at 8:30.

[Whereupon, at 5:31 p.m., the meeting was adjourned, to reconvene at 8:30 a.m., Wednesday, September 1, 2004.]