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EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

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P R O C E E D I N G S

Agenda Item: Statement of Conflicts of Interest, Announcements

MR. EMERY: Welcome to the 100th meeting of the BPAC Advisory Committee. I'm going to start with the reading of the Conflict of Interest Disclosure Statement.

The Food and Drug Administration is convening the April 28 and 29, 2011 meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all participants of the Committee are special Government employees or regular federal employees from other agencies, and are subject to the federal conflict of interest laws and regulations. The following information on the status of this Advisory Committee's compliance with federal ethics in conflict of interest laws including, but not limited to, 18 USC 208 and 712 of the federal Food, Drug and Cosmetic Act are being provided to participants at this meeting and to the public.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's

need for a particular individual's service outweighs his or her potential conflict of interest.

Under 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary, to afford the Committee their essential expertise. Related to the discussions at this meeting, members and consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for the purposes of 18 USC 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

The Committee will discuss, for topic one, testing of source plasma for hepatitis B, virus infection bionucleic acid testing. This is a particular matter of general applicability. For topic 2, the Committee will discuss current considerations on plasma obtained from whole blood donors for further manufacturing. This is a particular matter of general applicability. For topic 3, the Committee will discuss blood donor written statement of understanding and education materials for whole blood

donors. This is a particular matter of general applicability. In addition, the Committee will hear updates on several topics. The updates are not for discussion by the Committee, and therefore Committee members were not screened for financial interests relating to the updates.

Based on the agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 USC 208(b), (3) or 712 of the Food, Drug and Cosmetic Act.

Dr. Celso Bianco is serving as the Industry Representative acting on behalf of all related industry. Dr. Bianco is employed by America's Blood Centers in Washington, DC. Industry representatives are not special government employees and do not vote. There are regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals are not screened by the FDA for conflicts of interest.

This Conflict of Interest statement will be available for review at the registration table.

We would like to remind members, consultants and participants that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or impeded financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Committee of any financial relationships that you may have with any firms, its products and if known, its direct competitors. Thank you.

And I'm going to turn the time over to Dr. Hollinger.

` **Agenda Item: Opening Remarks**

DR. HOLLINGER: Thank you, Brian.

So this is the hundredth meeting of this group. I understand that Jay Epstein has been here for all 100 of these meetings - almost. Sometimes I feel like I've been here for the 100 meetings.

So we do have a full day and a half. As Brian mentioned, the first, today, we're going to be talking about testing source plasma for Hepatitis B virus bionucleic acid testing, and the second topic is going to discuss current consideration for the use of plasma either as a concurrent plasma or component plasma from whole blood donors for further manufacturing, and then tomorrow, a

discussion on written statement of understanding; that is, consent forms, what should they contain, et cetera, for blood donors.

Before we start today, I think I'll have the Committee go around and introducing yourself and saying where you're from. Celso, Dr. Bianco, let's start with you and let's start with you and come around this way.

DR. BIANCO: Celso Bianco. I'm the Executive Vice President of America's Blood Centers. I'm the Industry Representative.

DR. KUZMA: I'm Jennifer Kuzma, I'm Associate Professor of Science, Technology and Environmental Policy at the Humphrey School of Public Affairs at the University of Minnesota.

DR. ALTER: Harvey Alter, Department of Transfusion Medicine at NIH.

DR. MAGUIRE: James Maguire, Division of Infectious Disease, Brigham and Women's Hospital and Harvard Medical School.

MR. EMERY: My name is Bryan Emery, I'm the designated federal official.

DR. HOLLINGER: F. Blaine Hollinger, Baylor College of Medicine in Houston, Texas.

DR. LINDEN: Jeanne Linden, the Blood and Tissue Resources Program at the New York State Department of Health in Albany.

DR. NELSON: I'm Kenrad Nelson, I'm Professor of Epidemiology at Johns Hopkins.

COLONEL RENTAS: Frank Rentas, Armed Services Blood Program.

DR. TROXEL: Andrea Troxel, from the Department of Biostatistics and Epidemiology at the University of Pennsylvania School of Medicine.

DR. TRUNKEY: Don Trunkey, Oregon Health Sciences University, Department of Surgery.

DR. GILCHER: Ron Gilcher, former Director of the Oklahoma Blood Institute and now working as a consultant in Hematology.

DR. BAKER: Judith Baker, Administrative Director, Federal Hemophilia Treatment Centers, Region 9, based at the University of California, Los Angeles.

DR. HOLLINGER: Yes, thank you. And Ron, I want to thank you. You're one of the new members of this Committee, and we're appreciative of that.

This Committee has a very good group of experts in many disciplines, which is what makes it a good Committee, and also then, there are temporary voting

members who also have expertise in the areas we're going to be discussing.

So with that as a background, let's start the session with the AM Topic One, and the first paper to give us an introduction to the issue about testing a source plasma by nucleic acid testing for HBV, will be Susan Zullo. Susan? By the way, the speakers do know how much time they have, so we'll be keeping to those time periods because there may be questions that need to be asked afterwards. I'm going to try to allow some time after most of the speakers for questions, as well as through the discussion later on.

Topic I: Testing Source Plasma for Hepatitis B Virus by Nucleic Acid Testing

Agenda Item: Introduction

DR. ZULLO: Good morning. I will provide an introduction for the first topic, Testing Source Plasma for the Hepatitis B Virus by Nucleic Acid Testing.

After stating our issues, I will provide background information and potential benefits for product safety and for public health. This will include summary information on some industry studies. Then the companies will speak to you in subsequent talks to provide you with details.

I will also present the questions for the Committee's consideration.

Plasma Protein Therapeutics Association, PPTA, will be presenting information on their voluntary standards and on safety of plasma protein therapies with respect to Hepatitis B virus, directly after my presentation.

In this morning's session, FDA seeks advice from the Committee on whether scientific data supports the concept that testing Source plasma for Hepatitis B virus, HBV DNA, by nucleic acid testing, NAT, increases the margin of safety of plasma derivatives and whether such testing in donors adds to public health.

In April 2009, FDA sought advice from the Committee on issues related to whole blood donor screening for HBV DNA by HBV NAT to prevent transfusion transmission of HBV. The Committee supported routine HBV NAT, and establishment of a minimum sensitivity for individual samples.

HBV is an enveloped DNA virus, with a circular genome of about 3.2 kilobases. Virions are approximately 42 nanometers in diameter and contain a capsid core, seen here in gray, HBC, enclosing the genome and DNA polymerase. The outer envelope, also referred to as the lipoprotein coat in green here, contains host-derived lipids and

embedded surface proteins, HBs, that are involved in viral binding of, and entry into, susceptible cells.

There are three HBV particle types shown in this picture. Virions, also known as Dane particles, are seen here as complex spherical particles. They are the one infectious DNA-containing HBV particle. Excess viral coat, or surface antigen HBsAg, is found in the blood in two distinct forms, either spherical or filamentous.

The most abundant are these small spherical particles seen here. Tubular filamentous particles of various length are also present. Both of these smaller particles are about 22 nanometers in diameter and are completely composed of Hepatitis B surface proteins. They have no core or DNA, making them non-infectious, and not detectable by HBV NAT. HBsAg is produced in vast excess, depending on the phase of the lifecycle of the virus.

The ratio of infectious Dane particles to non-infectious HBsAg filaments and spherical bodies circulating in the blood varies quite a bit with the stage of infection, but DNA detection by HBV NAT is a direct measure of infectious particles.

Hepatitis B virus is transmitted through contact with infected blood or other body fluids. For example, sexual contact, IV drug use or vertical transmission from mother to child during delivery. There were over four

thousand acute symptomatic cases reported in the United States in 2008, resulting in an incidence of 1.3 cases per one hundred thousand. There are an estimated 800,000 individuals with chronic HBV infection in the United States, resulting in three thousand chronic liver disease deaths per year.

This figure depicts the markers during the course of acute HBV infection with recovery. HBV DNA appears two to five weeks after infection, followed by HBsAg six to eight weeks after exposure. HBsAg reaches a peak level during the acute stage of infection, and declines to undetectable levels during recovery. Antibodies to Hepatitis B core antigen, anti-HBC, appear after HBsAg and remain at high levels. During recovery, antibodies to HSsAg, anti-HBs, develop along with anti-HBC.

In chronic infection, you see the same sequence of appearance of markers. HBV DNA, followed by HBsAg and anti-HBC. In this case, DNA persists at a high level, and HBsAg remains detectable in the vast majority of cases. There is no appearance of neutralizing antibodies.

There is a need for added safeguards for source plasma with a high rate of HBV. Source plasma and recovered plasma are both used for further manufacture, or fractionated and plasma-derived products such as albumin,

immunoglobulins, clotting factors and alpha-1 proteinase inhibitor.

During the fractionation process, plasma is pooled, purified and processed to extract plasma proteins. These proteins are used to treat various medical diseases including hemophilia, primary immunodeficiencies and alpha-1 antitrypsin deficiencies, and acute conditions such as burns and shock. Recovered plasma collected from whole blood donors is also distributed for further manufacture, to make plasma derivatives.

As I mentioned earlier, in April 2009 the Committee discussed the scientific basis for testing plasma from whole blood donors using HBV NAT.

In 2008, 18.8 million source plasma units were donated in the United States, and this number continues to rise. Source plasma is collected by plasmapheresis, when a donor’s whole blood is separated into red blood cells and other cellular components that are returned to the donor, and the fluid portion, plasma, is collected.

Donors may donate up to twice a week, with a minimum two-day period in between donations, and are generally compensated. All source plasma for further manufacture must be tested for evidence of infection due to specific communicable disease agents, including HBV. Currently for HBV, source plasma is only tested for HBsAg.

FDA does not currently recommend that source plasma donations be tested for anti-HBC, because exclusion of anti-HBC reactive units would likely diminish titers of HBV neutralizing antibody to HBsAg anti-HBs, which is believed to contribute to the safety of certain plasma products, as both of these antibodies usually occur together.

Whole blood and blood components are screened for anti-HBC. HBV NAT is currently voluntarily performed on most, if not all, source plasma, but is not an FDA requirement. PPTA represents US and European source plasma collectors and manufacturers of plasma-derived therapies, and establishes voluntary standards for source plasma. I will briefly describe three of them before you hear their detailed descriptions from PPTA.

The first is the qualified donor program. Potential donors must satisfactorily pass two separate medical screenings and test negative for HIV, HCV and HBV two times to become a qualified donor. If the person does not return in six months, the status is lost. Plasma from one-time donors cannot be used for further manufacture.

The second is a 60-day inventory hold. This hold, for at least 60 days from the time of collection, allows time for retrieval of units from entering a plasma manufacturing pool prior to manufacture if post-donation information such as admission of high-risk behavior or

becoming reactive for HIV, HCV or HBV become available that would disqualify the donor.

HBV NAT screening is voluntary, but is required by PPTA for their quality standards of excellence, assurance and leadership, or QSEAL certification program for fractionators.

There have been no reports of transmission of HBV to recipients of plasma derivatives since the late 1980s. This is likely a result of the implementation of viral inactivation such as heat inactivation or solvent detergent treatment, and removal steps such as nanofiltration, that are especially effective for enveloped viruses like HBV.

FDA requires at least two orthogonal viral clearance steps to attain an acceptable margin of safety. The manufacturing process for plasma-derived product must be validated for its capacity to clear both enveloped and non-enveloped viruses. The total log reduction for enveloped viruses such as HBV should be at least 10 logs. This process will be discussed in a subsequent presentation.

Although there are clear safety measures in place for source plasma for further manufacture, addition of HBV NAT may provide an added margin of safety to reduce the risk of HBV contaminated collections of source plasma from

entering plasma pools that are manufactured into plasma derivatives.

There are currently three licensed tests for screening of source plasma, using mini-pool sizes of either 16 or 96 donations. Two additional HBV NAT assays are in development that are specifically designed for testing source plasma using larger pools of 512 donations.

Now I'll present information on four potential benefits from testing source plasma using HBV NAT for product safety and for public health.

Depending on the sensitivity of the assays, HBV NAT may interdict potentially infectious source plasma collections containing HBV DNA that are negative for HBsAg. These units would not be detected by serology testing and would enter manufacturing pools. These HBV NAT positive, HBsAg negative units are referred to as yield cases.

This table provides a summary of yield cases. These are HBV NAT positive, HBsAg collections detected in clinical trials. In this column you see the yield cases per total number of donations tested. These are the yield cases for the three licensed assays, and the yield cases claimed for the two assays in development.

The last column is the yield rate, based on these data. As you can see, there are yield rates from 1 in 9 thousand to 1 in 1.7 million. And this reflects a number

of variables, including the sensitivity of the HBV assay used, the sensitivity of the HBsAg assay used, size of the pool and population study, to some extent.

I'll focus later on NAT sensitivities as a key issue. You will hear more information on these yield cases from the companies.

Source plasma donors typically donate twice weekly for several weeks at a time. Therefore, if a donor seroconverts to HBsAg positive after several HBsAg negative donations, the 60-day inventory hold for source plasma collections would prevent some HBsAg negative units that are potentially infectious, that may be HBV NAT positive, from entering manufacturing pools. The benefit of yield case detection by HBV NAT is potentially mitigated by the 60-day hold, but again, the 60-day hold is voluntary and may not be implemented by all collectors.

Another potential benefit of HBV NAT for source plasma is the reduction of the window period and the impact of this on public health. The window period is the period when a donor is infected with HBV, but prior to the appearance of detectable HBsAg. As I mentioned earlier, HBV DNA is the first marker to appear in plasma during HBV infection. HBsAg appears on average of 6 to 8 weeks after exposure and declines to undetectable levels within 4 to 6 months if the infection is resolved.

This figure illustrates the window period during early acute HBV infection, when HBV NAT can detect HBV DNA, while HBsAg is below the detection of serological assays. This same window period applies to the early phase of chronic HBV infection.

The three licensed HBV NAT tests were able to detect HBV DNA from 0 to 40 days earlier than HBsAg, in some cases, using sensitive HBsAg assays. You will hear more information on window period closure by HBV NAT in subsequent talks.

Interdiction of potentially infectious HBV NAT positive, HBsAg negative window period cases may enhance the safety of plasma derivatives by removing units contaminated with HBV from further manufacture and lowering the viral titer of fractionation pools. Donor screening by HBV NAT also permits earlier detection of HBV infection in the donor, resulting in earlier notification, follow-up and medical intervention and prevention of secondary transmission to donor contacts.

An additional potential benefit of testing source plasma by HBV NAT is the improved analytical sensitivity of HBV NAT over HBsAg for detection of HBV. The limit of detection, or LOD, at the assay cutoff, at a 50 percent detection rate for PRISM HBsAg, one of the current more sensitive HBsAg assays, is estimated to be 1,664 copies/ml

compared to 336 copies/ml claimed for an investigational HBV NAT assay. This is for the individual sample in a pool of 512. This is an estimated 5-fold improvement in analytical sensitivity of donor screening for HBV, but again, this is at the 50 percent detection rate.

Based on the increased sensitivity of donor screening, HBV NAT is expected to lower the maximum viral titer in a plasma fractionation pool by an estimated factor of 5, or 0.7 logs.

The final potential benefit of testing source - plasma using HBV that I will present today is detection of collections during the post-antigenemia recovery phase of acute infections. HBsAg declines to undetectable levels within 4 to 6 months in the recovery phase of acute HBV infection. HBsAg may be undetectable, but virus is still present for a brief time, 1 to 2 weeks, making the unit HBV NAT positive. Anti-HBC is present, but as I mentioned earlier, not tested for in source plasma.

This figure illustrates the post-antigenemia period, when HBV DNA is still present, but HBsAg has dropped below the level of detection. Detection of these HBV DNA positive, HBsAg negative collections in the second window period is in addition to detection of the HBV DNA positive, HBsAg negative in the first window period in early infection that I presented earlier.

As you can see, anti-HBC is still present, but source plasma is not tested for this marker. Therefore, HBV NAT is needed to close this second window period, because the anti-HBC testing is not done.

In chronic HBV infection, HBsAg is almost always positive, but HBV NAT may detect HBV DNA in a very small number of asymptomatic, chronically infected individuals with undetectable HBsAg, so-called occult HBV infections.

The impact on public health from detection of these units in the second window period is earlier donor notification allowing for counseling and medical treatment, donor deferral and prevention of secondary transmission of HBV infection to contacts.

The next thing I will talk about is the analytical sensitivity of the HBV NAT assays and a proposed sensitivity standard.

This table summarizes the assay analytical sensitivity and LODs for HBV NAT assays. This is an LOD at 95 percent detection rate in IU/ml. These are the analytical sensitivities for the three licensed assays. These are the analytical sensitivities claimed for the two assays in development. This column shows the maximum pool size and the final column, the LOD for maximum pool size, in IU/ml.

As you can see, for the licensed tests, this ranges from 166 to 423. One HBV NAT assay in development has a similar reported LOD of 460 IU/ml. Based on this data, detection of HBV DNA at a sensitivity of at least 500 IU/ml, this again is at the 95 percent detection rate for the individual donation in a source plasma mini pool, may represent a reasonable and attainable standard for HBV NAT assays with added sensitivity compared to HBsAg.

The three questions for the Committee today are:

1. Do the available scientific data support the concept that testing of source plasma donations by HBV NAT increases the safety margin of plasma derivatives?

2. If so, is a sensitivity of at least 500 IU/ml for the individual source plasma collection suitable for HBV NAT when testing minipools of source plasma?

3. Please comment on whether detection of HBV infection in source plasma donors by HBV NAT adds benefit to public health compared with testing only for HBsAg.

And that’s all I have to say for the introduction. I think I’ve stayed on time, Dr. Hollinger.

DR. HOLLINGER: Thank you, Susan, I think we’ll go on. I was going to ask just one quick question. Could you pull slide 26 up a minute?

Thank you, that’s very quick. Wish I could act that quickly. On the – is that 336 copies or 336 IU/ml?

DR. ZULLO: Copies per ml.

DR. HOLLINGER: It is copies?

DR. ZULLO: Yes.

DR. HOLLINGER: Okay, thank you. So we're going to move on to the next speakers then, and the first one is PPTA's Voluntary Standards and HBV NAT Testing, and Dr. Penrod will be discussing this.

Agenda Item: PPTA's Voluntary Standards/HBV NAT Testing

DR. PENROD: Good morning, everybody; I'm Josh Penrod. Just to start, I will say that I am a salaried employee of the Plasma Protein Therapeutics Association, and part of my duty is to figure out how to advance the slides, so bear with me here if I'm a little bit remedial.

But just who we are, briefly: Susan touched on this earlier, but we are the trade association that represents the manufacturers of source plasma, or collectors of source plasma and manufacturers of the finished therapies. We occupy, our members occupy, about 60 percent or more of the world's needs for source plasma, and provide the majority of the therapies that are made as a result of those collections.

So here are our manufacturer members; these are global members with one regional member, and these are the companies that provide all of the safe and effective

therapies used by critically ill patients around the world today.

And as a part of – PPTA is a rather small organization overall, but we have a fairly complex membership structure, and as a part of that, the side of the shop that I work on, the source side, we have a mix of plasma collectors that are either subsidiaries or business units of the larger global members or regional members, and also independent plasma collectors that are unaffiliated with any of the global members. So that just gives you a taste of the diversity and profile of the industry.

So Susan mentioned this earlier, so I don't want to belabor it. Basically there's a panel of therapies that are provided by the member companies. These are all invariably familiar to members of the Committee and members of the audience and members of the agency, but it does create some different dynamics with the manufacturing process, which we'll be getting into a little bit later from subsequent speakers.

So, source plasma. We collect plasma, our members collect plasma, through the process of plasmapheresis in the US, Germany, Austria and the Czech Republic, and right now I'm going to be getting into more detail here in a few minutes about the content and scope of

the IQPP program, but there are about 400 IQPP-certified and FDA-licensed centers in the United States.

So we go back and forth internally in talking about sort of the strategic overview of what our standards programs are; is it one program, is it two programs? For purposes of the discussion here, for clarity, I think it's helpful for the Committee and members of the audience to think of them in two parts; one being the International Quality Plasma Program, which is the standards and certification program for collectors of source plasma, and the other is QSEAL, which Susan already mentioned earlier, which occupies the space involved with the manufacturers.

So I also want to note that these are standards that are voluntarily created by the source plasma industry, and plasma derivative manufacturers, in addition to regulatory requirements that the industry follows, or exceeds, not only in the US but Europe and elsewhere.

So first up, I'm going to talk about IQPP.

Just as a handy reference, I think, more than anything else, I wanted to talk mostly about the standards that are directly implicated by your discussion today, relating to Hepatitis B. IQPP is the set of standards that deal with plasma collection facilities, but we think of IQPP as sort of broken into two halves. There are nine

current standards, and the two halves are donor management and center management.

Of the five that are sort of related to donor management, two are of particular note for direct linkage to Hepatitis B and HBV NAT testing, and that's the NDDR and the Qualified Donor. And then on the Center Management side of things, our Viral Marker Standard.

So basically, the next three slides are what I'm going to be doing, is give you an overview of the three most pertinent standards, the common thread running through them being Hepatitis B NAT testing.

So first up is the use of the NDDR. Essentially, this is a national database used by all PPTA members in the United States, all IQPP-certified centers, I should say, where a donor who tests positive for HIV, HBV or HCV is entered onto the database. That record is permanent and as such, any time that donor would attempt to donate in a subsequent time, their name or identification would be entered into the database to make sure there isn't a previous entry, and if there is, they would be deferred at that point. That way, this prevents a donor who was notified, tested positive for HBV.

This standard has been in place now for almost 20 years or thereabouts. I'm very pleased to have had some new additions to it lately in technology and effectiveness, so

we're quite proud of the NDDR, and we think that this is one of the most important parts about discussions of PPTA standards, in terms of its web of linkages between the standards, regulatory and practice.

Essentially what it does is, it helps ensure that donors are deferred before they have a chance to donate, if they have tested positive in an earlier event.

Next up, with the qualified donor standard, is that this is another one of our cornerstone standards, and Susan mentioned this a little bit earlier too, before becoming a Qualified Donor – a person comes in to donate, they have to successfully pass through health screening, a physical examination, two panels of required testing, which does also include HBV, and I want to really underscore right here that the source plasma units collected from non-qualified donors are not used in therapeutic products.

So you can begin to see, at this point, the web forming between the regulatory overview that Susan gave, sort of how the NDDR works, and now the Qualified Donor standard, starting to work together.

And now the third leg on the trifecta is the Viral Marker Standard. Another one of our cornerstone standards for the IQPP program, and I think right at the beginning, I want to set out sort of, delimit, exactly what

the Viral Marker Standard is, and the scope of how it works.

The standard is a quality control standard for each individual center. It is not a repository or database or measure of donor epidemiology. What it is, instead, is it is considered to be a part of the larger network of safety measures that the industry has in place, and as a result of that, the data that I'm going to be showing you later are a measure of the QC Standard, and so they're not what you would call a typical research database as a result of that, but as a part of the viral marker standard, Hepatitis B is also tracked and noted as a part of it.

How the standard actually works is that it's based upon the industry average of confirmed serology and/or net positive qualified donors. In the standard itself, the limits are a part of the transparency of the IQPP program. The numbers are in there. They are based on a probability of exceeding a certain number of positives, keyed in on the volume of collections in a particular center.

So I'm not a statistician, I'm sure there are many in the audience and on the Committee, but essentially the distribution that is used as a part of the standards is a Poisson distribution, and then after that, each Center is assessed twice yearly and checked, basically its viral

marker levels are checked according to what those Poisson distributions have developed, and if a center is in excess of the standard, they are required to submit a Corrective Action Plan to the Association for review.

So those are the three major areas of impact from a history of Hepatitis B, in particular, on source plasma collection.

I'm going to turn now to the QSEAL side of things, and outline again three, touching on a fourth, standard. Susan mentioned these a little bit earlier, so I don't want to belabor them, and actually, to the extent that I just discussed the Qualified Plasma Donor and Viral Marker Standard, basically for QSEAL, they're the same thing as what you would find in IQPP.

But of more immediate note, for this particular question, is the requirement for NAT testing. It has been in place for a number of years now, in QSEAL, and also the 60-day inventory hold.

So the NAT standard, essentially what we're all here for. This standard does require NAT testing for HIV, Hepatitis C and Hepatitis B. The standard has flexibility for when the test is employed in terms of either minipool or the manufacturing pool, but we would note, too, that currently neither the US nor European regulators require HBV NAT testing.

In the US, HBV NAT has followed the same paradigm, the testing paradigm, as HIV and HCV, in terms of the donation mini-pool, and from what I have been able to find out, this is sort of considered to be a donor screening assessment.

So in terms of this with HBV NAT testing, PPTA members voluntarily started testing for HBV NAT eight years ago. The data that I'm going to present in a few slides are the ones that exist – they were not collected particularly for this presentation. They are what we were able to derive from the data sets that we had on hand. The data that I'll be showing, also, the NAT-only test results are due to the testing algorithm.

NAT testing is performed only, generally, on serology negative donations. So whenever I show you the NAT-only information, if you see a NAT positive, it's basically NAT only.

But I want to really emphasize this, because what happens is if a donor comes back, serology tests come back sooner that what we would have for a NAT test result, and if the serology test comes back reactive, that donor is not necessarily tested via NAT – that donor is deferred and excluded at that point.

The data represented also are confirmed positive donors over total qualification donations. And again, I

want to emphasize this because I know that this is going to be not confusing, but perhaps it lends itself to some misunderstanding about what the measurements actually are, and I want to emphasize here that the data represented are a part of the overall QC assessment system for particular centers, and not an epidemiological research database.

So with regard to US testing, I'm sure there's going to be some more discussion about this later, HBV testing performed under IND at the mini-pool level, what happens after a person comes back reactive? Well basically, any regulated company is going to follow the regulations that are implicated here. One is that the donor is deferred; the donor is advised of the reasons for deferral, test results and so on – we also recommend medical follow-up with them. All in accordance with the regulation.

One thing I would note here, that sort of does separate HBV from HCV and HIV, is that the lookback mechanism that's used by the industry is contained in a 1996 recommendation memorandum, basically spelling out the same processes that you would follow otherwise. And again, this was all a part of whenever the HBV NAT testing came into being. It was always considered to be a donor screening device.

We've already been over this. These are the assays, as far as we've been able to determine, that are currently being used by source plasma collectors in the US, and then the actual data that you're probably quite interested in.

This is one year of data. This is 2009. 2009, we felt, was one of the better years to use because we were more confident at this point that all of the industry was using the newest available test kits by 2009, and we don't have specific information on which test kit was used for which result, but again, because it's something that we collect on a daily basis, and that is not something that we would normally be asking our companies for.

But for 2009, these are test results for qualified donors, about 21.2 million qualified donations that year. Susan gave a number from 2008, which is also accurate. These are the most up-to-date information that we have in terms of the denominator data.

Of those 21.2 million qualified donations, there were 508 HBV serology or NAT-positive donors. Of those 508, 391 of them were serology, and the NAT testing was not performed. As I mentioned earlier, if you have a NAT test result it's probably a NAT only or a NAT-first test result. That is 117.

So the 117 is then broken down into donors that have a NAT first and a subsequent positive serology and then 82 of the 117 are donors just from a first positive donation. These are essentially the numbers that I think would most interest the Committee at this point. As a part of that question about days between HBV NAT and HBV serology positivity, basically ranges from 2 to 24 days. This is the breakdown of what you're going to see in terms of those results.

Of course these data are not without their own limitations, and I want to go through these. These sort of hearken back to some things that I said earlier in the presentation, but I just want to underscore them here so everybody is on an even level of understanding.

The limitations are such that the test data are operational. They're not research data. These are not NAT seroconversion panels for a determination of window period differences. We don't have any information on viral load data. The differences can also be driven, in some part, by the interdonational interval of donation, and also if the results are NAT positive first, the donor may not have additional donations or serology results recorded for subsequent donations.

And for donations that are identified as being serology positive, a NAT is not always performed on priority donations.

So in summary, where we are with it, we've been using NAT voluntarily now for the better part of a decade. The NAT testing that we had in this one minor data set from 2009 detected 16 percent of HBV positive donors that we had. Even with the limited amount of donors and even more limited for those with both NAT and serology-positive test findings, we believe we have demonstrated incremental value of NAT testing in order to detect earlier infection, and the PPTA voluntary standards, the Qualified Donor, NAT testing, Viral Marker Standards, 60-Day Hold, NDDR and so on, have a vital contribution to ensuring the safety of finished plasma protein therapies.

I am not Mary Gustafson. She is the contact person, should you have any further follow-up or technical questions on this. I've actually been asked to fill in for Mary because she is at the royal wedding, not at the Royal Wedding, but in London to spectate. So good for her.

With that, I'm welcome to entertain any questions which I'm capable of answering.

DR. HOLLINGER: So we'll have a few questions, perhaps from the Committee. We'll have time to discuss issues later on, prior to the questions and so on, but

anybody have some questions for Dr. Penrod? Yes, Colonel Rentas?

DR. RENTAS: On slide number six, you show that your companies collect plasma from different countries out there. I think you mentioned Germany, Austria and the Czech Republic. Where is that testing done?

DR. PENROD: Well, I think the companies are actually in a better position for that than what I would be doing. I would ask that my colleagues answer that later, because I do not know what the companies do with their own test results. There are test labs in the US for all the companies, and I do know that the companies also have test labs in Europe as well.

DR. HOLLINGER: Yes, Dr. Linden?

DR. LINDEN: In your penultimate slide, you said that NAT detected 16 percent of the total 508, to 82. So the 35 that were NAT-positive first and then serology later, you were not attributing to NAT?

DR. PENROD: Part of the problem with the attribution of it is due to the limitations that are inherent with it, because of the timing, viral load, the other things that came up as a result. We weren't able to discern that. So what that number comes about is the ones that we knew were NAT only at that point in time.

DR. LINDEN: Okay, and the other 82 – you said it was variable of how many had serology later, how many didn't. But what time frames were you talking about? Do you have means, or at least examples?

DR. PENROD: No, not with the data that we've collected, because again, once that NAT test result was in, there was not going to be a subsequent donation or anything beyond informing the donor of the test result and deferral.

DR. HOLLINGER: But on that same question, I take it these are first-time donors, is that correct?

DR. PENROD: No, that's not correct; these are qualified donors.

DR. HOLLINGER: These are donors who have already donated in the past, is that right?

DR. PENROD: Yes.

DR. HOLLINGER: But they've been individuals who've been serologically negative?

DR. PENROD: Yes. They would have qualified as Qualified Donors under the standard where they would have passed through two independent screening banks.

DR. HOLLINGER: So how are these different from the other – I'm confused about the 35 and the 82.

DR. PENROD: Okay, well it's probably more of an artifact of the way the testing algorithm works, because at that point a company would have reported, or would have

gotten results, for both serology and NAT. Most times, if they do get a serology back that's positive, then NAT testing is not performed.

DR. HOLLINGER: Yes, Dr. Alter?

DR. ALTER: There's no denying the data, but I think at issue here today is, here you have 117 detections, but not a single one of these detections, if you'd missed them, would have created an infection in the recipient, based on 20 years of experience, so I think that's what we're going to come back to, the data are the data, but the impact is zero.

DR. PENROD: And I think you're going to see more of that in the subsequent presentations too, because it's the manufacturing side of things that are going to go into more details on that.

DR. HOLLINGER: Dr. Nelson?

DR. NELSON: The other value that was mentioned in Susan's presentation was the public health value; in other words, you identify an infected person who probably doesn't know they're infected.

What is the protocol for follow-up on a positive donor? Are they just told, are they counseled, are they referred to care or further evaluation? Is there any standard in place that's uniform, or is it up to the –

DR. PENROD: Well, basically, in slide number 17, it has the regulatory requirements for what happens in the result of a reactive donation. First up is the deferral of the donor, and then donor notification, per the CFR requirement, advised of the deferral, the reasons why, the test results and just information for medical follow-up. But do we have a voluntary standard for that? No. We do have a voluntary standard for donor education, for high-risk behavior prior to donation.

DR. HOLLINGER: Thank you, Dr. Penrod. Yes, Dr. Ruta?

DR. RUTA: The question is, first of all, I appreciate the presentation, and I think the voluntary standards are very helpful, and can help protect the safety of the derivatives. I just note that there's always a difficulty with voluntary standards in that they're voluntary.

The other point I would ask you on a technical question is, you presented the data as 21.2 million donations. That's the highest number I've ever seen on a yearly basis. I see things are going up in terms of donations – can you tell us about how many donors gave those 21 million donations?

DR. PENROD: I don't have number of donor information, no. And I also can't make any prediction

about trending or anything like that due to anti-trust concerns.

DR. RUTA: I wasn't looking for trending, I was looking for a number – in the past you've told us it's around one million, so I'm trying to figure out did it jump to 2 million or – a ballpark number.

DR. PENROD: No, we don't have the actual information on number of donors, that's not part of our routine data collection process.

DR. RUTA: Do you know the average number of collections per donor?

DR. PENROD: No, I don't. I'm sure that some of the companies might have that information, but we don't keep industry-wide data on that. Historically, 15, 17, 12, but before you paint with a broad brush across the entire US, donation frequency varies, and can vary, by site, by center, by location, by population, everything like that.

And also, note that I guess I have to respectfully disagree that voluntary standard should be sort of an epithet. I think it's actually a great example of industry being proactive.

DR. RUTA: I'm actually agreeing with you, and I think some of the measures are very useful, and I think they've been recognized as being useful, and in fact we've proposed to require some of these measures in the

regulations because they're useful. I'm just pointing out that the difficulty with voluntary is that they can be dropped as some of the voluntary standards that PPTA has had in the past, you know you've decided were not necessary anymore and have dropped, and that's one of the issues that we faced with voluntary standards, but I agree with you.

I think these things are helpful in terms of improving the safety of the derivatives.

DR. PENROD: Well, thank you for that. I can also say, too, that the industry has no intention of stopping HBV NAT testing, irrespective of Ian's(?) document or not. We've been doing it for more than eight years without one, and it's viewed as good practice and has value by the members of the industry.

DR. HOLLINGER: Just for a second – but notification of the donor and telling him the test results and providing information about medical care and so on, that's not voluntary, is that correct, that's a regulation?

DR. PENROD: That's correct, that's in the CFR.

DR. RUTA: Sorry, I have to slightly correct that. I don't want to disabuse the practice -- we want people to do that. Under the IND you're required to notify – we can require whatever we want. Under the regulations we require for deferral for tests that are required, so we would have to require the testing in order to trigger the

deferral. We're happy that the industry is doing it voluntarily on their own, but that would be one of the outcomes of requiring the NAT testing, that it would automatically trigger the deferral notification.

DR. ALTER: First of all, I want to congratulate the industry, PPTA, making the worst blood product imaginable 20 years ago into the safest blood product we have. I think that's a remarkable thing. But secondly, since you're not going to be able to demonstrate – you can demonstrate yield but you won't be able to demonstrate benefit, the discussion may come down to the public health issues and the donor aid issues, and so the data I'd like to see, which you probably don't have, would be how many donors were notified of their NAT result before they came back and were found to be HBsAg positive, what's the interval between the detection and the actual counseling of the donor – these donors come back so often, would they have become surface antigen positive by the time they're notified? So the bottom line is how many of these 117 people actually benefited by early knowledge?

DR. PENROD: You're right, we do not have the data on that, especially as an industry.

DR. HOLLINGER: I'm surprised you don't have the data on that. That's a little disturbing.

DR. PENROD: I should say that as a part of the PPTA standards, these data that were shown were ordinarily generated through the course of business; whether there is information or are data available, I would imagine so, but I don't have them here because these data were generated from the standards program.

DR. HOLLINGER: Thank you. Yes Ron?

DR. GILCHER: Just a comment. When we look at the volunteer sector testing, in a sense we have backup. If you look at the HBV, HCV, HIV, we essentially are doing two tests; serological and NAT. The sector that we're talking about here that is the paid sector for plasma collection, involves only one test, for HBV; that is, HBsAg. I see this as a real positive addition by, again, being a believer in redundancy and backup and providing a backup kind of test. So I see real value in the HBV NAT.

DR. ALTER: Just to respond – the redundancy is built in with the inactivation, with the fractionation, so you have better than another test, you have enormous, 10 log reduction by the backup.

` DR. GILCHER: I know that, but I feel that if the HBsAg were missed, you'd present a large viral load into the pool and that could theoretically obviate the limits of inactivation. I realize that hasn't happened and it

probably won't happen, but I see this as a valuable addition toward safety.

But I think you introduce a small viral load, you introduce pre-surface antigen when the HBV DNA is probably very low, so you're introducing a small viral load into a huge pool which then goes through a 10 log reduction.

DR. KUZMA: I have two comments. I have a question about the percent compliance with these voluntary standards. Do you capture the entire industry? So that's my first question, and then the second question relates to the comments as how do we know there's been zero transmission through transfusion. Lack of evidence does not mean actual lack of transmission, so what's the post-market sort of monitoring for that?

DR. PENROD: I'll take the second question first; and that's an easy one, because I'm just going to defer to the gentleman sitting right there, because he's going to have information that I think would help you understand that.

In answer to your first question, we represent all the major manufacturers of finished products in the US and Europe except for one –

DR. KUZMA: Except for one? And what about the minor – I mean, how many minor manufacturers are there?

DR. PENROD: In the US, for example, I don't know of any. I try to think in terms of the global footprint; I mean, we know, for example, there are 20 or more fractionators in China; none of them are members, as an example. A fractionator in India is an example. The state-subsidized sector of national fractionators in Europe is not a member.

DR. KUZMA: Thank you.

DR. HOLLINGER: Yes, Dr. Nakasi, and then we're going to move on to the next step.

DR. NAKASI: I just wanted a couple of – one a comment and one a question. The one comment is basically responding to Dr. Harvey Alter's question, what impact, and I think I echo Dr. Gilcher's response that it is an added value, which lowers the plasma pool and the viral titer in the plasma pool to begin with, and not seeing anything for the last ten years, also attests to the fact that HBV NAT testing has been done, so I think that helps a lot to make the argument that obviously it's important to have safety, even though yes, we do understand it's a small, only five-fold impact on that.

With regard to your slide, which I think Dr. Ruta was asking questions, number 19, it would be nice to know, because you are jumping from donations to donors, so that number, is that going to be changed? Because each donor

will give you so many donations, and how that number, because 82 out of, because those are 82 donations, whereas what you are – and denominator is 508 donors, so how many donations were given by that 508 donors will also have an impact on that. So you know about that?

DR. PENROD: I mentioned that a couple of times, again, the viral marker standard under which these data are collected is not an epidemiological research data base. It's part of the QC vision and mission for the industry that's devoted towards manufacturer of safe and effective therapies. So in terms of changing the standard or how it's counted or anything like that, there are no plans to do that because the standard works for the end of the manufacturer's finished therapies.

Then in terms of what you're saying, as far as I understand, if you're talking about the 82 out of 508, those are donors over donors.

DR. NAKASI: Those are donors over donors?

DR. PENROD: Yes.

DR. NAKASI: Because the way it says, it's donations, so that was why I was confused.

DR. PENROD: Well if you look at the topmost box, it says donations, and then the one below that says donors and then NAT positive donors.

DR. NAKASI: Okay.

DR. EPSTEIN: Thank you, Mr. Chairman. I just want to clarify one point, which is perhaps troubling the Committee. No one has an estimate to what extent HBV NAT screening would quantitatively reduce either the number of positive units in a pool or the actual titer in a pool. What you're hearing is evidence that it does some of that, but exactly how much we can't say, and we really do not contest the point that Dr. Alter made, which is that we do believe that the pathogen clearance through an activation and removal has rendered end products safe. So we're not disputing the notion that screening, with its non-quantitatively estimated benefit to reducing viral titer in a pool, might marginally contribute to a benefit of safety, but that's in the larger context of effective clearance, so I think that Dr. Alter framed the question correctly, and what remains is to hear the evidence.

But I think dwelling too much on the numbers may, in fact, confuse us. We're showing you the best numbers available, but in the final analysis we can't be precise.

DR. HOLLINGER: Let me just clarify, the one thing is that the viral load that is found in an individual who is HBs antigen negative, but HBV DNA positive, is low. It's not going to be high because it will be an HBs antigen positive. So I think that's a critical piece of information.

So let’s move on to the next session; Safety of Plasma Protein Therapies With Respect to HBV, and this is by Dr. Lee.

Agenda Item: Safety of Plasma Protein Therapies with Respect to HBV

DR. LEE: Well first of all, let me thank the Committee for the opportunity to speak today. While I am speaking for PPTA, I am not employed by PPTA; I’m not salaried by PPTA. I actually work for Talecris Biotherapeutics.

We’ve already talked a little bit about this, and what we want to do is put back into context, and these questions have already started coming up, and one of my goals here is to talk about the context of the plasma-derived products relative to the testing and how it plays into effect in the viral reduction. So as Josh indicated, these are the PPTA member companies. This data that I will present represents many of those companies. As Dr. Zullo indicated earlier, the starting material is human plasma for these products. They follow in various classes, including clotting factors and immunoglobulins, and they are separated in a highly complex manufacturing process that incorporates viral inactivation and reduction methodologies internally are integral to them.

They are stable products, defined shelf life as with all pharmaceutical products. They are globally distributed and what we would like to make the distinction today is to make sure everyone's aware, these are distinct from the labile blood components that are typically used, that may be confused, from those used for transfusion, and they are highly regulated products.

This graphic is basically a representation of the relative improvements that these safety measures for pathogen safety typically are enjoyed by these products, and different measures, from managing donors to managing the donor selections, the donations, NAT testing, VMT testing, inventory hold, virus inactivation and then surveillance of the finished product in the field, all contribute to the pathogen safety margins that are enjoyed by the products today. Obviously, relatively speaking, the virus inactivation and removal steps that are incorporated within the manufacturing processes have the greatest impact on the safety, or the pathogen safety profile, for these products.

This basically reiterates the point earlier, the check marks; with a little bit more granularity here, the check marks indicate some of the areas that I want to be taking this talk to, and we can focus a little bit more on as we move through the day.

Again, just as a reminder, it's from the donor to the patient. The pathogen safety, as integral to the company's perspectives, doesn't start or end at the product, it actually goes from the beginning to the end, management of the donors, management of the donation centers through the manufacturing process and then ultimately to the patient, which includes a surveillance component that was asked about earlier today.

By far, if you look at the margins of safety afforded by the various processes, the current beliefs and understandings are that selection and testing do contribute to the relative risk or the relative safety of these products, but again, by far, the reduction steps, the solvent, detergent(?) and activations, the caprylate inactivations, the heat treatments, the nanofiltrations, that are afforded or incorporated in these processes, give rise to a large, significant contribution to the final safety margin of these products.

Some of this was alluded to earlier, but I think for a complete picture, we need to be reminded from a PPTA standpoint and a member company standpoint, it's not just testing donations, it's a whole algorithm of control around the testing and the donations and all.

If you look here, obviously we do the serological testing on the individual donations, and HBV surface

antigen is one of those tests. For NAT, which includes, of course, PCR as well as TMA, we perform minipool testing for efficiencies and again, HBV, HIV and HCV, the chronic pathogens, are well-regulated within this industry and controlled. Positive units are removed and once these units wind up in a production pool, the testing is repeated again.

So that was something that was missed a little earlier today, or in the earlier discussion, is the viral marker tests are repeated, but in my opinion, most importantly, the nucleic acid testing is repeated on those as well, again, to ensure the titers of those pools are quite low, or are negligible or negative, frankly.

In terms of inactivation or removal, for the chronic pathogens, including HBV, we've basically spent a lot of time in our development, as well as for our commercial products, looking at and incorporating inactivation and removal methodologies. The validation of these methodologies includes demonstrating and providing evidence that the selective steps can effectively perform the function that they are designed and required to do. We also look at this from an indirect methodology, where the manufacturing process is designed to inactivate and remove not only targeted viruses, but a wide range of viruses, that may include emerging pathogens as well; enveloped/non-

enveloped viruses with varying and diverse physical and chemical characteristics.

This slide is just here to remind you of several of the current methodologies that are employed by the manufacturers for reduction. On the left are inactivation methodologies: pasteurization, dry heat, low pH are some, caprylate and solvent/detergent. On the right are the physical removal methodologies that are incorporated in many processes; could range from precipitation or fractionation, chromatographic methodologies; again, things that separate the potential viral load from the targeted product string. Obviously it's critical that these processes that we use to inactivate and remove viruses or pathogens there do not injure or harm the targeted attributes of the product that we're looking for.

So it's critical that not only do we reduce the viral load, but we maintain the integrity of the product at the end of the day.

For HBV, its size and susceptibility to inactivation agents are considered when assessing a particular removal step.

This slide is just a cartoon, basically to show you how one of these experiments is performed. We take a manufacturing setup and translate it to a smaller scale, bench scale, that can be performed on the bench, and then

confirm the validity of that model at that scale. We add a known amount of viral load, perform the step and then measure the output and input fractions. Our subtraction of the output titers from the input titers gives you your LRV, or log reduction value. In this particular example, we show a 4 log, but again, this is just for illustrative purposes only.

The model virus concept is one we employ to not only address those known pathogens such as HBV, but also the unknown pathogens as well. It uses a panel comprised of a wide range of diverse viruses, both physical diversity as well as chemical diversity, and the goal is to predict the behavior of a specific virus of interest, in this case HBV.

For HBV, we can't use HBV specifically in the laboratory. We don't have a reproducible redundant assay that's easily validatable or even readily validatable, so we do rely on a panel of viruses with physical attributes and chemical attributes that are similar to HBV, and we interpolate that data to HBV.

Just as a reminder, again, HBV is a Hepadnavirus. It's lipid enveloped, spherical, with 40 to 48 nanometer diameter. It has a DNA genome. It is quite susceptible to many of the inactivation methodologies that are used in these processes, including solid detergent, which has been

around for years, non-ionic detergents, Triton, caprylate and heat treatments.

This slide here is just simply an example of a panel which would be used, or could be used, in the assessment of the pathogen safety profile for any product. Again, as I indicated earlier, there's no simple or readily available in vitro assay system that directly models HBV, so we rely on the panel of diverse viruses with diverse physical and chemical attributes that do relate to HBV to assess its ability to remove that particular virus.

The next series of slides is cumulative data from the industry on global reduction factors. Global reduction includes all of the reduction factors for a particular product that can be used, or that can be attributed to, each different product, and each company has provided their data.

I would remind everyone that this data is publicly available, in both product inserts as well as the FDA website, for any licensed product in the US. The whole goal here is just to kind of give you a general feel for the global reduction that these various products enjoy.

For the Factor VIII concentrates, looking at the various companies, we have five companies represented there. You can actually see, there's a wide range of viral global reduction that's associated with various

viruses that were used as models in this particular case. They range anywhere from 9 to up to 20. Factor IX concentrates: There are three companies represented here, again. You can see the range of reduction, or global reduction, that this particular product appreciates.

Ig IV has a very broad range of inactivation, but very – it actually is quite high as well. Again, using viruses that model and have attributes similar to and attributable to HBV. Albumin, we have four companies represented here. Again, very wide range but very high levels of global reduction that's appreciated here.

This slide actually shows additional data that we typically collect during inactivation procedures. It demonstrates the robustness, or it helps us to assess the robustness, of various inactivation technologies against enveloped viruses in these particular examples. You have three different methodologies presented here, caprylic acid, dry heat as well as solvent detergent, for two different products, Ig IV and Factor VIII. And you can see, for the model viruses employed, the information suggests that the inactivation is quite quick, and actually to four logs or beyond our ability to even detect.

This is just for me to remind you that this data and more is actually available and in the public domain. PPTA has chartered reviews that are published in two

different manuscripts; one in Transfusion 2009 that has a collection of this data, as well as one that's currently impressed; both are in Transfusion.

I didn't go over other plasma-derived therapies that are also available. Again, time not permitting, but I wanted to make it clear that there are other products that enjoy these reduction technologies as well. That information is available from both the manufacturer as well as the FDA, and associated with the product inserts.

So the last two slides; a couple of summary slides. One, HBV as a lipid-enveloped virus, is quite susceptible to agents that are commonly used in the manufacturing process to inactivate pathogens. The current testing paradigms for source plasma is quite redundant; we have orthogonal methods for not only testing with VMT as well as NAT, but also orthogonal test points, or multiple test points, within the process, including the donation and the production pool.

In addition, the virus removal and capacity of HBV in today's manufacturing processes are actually quite high, in magnitudes of 9 logs or even greater than that. The pathogen safety measures that have been introduced by regulatory agencies and PPTA and member companies have significantly improved the safety of these products over

the years, and especially these pathogens that cause chronic diseases such as HBV.

Since 1988, there's been no reported transmission of HBV by a plasma-derived medicinal product. Regulatory requirements applied to these products are quite stringent and challenging, but they actually help afford a good, safe product along the way.

In addition, as Josh indicated earlier and it was discussed in the subsequent conversation, there are additional industry standards that have been applied for donor selection and screening, testing and have been applied within our manufacturing process for these finished goods.

So I hope I've given you guys an overview, the committee an overview, of what we're doing here in PPDA member companies. Thank you.

DR. HOLLINGER: Thank you, Dr. Lee. Questions? Dr. Nelson?

DR. NELSON: Actually no. The blood donors are both tested but also excluded, for particularly variant CJD. Do these same exclusion criteria apply to a donor for plasma production?

DR. LEE: There are regulations around TSC and individuals who have lived in the UK and Europe for certain periods of time. Again, we're talking about North American

donors, and the products are associated with FDA-licensed materials, and there are overlaps with that as well, from not only TSC but from – and I don't want to mix up your question, but there are exclusion criteria for viruses that are non-TSE related that are specific for them as well, social behaviors, et cetera.

DR. RENTAS: We keep on going back to the 1988 case. For the benefit of the Committee here, could you tell us a specific of that case? Of course I was not no pattern in the activation at that time, I assume, and we didn't have NAT testing either, but could you tell the Committee what the specifics -

DR. LEE: I am actually not familiar with that case, and I'm not sure if it's coagulation factor that the individual – are we familiar with that at all? We'll certainly be willing to provide that to Committee and provide the manuscript that it was probably referenced in.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: First on that point, there were a cluster of HIV transmissions from plasma-derived clotting Factor VIII related to a manufacturing process that involved low-heat treatment. Also in 1994, there was transmission of Hepatitis C from certain immune globulin products that were made in a certain way –

DR. HOLLINGER: That's immunoglobulin, right.

DR. EPSTEIN: Right. I just wanted to comment for a moment about safety margins and redundancy, because this is going to become a common theme. Blaine, you commented quite correctly that NAT screening in the face of HBsAg screening would only pick up low titer units. That is entirely true. But back to Dr. Gilcher's point, the notion of belt and suspenders, because the system of donor screening is not entirely error-free, and you could have wrong sample in a tube, sample mixup, unit released in error, failure of testing, et cetera. So a positive unit that could have been detected by HBsAg could potentially end up in a pool, albeit rarely.

So if you also NAT screening, you've screened twice with effective tests; that's one point. The second point is that when we talk about a margin of safety, that's in relation to all the entering units having been properly screened, that's in relation to all the entering units having been properly screened and removed.

If a unit was for whatever reason, and albeit rarely, improperly screened or not properly removed or diverted, then you do have the possibility of high level contamination, and that's where the standards come in for assuring an adequate safety margin based on clearance. So if you had 10 to the 10 infectious virions in a hot positive unit, for whatever reason was not interdicted, you

would contaminate a pool at a reasonable high level, even with a one to ten thousand dilution due to pooling, and then you're totally dependent on clearance.

I would also ask one question of Dr. Lee, which is, you mentioned doing NAT testing on the pool. Dr. Penrod remarked that that's a voluntary standard, and I would just like you to clarify whether there is or is not either a European requirement or a European practice to test the fractionation pool by HBV NAT?

DR. LEE: Not HBV NAT, it's a voluntary standard for HBV NAT. The only requirement that I'm familiar with is the HCV one.

DR. EPSTEIN: Okay, thank you.

DR. LEE: But it is important to remember, though, and I'll use my case, that the testing of the pool is performed with similar assays, or the same assays, so the sensitivities are applied to those pools. Obviously not at the donor level, but at the actual analytic sensitivity.

DR. KUZMA: I have a question; how much does one test on a pool cost, a NAT test?

DR. LEE: On a manufacturing pool?

DR. KUZMA: Yes.

DR. LEE: I don't know that off the top of my head – a few hundred dollars, probably.

DR. KUZMA: A few hundred dollars? Okay, thank you.

DR. HOLLINGER: Are you offering to pay for it?

DR. KUZMA: Just think when we're talking about additional margins of safety, the cost is somewhat important.

DR. LEE: Typically our cost structures are around the cost per donation and not necessarily around the pool testing, that's additional cost.

DR. HOLLINGER: Okay, if there are no further questions of Dr. Lee, then we'll move on to the next speakers. These are three speakers which are going to be discussing various assays for source plasma testing for HBV by NAT. The first one is from NGI, or National Genetics Institute, Dr. Smith.

Agenda Item: Source Plasma Testing for HBV by NAT

DR. SMITH: Good morning. Dr. Epstein already addressed the question of redundancy, but I just wanted to address Dr. Alter's question regarding the units detected by HBV NAT. As you'll see in the presentation, most of the units that we do detect, because HBsAg has already been screened, are from the chronic infections, which in many cases are never detected by HBsAg, albeit those are low

titer HBV NAT positives, but they don't come up positive with HBsAg.

So I'll go ahead and get started. Good morning. Thank you for the opportunity to give you an overview of the HBV screening being performed at NGI. This will be a brief presentation in which I'll provide an overview of our assay, a description of the pooling algorithm used at NGI, a summary of our clinical study data, just a little data from the years since our clinical study was completed and hopefully, there will be some time, if anyone has any questions.

NGI's UltraQual HBV PCR assay involves time-honored and proven molecular biology techniques used worldwide for over 25 years. For the screening assay, we start with a proteinase K DNA extraction from a full 2 ml of plasma. We amplify two-thirds of the extracted material in 8 separate polymerase chain reactions, employing four distinct HBV specific primer pairs, in duplicate reactions. Detection is then achieved through agarous gel electrophoresis, followed by Southern blot analysis for each reaction.

This slide shows the results of one full HBV run, consisting of only ten unknown samples and ten controls, positives, negatives, region blanks(?), et cetera. We add

baculovirus to each sample, and each amplification reaction includes primers to amplify this internal control.

After membranes are probed for HBV-specific sequences and the results are scanned, membranes are then reprobed for baculovirus and the success of each reaction, as well as the rest of the procedure, is determined. Results for two different HBV primers are shown on each of the two separate membranes, so the set of 30 results on the top half of this membrane represents exactly the same samples as the 30 results on the bottom half, as well as those on the two halves of the other membrane.

This slide shows the results from the same run, with the 8 reactions representing one HBV-positive master pool sample highlighted. As you can see, not all the reactions are positive for HBV, and this demonstrates why we perform so many amplification reactions in order to increase the sensitivity of the assay. Samples are determined to be positive when as few as one of the eight reactions produces a detectable HBV signal.

This slide shows the same run again, with the eight reactions representing a negative master pool highlighted, and then the internal controls come up showing that those reactions were successful.

The vital statistics of our assay are shown by this table, by extracting from 2 mL of plasma and using

Southern blotting as our method of detection, we achieved the 95 percent detection cutoff of 0.9 IU per ml for our screening assay, which was performed on pools representing up to 512 individual plasma donations. This translates to a 95 percent detection cutoff for an individual sample of about 461 IU per ml.

In order to resolve positive master pools and identify positive individual samples, we perform up to 2 variations of the assay involving less plasma input volume and fewer amplification reactions. However since these are performed on much smaller pools, the resultant sensitivity per individual sample is much better than the initial master pool assay. Also, using commercially available panels, this assay has been validated to detect HBV genotypes A through G.

Because the assay is so very sensitive and due to the high cost of high volume extractions coupled with Southern blot detection, we screen plasma for HBV in pools representing up to 512 individual samples. This diagram shows a virtual 8 x 8 x 8 cube in which each cell represents an individual sample. Using the automatic robotic sample processors, we aspirate from 8 samples at a time and dispense each sample into three different primary pools. Our algorithm involves the creation of 24 distinct pools representing 64 samples each. Each sample is

dispensed into a unique combination of one of eight row pools, one of eight column pools, and one of eight layer pools.

For example, the darkened samples shown on the top of the cube would be combined into Layer 1, Row 3 and Column Three. No other sample is presented by the combination of these three pools.

And now I'd like to pause, and I have a brief animated video that will show the same concept. Hopefully this will work.

Here we see a 512 sample matrix. The eight layers, the rows and the eight columns. Next, we have the first eight samples being aspirated and dispensed, such that all eight go into the first layer pool, then into the eight different row pools, and finally into the first column pool. The same thing happens to the next eight samples, except that they all go into the second column pool rather than the first.

Now the video goes on to show the rest of the samples, for the first layer being pooled, resulting in 64 sample aliquots going into the layer one pool, completing that pool, and 8 aliquots going into each of the row and column pools.

I'll just pause a little bit here and let the video catch up. I like to show this because we talk about

these matrices that we make, and this sort of shows the redundancy of our testing, since each sample is representing three of these primary pools, and then those go on to be combined to make the master pool.

And don't worry, we're not going to go through all 512 individuals.

We then change from showing the actual pipetting scheme to illustrating the samples that are represented by each of the 24 primary pool tubes, and again, notice that each sample was represented by three of those primary pools. We refer to these as primary pools because they are made first; the master pool representing all 512 samples is then created by combining aliquots from each of the 24 primary pool tubes, and that master pool then goes into testing.

Thank you, if you can start the slide presentation back up again.

This is the basic testing algorithm for pooled NAT at NGI, which has been presented here several years ago. The first test is performed on the master pool. If that's found negative, all the component samples are reported as not implicated for HBV. If, however, the master pool is found positive, we then test all 24 primary pools, resulting in three independent tests of each sample, since each sample is represented in the three pools, and

finally, samples implicated by primary pool testing are tested individually to confirm their HBV status.

In rare cases, a primary pool testing will not confirm the initial master pool result, in which case an investigation will be performed, but in all likelihood, all component samples will be reported as not implicated.

Now this is an old slide some of you may have seen before, basically showing two different types of HBV positive donor, identified through NAT testing. On the left we see the path taken by 90 to 95 percent of the people infected by HBV: Acute infection leading to high viral loads, high concentrations of HBsAg, a rapid transition to antibody positivity and eventual clearance of the virus within several weeks.

On the right, we have the path taken by only about 5 to 10 percent of infections, but due to the chronic nature of the infection, and the low concentration of HBsAg, this is the type of donor identified more often through nucleic acid screening. In these cases, viral loads and HBsAg levels stay relatively low and anti-HBs antibody can eventually reach an equilibrium with surface antigen, masking both in traditional ELISA assays. In these people we often find that we'll detect one donation in a pool of 512, but titers can drop so low that we'll

miss the same donor on a subsequent or prior donation, even though the person remains chronically infected.

Confirmation of infection is typically very easy, by showing that anti-HB core antibody is present in these individuals.

We performed a clinical trial in 1999 to 2000 in which we screened over 1.4 million plasma donations and identified 107 HBV NAT positive, HBsAg non-reactive donations. Four of these donations had no follow-up testing performed, but 93 of the remaining 103 confirmed by alternate markers on the index sample or on follow-up. Ten donations did not confirm on follow-up. Several of these were in matrics with high concentration of true positives and may have been the result of cross-contamination at some point from collection through pooling.

Of the 93 that did confirm, 37 were confirmed by anti-HBC, either on the index or on follow-up. Many of these also confirmed by HBV NAT on subsequent bleeds, but HBsAg remained non-reactive in these donors throughout follow-up.

Another 22 confirmed by NAT alone, twelve were confirmed by one of our study co-sponsors, but the confirmatory data wasn’t provided to NGI. And only 22 were confirmed by becoming positive for HBsAg. Our yield for this study, counting only those donations from confirmed

donors, was approximately 1 per 15,000 donations tested, and as you can see, as I mentioned earlier, just under a quarter of the HBV NAT positive donations identified were from so-called window period cases, which were later confirmed by HBsAg.

However, in this table, which is shown on the next slide, I look at these 22 in more detail. These 22 donations came from 13 different donors and the time from the index HBV NAT positive bleed to the first HBsAg positive bleed ranged from as little as five to as many as 123 days. However, that donor which took 123 days to convert, didn't return for follow-up during the interim period, so the 123 figure is misleading in that case.

In fact, it's difficult to use most of these donors for a window period calculation since we don't have the dates of the last HBV negative donation, and therefore many of them could have been positive for HBV DNA for weeks before we had a chance to test them.

However, four of these donors did donate frequently during this window period, and for these, at least, we have a good basis for calculating the time between detection of the HBV DNA and HBsAg, remembering, of course, that the HBsAg assays used at this time were the previous generation and less sensitive than those used today.

For these four donors, the time from HBV DNA detection to HBsAg detection ranged from 7 to 16 days. However, window periods are usually calculated in a slightly more calculated way, as shown in the following slides. You see a timeline marked in red on the days that a plasma unit was collected from a donor. HBV NAT and HBsAg results are indicated underneath each bleed and positive results are indicated by white text on a black background, in addition to the plus sign.

The dates for each bleed are also indicated below the results. For this particular donor, the last negative unit was collected on July 1st. Five days later the donor was positive for HBV DNA but not HBsAg. One more DNA-positive, HBsAg-negative unit was collected two days later and after another five days the donor was positive for HBsAg.

Assuming that the donor became HBV DNA positive at the midpoint between the last negative bleed and the first HBV DNA-positive bleed, and assuming the same for HBsAg, we come up with a seven-day seroconversion time for this door.

As it turns out, this donor was rather interesting because even though the donor remained HBsAg reactive for 98 days, no anti-HBS antibody was detected in follow-up, staring approximately five weeks after the

initial positive bleed, although anti-HBc antibodies were found throughout follow-up testing, and this is a case where it’s possible that the anti-HBS antibodies were masked in the tradition ELISA assays by the excess of HBsAg.

This next donor had a seroconversion time of 8.5 days by the same method, but in this case the donor was found positive for HBsAg on only one sample. In follow-up testing the donor was found to have antibodies to both the core and surface antigens and was positive for HBV DNA on only the first follow-up sample, and negative on the next seven samples. This appears to be the profile of a person who cleared the virus on their own, leaving them positive for antibodies but negative for both HBsAg and HBV DNA.

Donor No. 15 from this portion of the study exhibited a 12 ½-day window period, and upon examination of the follow-up results, appears to have entered into a chronic infection with HBsAg and anti-HBS detected only intermittently, but remaining HBV DNA and anti-core reactive, that is, the donor remained HBV DNA and anti-core reactive throughout the end of follow-up testing.

This donor also shows how a chronic infection can be DNA positive and then drop below detectable levels, as shown on the August 24 bleed, and then come up positive again.

Finally, another donor who returned very regularly during the initial infection and with the profile of a cleared infection, demonstrated a window period of 14 days between HBV NAT and detection of HBsAg. By the end of follow-up testing, this donor had been found negative for HBsAg on the last nine dates and negative for HBV DNA on the last eleven.

Last, I have HBV NAT positivity rates for more recent years. Data on this chart are derived from screening of over 20 million plasma units, and it should be noted that NGI's UltraQual HBV PCR assay has remained unchanged since 1997. This particular time period was chosen to illustrate the decrease in HBV DNA detection since the introduction of more sensitive HBsAg assays around the middle of 2008.

During the clinical trial and in the years following, we detected HBV DNA in approximately one out of every 15 thousand donations. More recently, after implementation of these more sensitive HBsAg assays, these rates have dropped to around one in 25 thousand. That's the last of my slides, and I know that this was only a brief presentation and I wasn't able to get into too many details, so if anyone has any questions, I'd be happy to answer them now.

DR. HOLLINGER: Thank you, Dr. Smith. Any questions? Yes?

DR. KUZMA: I think it's slide 10, where you show the 1.4 million and you break it down – how many out of 1.4 million were HBsAg positive?

DR. SMITH: Those are data that I didn't get – most of these – actually sorry, out of those 14 million none of them were shown to have been HBsAg positive, because the intent was that the people supplying the plasma for screening would have already screened for HBsAg and removed those samples that were positive for HBsAg before sending them for NAT testing.

DR. KUZMA: I see, thank you – How many would you typically see that would be HBsAg positive if they had not been screened, what's the prevalence?

DR. SMITH: I would typically see none, since we only do NAT testing, so I don't have those data.

DR. HOLLINGER: Okay, if there are no further questions, we'll move on to the next speaker, and that's John Saldanha, with Roche. John?

DR. SALDANHA: Thank you. I'd like to thank the Committee for giving me the opportunity to talk in this meeting, and I'd like to state that I am a full-time employee of Roche Molecular Systems.

So in this brief talk, I'm going to give you an introduction to our two screening assays that we have for Hepatitis B virus. The two assays are the Roche COBAS AmpliScreen Hepatitis B test and the second assay, which is the more recent one, is the cobas TaqScreen MPX test, which is a multiplex test, and I'll present the data off two clinical trials that we ran in the US, one in 2003 for the AmpliScreen test and one in 2007 for the MPX test.

So looking at the two tests that we have from Roche, the first one is the COBAS AmpliScreen HPV test. This is qualitative in vitro test for the detection of Hepatitis B virus in human plasma, and the Roche MPX TaqScreen MPX test is a more recent test; this is a multiplex test for the simultaneous detection of Hepatitis B, Hepatitis C, HIV 1 and 2, and this can be used for testing both in source and donated blood.

So the plasma donations for both tests can be tested in pools of up to 96 donations. The pools can be deconstructed to identify the positive donation, and the same for the cobas TaqScreen MPX test; these can be tested in pools of up to 96 and there is a deconstruction algorithm to identify the positive donation.

So to give you some background and I'm not going to go into detail on this because the previous speakers have covered this very well, we know that for plasma for

the manufacture, there are at least two plasma pathogen reduction steps that are used during the manufacturing process, and to look at the guidelines, the first guidance for testing for plasma for further manufacturer was brought into force in Europe in 1999, and this was for plasma testing for Hepatitis C virus, and the requirement was that the test should be able to detect a sample containing 100 IU per ml of Hepatitis C virus.

So at that time, it was looked as an additional safety measure to reduce the viral burden with which the manufacturing process was challenged, so I think it was felt that they could, if you're constantly putting through plasma that's infected with virus, albeit low levels, this could maybe result in a buildup over a period of time, and this was just an additional safety step in addition to the viral pathogen and activation.

And the other thing is that plasma, as we've heard, can be tested in pools up to 512 donations, depending on the analytical sensitivity of the test. So as I stated, in Europe the regulation was brought in in 1999, but the final manufacturing pool had to be tested with an assay that could pick up a control containing 100 IU per ml of Hepatitis C virus RNA. In the US the recommendation was to be able to detect 5000 IU per mL of Hepatitis C virus

RNA or 10,000 IU per ml of HIV-1 RNA for the individual donation.

The other requirement in Europe is for Parvovirus B19 testing, in which it's required that the final manufacturing pool should contain less than 10 to the 4 IU per ml of Parvovirus B19, but that's something I'm not going to cover.

So what these regulations mean is that the requirements would allow some flexibility in the pool size that's tested. For example, with a very sensitive test one can use a larger pool size for detecting the 5,000 or 10,000 IU of Hepatitis C or HIV-1, and a less sensitive test would require the use of a smaller pool size.

` So, one of the things that we looked at was the optimum pool size for our tests, based on the analytical sensitivity of the test. The analytical sensitivity for Hepatitis C and HIV-1 for the two tests, and I'm considering these two because these were the ones that had the requirements around them – 28.8 IU per ml for the COBAS AmpliScreen for HCV, and 78.4 IU per ml for HIV-1.

You can see that if samples are tested in pools of 96, the effective sensitivity for the individual donation is within the limits required, or the guidance that's set up in the US, and the limits which are identical to the limits set up by the Paulek(?)Institute in Germany.

So for HCV, in pools of 96, you can pick up about 2,700 IU per ml, and for HIV-1 it's 7,500 IU per ml.

The TaqScreen MPX test, which is the more recent test, is actually more sensitive analytically, so in pools of 96 the limit of detection would be around 1000 IU per ml for Hepatitis C and around 4700 IU per ml for HIV-1.

What I'm going to do now is to go through the results of the two evaluations we did; the first one in 2003 with the AmpliScreen HPV test and the second one with the MPX test.

The evaluation in 2003 was done by Bayer Health Care Labs, which is now Talecris, of course, and they were using renumerated source plasma donors. The clinical study was done on just over 100,000 donations, which were collected from 40,000 unique donors, so you can see that most donors donated at least two or three times during the study period.

Samples were tested in pools of 96 and positive pools were deconstructed to identify the positive donation. So the results were that there were three NAT-reactive, serology clean negative donations, and all these donations came from a single donor, and the reason for that is with source plasma, a donor can come back and donate at least twice in a week and they've donated two or three times before the result for the first test is available, so once

the test is available and they're reactive for either NAT or surface antigen, the donor is then deferred.

All three donations came from a single donor and this gives the NAT yield of 1 in 40 thousand donors, or the NAT yield per donation is 1 in 34,500. The donor, unfortunately, in this study, was not followed up. The sample was reactive for antibodies to Hepatitis B core antigen and E antigen, and it was probably that this donor had an occult HPV infection.

Looking at the study that was done in 2007, with the TaqScreen MPX test, this was a study, again, done by Talecris on source plasma donors. They were tested in pools of 96, and because at that time the test of record at Talecris was the AmpliScreen HPV test, the samples were tested in parallel with the AmpliScreen test as well.

Again, samples were tested in pools of 96, and deconstructed to identify the positive donation. The serological results were also obtained with the NAT results, and where possible, we tried to follow up the donors until they seroconverted.

And here I should also add that the antigen test for surface antigen was not the PRISM, it was the Abbott Auszyme Hepatitis B surface antigen test, run on the Commander system. So both in the 2003 study and the 2007 study, the PRISM was not used for surface antigen testing.

In the second evaluation, there were 107,000 donations collected from far fewer donors, from 24 thousand donors, and they were tested, as I said, with both the AmpliScreen and the TaqScreen test in pools of 96. We picked up a total of 13 NAT-reactive, serological negative donations for Hepatitis B. That was the yield. Twelve of these thirteen were picked up by the TaqScreen test and nine out of the 13 were picked up by the AmpliScreen test. So for the TaqScreen test, the yield is 1 in 8,900 donations, and if you look at the donors, these donations came from six unique donors, giving a yield of 6 in 24,000, or 1 in 4,000 donors. So, one in 4,000 of the donors who donated in this study were infected with Hepatitis B virus.

As I said, we also looked at the AmpliScreen test in this evaluation, and with the AmpliScreen test, out of the 13 donations that were picked up by the AmpliScreen as well, giving a total of 1 and a yield of 1 in 11 thousand donations. These 9 donations came from four unique donors, giving a NAT yield for the AmpliScreen test of one in 6 thousand donors.

So the donors were followed up, and we did viral targets. We did the viral loads and the genotyping. Out of the six donors that we had for Hepatitis B, we were able to follow up five. One sample had a target that was not detected and one was below the limit of quantitation. The

other four samples, as we've heard before, had very low viral loads. They were somewhere between 250 and 1600 IU per mL.

We also genotyped to these five donors and they were all genotype A, which is a predominant genotype in North America. The second point is that all these donors eventually seroconverted to Hepatitis B surface antigen, so there was genuine window-case donations, and the time to seroconversion was anything between 18 to 38 days.

And one of the points – I want to make two points here. One is to the discussion that we've had previously. One of the values of NAT is either picking up donors in the window period or occult HPV or they're either serologically negative for Hepatitis B surface antigen, but there have been cases in the literature where there have been individuals who have been infected with Hepatitis B in the window period where they have high levels of Hepatitis B DNA and undetectable levels of surface antigen. This was published by Professor Gerlich in Germany a few years ago, and the reason for this is that some individuals, or some genotypes of Hepatitis B, may not produce excessive surface antigen, so the reason why this test works is there a vast success of the 22 nanometer particles and the long filamentous particles that are produced in a natural infection, which are able to be detected with the surface

antigen test, but there are cases where sometimes excessive surface antigen is not produced.

The second scenario is something that has been reported by Dr. Stramer in the U.S., and Dr. Strong at Puget Sound, and recently in Thailand, where you have donors who have been immunized either naturally or deliberately, who can be reinfected with Hepatitis B virus, in which case they have a subclinical infection with detectable DNA but no detectable surface antigen, because this is removed pretty rapidly.

So again, those are two cases where you may have high levels of DNA and undetectable surface antigen, as opposed to the cases we're seeing here.

The second thing is, with any test, it has to cover good genotype coverage, and as we see, the major genotype in North America is Hepatitis A, so as well as analytical sensitivity, a test should good genotype coverage.

In summary, what I am showing on the last slide is the yield, both per donation and per donor, so for the AmpliScreen test, the yield per donation is about 1 in 34,000, which translates as about 1 in 40,000 per donor and for the cobas MPX test, it's about 1 in 9,000 per donation, or 1 in 4,000 a donor.

On my final slide, I'd like to acknowledge Dr. Gierman from Talecris, who conducted the studies, and Dr. Simon and Mr. England from the two collection labs who provided the samples for these studies. Thank you.

DR. HOLLINGER: Yes, Ms. Becker?

MS. BECKER: Thank you. You have information on follow-up for most of the donors, but for the minority for whom you do not have follow-up, two questions.

Do you have any information about the circumstances about why they could not be followed up, and two, were there any patterns and why they were not followed up, and secondly, that they were not followed up and could you estimate how that might affect some of your results?

DR. SALDANHA: Of the donors that were positive for NAT and serologically negative, there were six for Hepatitis B, we had 4 Hepatitis C's and one HIV. As of those 11 donors, only one was not available for follow-up, that was the Hepatitis B, and the reason being, I guess it was up to the donor. We were not responsible for the collection sites, so the collection sites enrolled the donors under an IRB to do a follow-up study, and I guess this donor chose not to be enrolled in the follow-up study. I don't know the reasons why.

DR. HOLLINGER: Other questions? I don't know what the Committee feels, I'm struck, often, by these

numbers in the source plasma donors. The high risk of these populations despite the donor screening of them in the first place. I mean, these are really high risk donors, when you compare them with the whole blood donors, the individual donors that are looked at, really very high level.

DR. NELSON: I guess many of these donors are paid, right, do we know what proportion of these are paid donors?

DR. SALDANHA: They were all paid donors.

DR. HOLLINGER: It is striking though. And not just from chronic disease, but the large majority of them are acute infections that have occurred during the time that they are donating the plasma.

DR. RUTA: This was really a nice presentation. Thanks very much. But I had some questions also about the data, and sorry I had a senior moment for a second, but the data that you presented on the one in ten thousand donations that were positive, those were first HBsAg negative and then NAT positive, right?

DR. SALDANHA: Yes, that’s exactly correct. All the data I presented were the initial test that was done was NAT positive, surface antigen negative.

DR. RUTA: These were NAT yield cases?

DR. SANDANHA: Yes.

DR. RUTA: I was trying to take your NAT yield cases, the one in ten thousand, and compare it to what we saw from Dr. Smith, it's about the same, one in 15 thousand. You said an average of one in 10 thousand, and then if you think it's one in ten thousand, you would have expected, if I did the math right, 2,200 yield cases over the 22 million donations that we talked about being donated in 2009, and what we saw is a much lower rate than that, and I was a little confused as to the differences in the numbers there.

DR. SALDANHA: I think if I understood correctly, the data that were presented on the 21 million were composite data from all the companies, using a whole variety of tests for different poolings, algorithms and different sensitivities, so I think it's very difficult to compare composite data with data from a single test, with a different analytical sensitivity.

DR. RUTA: But the 22 million were 22 million donations, not 22 million donors.

DR. SALDANHA: That's right, yes.

DR. RUTA: A person can only be a yield case once, I think.

DR. HOLLINGER: Yes, Dr. Alter?

DR. ALTER: If you can pay all these donors, and not create any problems, I don't see why you can't pay this Committee for the work that they do –

DR. HOLLINGER: I'll second that.

DR. RENTAS: One of the questions that the Committee is being asked is the 500 IU ml sensitivity limit there. Did your presentation show that one of your yield cases had a titer lower than that?

DR. SALDANHA: Yes, it did. In fact one of the donations had around 250 IU per ml.

DR. RUTA: General, I'll ask you, but if any of the other presenters know this – Did you find any surface antigen mutations during the course of your studies; so NAT positive that were not detected by surface antigen that might have been mutations in surface antigen?

DR. SALDANHA: No, because of the NAT yield cases that we had, as I showed you, all of them seroconverted, so if there was one that was probably a surface mutant, I wouldn't expect that donor to seroconvert in the follow-up period.

DR. RUTA: Right, I meant in general for the other speakers too, but thank you.

DR. HOLLINGER: Robin, I think you mentioned that your testing for HBS antigen was with the Auszyme, is that right? So for the PRISM, it's somewhere down around 0.04

ng/ml, or 0.06, and I think the Ortho Version 3 is about the same, maybe a tenth, what is it for the Auszyme?

DR. BISWAS: I don't have it at the top of my head, but it's something, I don't know if there is an Abbott representative here, but remember that Auszyme had three or four different processes, test procedures, and it really depended on whether you were doing sort of the half-hour incubation procedure, the three-hour or the overnight. The most sensitive Auszyme, which I don't know how much that was used, but sort of about 27 nanograms, something like that, and the overnight one was something like – I don't really know, something about 50 to 60 nanograms. The PRISM, and also the newer tests, they all have about sensitivity in the same ballpark, and that's about 0.01 nanograms. You know, they vary from 0.07 to 1.102, something like that, 0.12, something like that.

DR. SALDANHA: I can also add that we did do a study with the AmpliScreen in pools of 24 for the clinical trial, and Dr. Mike Strong, who was the (inaudible) at that time, published a paper where we had 8 yield cases tested in pools of 24, and only 5 of those were picked up with the PRISM, and there was one that had quite a high viral load, which was missed by the PRISM. But in general, I think if you want to relate the PRISM sensitivity to NAT, I would say it's around 400 IU per ml of NAT.

DR. HOLLINGER: So let's move on, then, to the last presentation for this session, Dr. Zerlauth from BioLife Plasma Services.

DR. ZERLAUTH: Good morning. I would like to thank, first of all, the Committee for the opportunity to present some of our data here. We are presenting data of ten years of routine screening by HBV NAT of North American sourced plasma donations, all of which have been derived in the frame of our own plasmapheresis centers, BioLife Plasmapheresis Centers here in North America.

First of all, I would like to give you some overview on the assay systems that we are using. Because of the time span, there were some changes.

First of all, the NAT assays – we are using two. One is a Baxter-owned BioLife test, under FDA license 1640, which concerns HIV and HCV, and HPV assay under IND number 9465. In addition to this Baxter-owned assay, we also make use of NGI under contract testing agreement and as you have seen, NGI has also FDA-licensed assays and their HPV UltraQual assay is also under IND. So these two assays are routinely used in the frame of our screening of North American plasma donations.

In addition to this, of course we do HBs antigen donor screening of each individual donation, and here we employed three laboratories originally, until 2004, end of

2004, one in Round Lake and one in New Brunswick, and they used Abbott Auszyme monoclonal antibody assay, and a third facility in Hoover, Alabama, where we had employed a genetics system, HBs antigen I 2 and 3.

Since November of 2007, we have generally concentrated all our testing on Abbott PRISM test in our Hoover, Alabama facility, so all donations are now run through this test in Hoover, Alabama in a concentrated format.

Also, our HPV screening is done in pools, in pools of 512 samples, and this pooling was originally performed in our facility in Round Lake, Illinois, and since September 2004, we have everything concentrated again in our Hoover lab in Alabama, where all the donations are pooled for further testing.

Here, I show you results of ten years of routine screening of BioLife North American plasma samples. As you can see here, the HBs antigen screening test, we have split in two rows. This set of data concerns the Abbott Auszyme and genetic systems tested donations, where we had some subjected about 5 and a half million donations, and we found 27 HBV, not only positive donors – this is not donations, this is already donors, in five and a half million donations, which resulted in a net yield of 1 in 232 thousand donors per tested donations.

When we switched into Abbott PRISM routine screening, we subjected ten million donations to this BioLife HBV PCR and we found 8 positive, not only positive donors, which resulted in 1 and 1.2 million HPV, not only rate. As you can see, the introduction of Abbott PRISM has reduced the NAT only yield by a factor of 5.5. This, I think, is quite remarkable, and of course reduces the importance of NAT screening for HPV with such a sensitive antigen testing serology test.

We have added, as I told you, or used NGI also to test some of our samples, and this is the result here. We have summarized here the data from 2007 to 2010, and again split in the two assay systems used. In 2007 we still used the Genetic systems, sent 3.3 million donations to NGI. They found 18 of them not only positive, which is 1 in 185,000, quite remarkably comparable to what we have found with the BioLife assay.

Again, after 2007, we had used Abbott PRISM only, sent 4.2 million donations to NGI. They found 4 HPV NAT only positive donors, which gives a result of one in one million HPV NAT only positive donor tested donation. So this data set is remarkable, comparable as we also found that in the case of using NGI as a system, we also got the 5.7-fold reduced NAT-only yield with donations that we had subjected to this screening.

It’s also very important to note that all the other aspects, of course, are similar, so only two different tests have been used, which are independent of each other and yielding very comparable results with respect to NAT-only positive donors per tested donations.

So in summary, we believe that the implementation of this Abbott PRISM screening system has changed the number of NAT-only positive donors by nearly six-fold as compared to the previously used HBs antigen donor screening assays without changing anything on either test, both the BioLife as well as the NGI test are remaining the same over this period of time.

Now the question has been asked whether the sensitivity of HPV NAT has an influence, or if you ask what influence it has, and just to set the screen, and it has already been touched upon, first of all we refer to 95 percent cutoff. You can see other numbers, 50 percent or so, but the 95 percent is the common denominator, which is the concentration of HPV DNA that is detected positive in 95 percent of NAT tests. The other type of sensitivity, if I may say so, is the sensitivity that is seen on a single donation level, and that of course is derived by the fact that NAT is tested in mini-pools and making mini-pools means that the single donation is diluted and of course

then has to contain more of the virus to be detected positive, 95 percent in a mini-pool situation.

So the calculation of the 95 percent cutoff in a single donation is straightforward. You have an analytical sensitivity in the case of an assay, 11 IU/ml, and we use 512 samples in one mini-pool, so in order to detect 95 percent of our tests, we need 5,632 IU/ml to have a reliable positive result.

There are, of course, factors that influence the kind of calculation or sensitivity, and it's very obvious; either you have a very high analytical sensitivity or you have to choose the right mini-pool which, in other words, is the dilution factor, in order to play with the sensitivity on a single donation level, and here I show you the 11 IU of our BioLife assay in a pool of 512 results; it is already stated, 5600 IU/ml, the Novartis Ultrio commercial assay available on the market has an analytical sensitivity of 10.4, but they are usually implementing this assay in pools of 16, which gives you a sensitivity on a single donation level of 166.

Now this is, of course, a difference, but it's very interesting to note that the BioLife assay, as I say, it refers to 5,600 IU/ml while the NGI assay, having an analytical sensitivity of 0.9, used in pools of 512, comes out with 460 or something IU/ml, so this is a lot more

sensitive, but I have shown the data in our hands; we didn't find a single donation yield case more, so obviously in our scenario, using highly sensitive PRISM to screen single donations before we subject the - non-reactive, qualifying donations to NAT did not yield more cases in a sensitivity of 5,600 or 460.

Now there are some data published, mainly from the blood transfusion scene, as compared to our data that I have shown you, which is of course plasma for fractionation based on serology screening in PRISM. I showed you 1.2 million donors, one donor in 1.2 million donations. When we look at data that have been published for transfusion, seen in pools of 16 or even ID NAT, there is a better, higher yield, of course; but when you really study all these data you will see that there is a lot of chronic infection or occult, very low level donations which are caught by such small mini-pools or even ID NAT. So in other words, compared to 512 pool, this is a 50 to 500-fold increase in test numbers, so this is one or two logs, and the test yield is relatively small, maybe a factor of two or three.

Similar data have been published using the Roche systems that you have seen more details; they were carried out in 24, 6 or ID NAT volume or mini-pools, and you can see that they had a yield in 1 in 600,000. Also they were

still using the previous assays to previous generation, and we have, of course, no indication what that would mean in case of PRISM in front of this testing.

More recent data that have been published just a couple of days ago, at least available on the internet, from transfusion conducted by Dr. Stramer, comparing Ultrio and Roche assay, they came up with numbers, with ARC, using PRISM as a screening assay, they have published now a number of 1 in 900,000 donors per 900,000 donations. This is in this new paper.

So is there a benefit for the patient? We believe yes, there is a small added value for the patient by preventing transfusion of the low level HPV DNA-positive units that have escaped the HBs antigen screening, and they could potentially transmit Hepatitis B.

For plasma that is intended for fractionation, we do not see an added value in having small pools or higher sensitivity because that very low viral load of HBV that is possibly entering the production pool is very reliably inactivated and removed, and you have seen the measures in place by the previous speakers. So the current HBV of 512 minipool assay in our hands assures that the maximum level of virus potentially entering the production pool cannot exceed the validated safety level of the virus inactivation measures.

So in other words, we are assuring a safety margin which can be achieved by these measures and we can assure that the safety margin is not exceeded and all the other following measures can, of course, work according to need. So we maintain a virus reduction and inactivation capacity for HBV on the order of 9 logs or greater.

So in conclusion, we believe that the introduction of HBS antigen screening with the PRISM assay has already reduced the number of HBV, not only donors, by a factor of six, and testing in small mini-pools, or in other words, in very high sensitivity on a single donation level, increases the yield of HBV NAT, only donors by a factor of 2 or 3, as compared to a minipool of 512, so in other words, for patients who receive blood products for transfusion, such testing may be beneficial because these very low contaminated donations may be screened out or intercepted, however for plasma for manufacturing, testing in such small minipools does not provide the definite benefit over the current process, taking into consideration pathogen inactivation, and at the same time, we add a tremendous workload and additional complexity when we have to handle 100 to 500 times more samples, and therefore we think that the intended use of the product, either direct transfusion or further manufacture, should determine the most suitable testing regimen. Thank you very much.

DR. HOLLINGER: Questions? So I guess, Dr. Zerlauth, so you're saying that from your standpoint, if a sample is not HBs antigen positive, given the inactivation procedures which are in place and so on, with the testing and so on, then there is very little relevance to worry about samples which are not HBs antigen positive.

DR. ZERLAUTH: Yes. We believe that in this regimen that we apply, if an HBs antigen-negative donation which is further processed for NAT screening, will be screened out if the individual viral load is beyond 5000 IU/ml, otherwise it may or may not be detected, of course as a matter of statistics, but basically it may not be detected, may enter the production pool, and the production pool may never be more loaded as compared to this limited number; everything else will be screened out anyway.

DR. HOLLINGER: Yes, Dr. Gilcher?

DR. GILCHER: With more and more donors that are entering both the voluntary sector donor pool and the paid sector donor pool being immunized with Hepatitis B vaccine, how important is this in terms of adding a safety margin, but also of reducing the detectability by surface antigen and therefore making HBV NAT even more important?

DR. ZERLAUTH: Vaccination for HBV, I think, is certainly a very useful protective measure, but it is not implemented all over the world in the same way.

DR. GILCHER: But in the United States, virtually every child entering the school system today is immunized for Hepatitis A and B, and I would think that this would play a role in reducing the number of surface antigen positives that we're going to pick up; both in the voluntary sector and in the paid sector, because these donors are getting older and they're entering the donor pools, is what I'm getting at, that's a comment, but my question is how important is this, and would it affect the detectability of surface antigen, because you're going to have neutralization occurring; if somebody were reinfected at a later point, they would respond more quickly, as we heard from a prior speaker, it would be a subclinical infection, but therefore, the surface antigen would be removed more quickly and there would be more likely to be HBV NAT present in the plasma. I think that's what I heard.

DR. ZERLAUTH: First of all, data that are occurring now in the literature relatively recently with breakthrough infections showed that the viral load is extremely low, so even at the level of 500, we wouldn't see it. You would have to go to ID NAT, or maximum pools of six, to have a chance to see these infected people. That is published.

About the health impact, I would rather refer to specialists in infectious disease, like Dr. Alter, what that would mean in the population, but from a screening point of view, I'm absolutely convinced that these viral carriers, or carriers of virus, will not be screened out by 500 either; that is pretty clear from the data that we have so far. Either you can have a relatively high level, as we have shown, which is in the range of 5000, or you have to go to ID NAT; there is hardly any gain in between.

DR. HOLLINGER: Yes, Colonel Rentas and then Dr. Biswas?

DR. RENTAS: Would you say that testing of a minipool of less than 512 would actually increase the safety of this product as far as yield cases?

DR. ZERLAUTH: No, I don't think so.

DR. HOLLINGER: Dr. Biswas?

DR. BISWAS: I just needed to correct something that I said earlier. In regard to the older HBsAg tests I forgot the decimal point. What I should have said was that depending on the procedures that were used in the OSIGN(?) test, the sensitivity was 0.27 nanograms per ml, to something like 50.46 nanograms per ml, so I wanted to correct that.

Now in regard – can I just say something about the breakthroughs? We discussed this quite a bit two years

ago, when we were discussing blood for transfusion, and at that time, Sue Stramer had looked through the breakthroughs, and what you see, basically, is a low viral load. Sometimes they do seroconvert to HBsAg, sometimes they don't. If you follow long enough, you do see, generally, an anti-core does develop. What's important is that of course, these people who get breakthroughs are anti-HBs positive, you know, because of the vaccination that they've had earlier.

Whether they're infectious or not, as far as transfusion is concerned, we don't know, but I think Harvey Alter mentioned the precautionary principle, and our sort of assumption is that unless proven otherwise, these could be infectious when transfused into a patient.

So I just wanted to mention that.

DR. HOLLINGER: Yes, I think just in correction, I think that when Harvey – and I'll let him speak about it, but when he was talking about it, we're talking about whole blood, not plasma products –

DR. BISWAS: That is correct. How it works out in what we're discussing here, that's a different story.

DR. HOLLINGER: Yes, Dr. Nikasi?

DR. NIKASI: I'm struck by the yield cases in your analysis; 1 in 1.1 million or 1.7 million or so; and when we heard the other presentations; we heard a yield of

1 in 15 or 1 in 35, or whatever that was. In my opinion, do you think that you are missing the yield because the sensitivity of your assay LOD is not that sensitive as compared to what we heard, other ones? Or is it because of that, or is it because your source plasma donors are so good that their problem rate is much, much lower?

DR. ZERLAUTH: There are two answers; one is, first of all, we report donors, not donation by donation; that makes a difference in the repeat donor scenery. We can have five or six donations before we have a result. We count the donor, or whatever positive donations, that's one thing which is very important. Otherwise, from a sensitivity point of view, I'm absolutely convinced that we're not missing positive donors, because the NGI assay and our assay are absolutely independent and yield very comparable results in a cohort, which is very much framed BioLife donors of North America, so I do not think that we miss any positive or significant amount of positive donors. I think this data are very consistent because we have two absolutely independent assays yielding very comparable results.

DR. HOLLINGER: Okay; I think we're going to take a break at this juncture. Wait, I'm sorry, Susan, you had – sorry about that.

Agenda Item: Summary

DR. ZULLO: I promise I'll keep this very brief. It's thirty-six.

Okay; I just wanted to come back for a minute after you've heard all of these presentations which we appreciate, I just wanted to provide you a very brief summary of the potential benefits for HBV NAT for source plasma from the FDA presentation this morning, just because it's been a little while, before we present the questions to the Committee after the break, and the discussion.

We just want to. FDA would just like to emphasize that source plasma for further manufacture for plasma derivatives is safe, with current standards.

But HBV NAT, from what we've heard, would marginally increase the safety of fractionated products; even with the viral inactivation that we've heard is very robust, particularly for HBV, but there is an added margin of safety, and HBV would have a secondary public health benefit for source plasma donors and their contacts.

Again, HBV NAT for source plasma may enhance the margin of safety of plasma derivatives by interdiction of these yield cases that we've heard about today. We've seen yield rates of approximately 1 in 9 thousand and 1 in 35 thousand in most cases, and these are those HBV NAT positive, HBsAg negative units. By closure of the window period, when the donor is infected with HBV but does not

yet have detectable HBsAg, and again, there is the second window period that we talked about, when HBV DNA persists but the HBsAg has also dropped below detectable levels, and by an estimated five-fold improvement in analytical sensitivity over HBsAg, and this is, we're trying to lower the maximum viral titer in the plasma fractionation pool, and this suggests, by an estimated factor of 5 or 0.7 logs. And for public health, we believe that HBV NAT for source plasma may improve health by allowing for earlier donor notification based on both HBV NAT or serology results, earlier counseling and access to medical treatment and prevention of secondary transmission of HBV infection to donors.

And with it, I'll just leave you with the questions for the Committee; I don't know, Dr. Hollinger, if you wanted me to come back to those afterwards.

DR. HOLLINGER: Thank you. Okay, so we are going to take a break now, and I have 11:12, so we'll take a break until around 11:30.

(Break)

Agenda Item: Open Public Hearing

DR. HOLLINGER: This is the open public hearing. I'm going to read the Open Public Hearing statement.

Both the Food and Drug Administration and the Public believe in a transparent process for information

gathering and decision making. To ensure such transparency at the Open Public Hearing section of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. So with that as a background, we have two speakers who have asked to talk at the open public hearing, and the first one is Dr. Jeff Linnen. Jeff if you want to you can come down here, but it's up to you.

DR. LINNEN: I am Jeff Linnen; I'm from GenProbe in San Diego. We're primarily a molecular diagnostic company. We have been in a long-term partnership with

Novartis for blood screening products that started in 1998 and actually a while back, we extended our contract until 2025.

But what I'd like to do is provide a little bit more information about the Ultrio assay, some current data on the yield in whole blood donation. I'd like to give a real brief update on some of the results with respect to source plasma screening for the next generation for our Triplex NAT assay, the UltraPlus assay.

The Ultrio assay, as I said, is a triplex assay. We screen for HIV, HCV and HBV. This assay is based on TMA, transcription media and amplification. The assay detects a wide variety of genetic variants of HIV, all the genetic variants of HIV, M, N, O. We use two regions of the HIV genome to amplify and detect. Likewise for HCV and HBV, all the genetic variants are covered by the assay.

This assay is, as mentioned earlier, licensed for individual donor samples and pools of up to 16 donations, and this includes a claim for screening source plasma. The assay can be used on two platforms, and a semi-automated platform, but it's primarily used worldwide on a fully-automated TIGRIS system.

And this is the TIGRIS system. This is a high throughput instrument, and by that, I mean the instrument generates a thousand results in 14 hours, and you see the

first result in 3 hours and 38 minutes, and that's followed by about 100 results every hour.

The important thing about a system like this is it's fully automated and has process controls for all the steps that occurred, so what I mean by that is there's positive identification of the sample from the time you put the primary tube on the instrument to the time you get the result, all the incubation times and temperatures are tightly controlled. If any are out of specification, there's a flag that would invalidate the result, so that's one of the major advantages of where NAT assay testing has evolved to.

This assay is in routine use, now, for donor testing and pool testing worldwide, and there are about 300 instruments installed. So the point here really is that NAT screening is practical, there are systems like this available, and they're in routine use worldwide.

Just very quickly, you've seen some of the analytical sensitivity data, also shown the data for HIV and HCV, but what I've also added here are the 50 percent detection levels for HBV, that's in IUs per ml. The other thing that I want to point out with these kind of data is that there's a competence interval around the value, and it varies from experiment to experiment, so a lot of times we talk about as if it's engraved in stone, but it can vary;

it can vary from each time you re-suspend the WHO standard, the kind of results you'll see.

But this is what we see, again, 10.4 IUs is the 95 percent detection level and it ranges from about 9 to 12 IUs. This is directly from the Ultrio package insert.

Now here's some up-to-date data. This was provided by Sue Stramer at the American Red Cross. What this is showing is Ultrio yield cases, shown by donation testing site. So you can see Charlotte, Detroit, Philadelphia, Portland, St. Louis. And this is all, I have to emphasize, whole blood screening, and this was done in 16 donation pool testing, and it covers the period of June 22 of 2009 to February 28, 2011. So it's pretty current data and it gives you an idea of how much HBV is being found in this population with an analytical sensitivity that I showed you on the previous slide.

So you can see, the HIV yields. HIV, if you add the data from all the sites, is close to 1 in a million. HCV is seen at a much higher rate of about 1 in 180,000, and you can see the HBV yield when you look at all the testing in the American Red Cross system, is currently running, at least for this period of time, around 1 in a million. And this varies somewhat from what was demonstrated in the post-marketing trial for the Ultrio assay. In that study, which was published a while back in

the New England Journal of Medicine, in January, showed a yield rate of about 1 in 410 thousand. That was nine additional yield cases to the eleven that are shown here. And the reason that differs is because the trial did not include the entire United States, but it did include the Charlotte site. That's one of the things that probably becomes pretty obvious, is that the yield rates vary considerably based on the geographic region of the United States. The Charlotte testing includes a large portion of the Southeast of the United States, so you can see, for all three markers, the yield rates are higher than the other American Red Cross testing sites.

The next slide, and I think this is my last slide, I just want to say a few things about the next generation screening assay. This assay we call Ultrio Plus. This also runs on the TIGRIS system. We received a CE mark for this assay in 2009, so it's currently being adopted in Europe and in Asia. In a number of experiments, what we see analytically is a threefold enhancement of HBV analytical sensitivity versus the Ultrio assay, so if you remember the 10.4 IUs for Ultrio, you'd basically divide that by three, so the analytical sensitivity for the Ultrio Plus assay is somewhere in the ballpark of 3 IUs.

We are seeking licensure in the US, and we recently completed a clinical trial in March of this year,

and there is one presumptive HBV yield case that's come out of the source plasma testing, and this has been confirmed by an alternates NAT, which was a PCR assay. We have not demonstrated sero-conversion of this sample. We have done additional testing of the sample because, as you've heard previously, anti-core testing is not done in this population. We tested the sample for anti-HBC and found that it was nonreactive. We are in the process of getting some anti-HBs results for this sample.

So the yield rate in the clinical trial was 1 out of 16,000 source plasma donations, and we are seeking a claim for source plasma screening in pools of sixteen, so this will be very sensitive testing for this population.

I just want to emphasize this is not FDA-licensed, and the assay data that I'm updating right here have not been reviewed by the FDA.

I think that concludes my presentation. I just want to thank you for the opportunity to give this talk.

DR. HOLLINGER: Thank you, Dr. Linnen. Any questions? Not seeing any, I think we'll move on then, to the second person who has asked to speak, Dr. Andrew Heaton, from Novartis.

DR. HEATON: Good morning, and thank you for the opportunity to speak. My name is Andrew Heaton, and I am the Senior Director of Transfusion Medicine at the North

Shore LIJ Health System, which is the United States' second largest not for profit, non-sectarian health system. I'm also Professor at the newest American medical school, Hofstra University Medical School. We're also a very large consumer of blood products. Our blood bill is 60 million US dollars per year, of which approximately 25 million is derivatives and 35 million is traditional whole blood components. So we're a major consumer of both derivatives and whole blood products.

My remarks today are driven by my past experience, where I was Chief Medical Officer of Chiron Novartis, during which time I was responsible for the design of a number of clinical trials and also for three scientific advisory committees looking at HBV in different global sectors of the United States, Europe, especially Eastern Europe, and Asia.

As you know, plasma safety is really driven by three key avenues. One is reduced HBV load inactivation and HBsAg neutralization. I obviously will not comment on the second phrase, but I will comment on the HBV load implications of some of the trials that we supported and also talk about some of our experience with global vaccination.

Finally, this is one of the first NAT tests that's being introduced into a patient population that's

being vaccinated, and is therefore undergoing changes while you are introducing a new assay, and the implications of that vaccination are probably more significant ex-US than they are US, in areas of very high end domesticity.

And lastly, I'd like to express appreciation to both the National Heart, Lung and Blood Institute, and the FDA, who have driven nucleic acid testing, because this has been a major public health initiative, and has brought benefits to numerous patients.

The Red Cross trial was a very large post-marketing trial and included the TMA Ultrio assay. This trial included testing, epidemiology and follow-up. When we established the trial, we were very nervous about the pool size, because our original intention was to have a very small pool size, but Dr. Stramer, the principal investigator, was anxious to have a very large pool size. It's a huge trial, 3.7 million donations, 600,000 in IDT and 3.1 million pooled.

Several issues drop out of this. First of all, there were nine yield, of which six were immunized, five having low anti-HBs levels. So immunization has already affected this trial. These individuals were immunized; never were HBsAg positive, and therefore were only detected by NAT. In this trial, the yield was one in 410 thousand donations, and three donors became HBsAg positive. Of

interest, one incident case did not become HBsAg positive and in fact, we've now, in effect, created a new definition which is primary occult HBV infection, where the donor never is HBsAg positive and passes directly through DNA to anti-HBs and anti-HB core.

Interestingly, 44 percent of the randomly selected donors were positive for anti-HBS, and the cases which developed, which were NAT positive, tended to have HBsAg levels at the lower end of the range, in the population that was studied.

Finally, you can see some of the effects of the vaccine, and this is mostly a recombinant vaccine, which is targeted toward the A2 antigen, and you can see the bulk of the individuals who developed bypass infection, who were infected with variants, not A2.

The next slide begins to look at the infectivity of occult cases. Remember, the US, Canada and a few other countries; Germany and the UK, now test for Hepatitis core, the rest do not, and in non-HB core testing countries, 60 percent of NAT yield in general is occult yield, and 40 percent is window case yield. There has been a tendency to view the window case yield as not especially significant. This trial summarizes a series of reports, the best of which is by Dr. Gerlich from Geissen, but a group of other reports, which shows NAT-negative cases, the majority of

which, six out of the eight, were anti-HBC positive, most were anti-HBs negative, most had relatively low viral loads, but four of these cases were fatal in the recipients, so you may reasonably conclude that occult infection isn't necessarily of minor risk.

If you look at look back studies, and there's really four good quality look back studies, for one US, which is the Moseley study, very good theories out of Japan, a more recent one out of Hong Kong, and the most recent one from Saledo(?) in Spain.

The US study really established a lot of our current thinking in that it showed that donors who were positive for both anti-HBC and anti-HBs had a relatively low infectivity rate, that the highest risk was the HBC-only donors. This, in fact, was compounded by the Japanese study, though this was somewhat different. The Japanese study was a retrospective study driven by donors who had sero-converted to HB core or who were positive on pools and they went back and looked at IDT testing, but nevertheless they showed low DNA window period positive high infection, whereas in the presence of multiple antibodies or low load, there was lower infection.

The Hong Kong study, which is probably the most recent one, studied 67 occult B donors. All were anti-HB core positive. Ninety percent had anti-HBsaB. They had

one yield case definite, and they had seven other cases where the recipients experienced a sudden and very significant increase in anti-HBs, after the transfusion, probably implying subclinical infection.

So what you can conclude from this is that occult cases are infections; they do confer significant risk, there's no doubt that anti-HBs adds to the protective effect but is not necessarily complete.

In addition, HBV NAT testing is also a vast public health experiment in that large numbers of normal people are now being tested for HBV NAT and it's possible to begin to detect different modes of HBV infection, and in fact, there's now a series of reports which are summarized here, which are cases that develop HBV DNA, they pass to HBsAb and HB core AB positivity without ever being HBsAg positive. And these are conventionally classified as probably primary occult infections.

Now we heard this morning that the plasma industry's perspective is that these cases are low viral load, of low infectivity, and they don't present a very significant risk to the system, but in practice these are PRISM negative, core testing is not done for source plasma donors, and a number of these have quite significant loads, and in fact, in a number of studies, there's a South African study about to be published, somewhere around six

percent of the HB seroconversions are primary occult and 95 percent are HBsAg positive, so I think that one would have to reasonably conclude that through a vast public health experience, we are identifying a subgroup of patients who do have high viral loads, who do seroconvert, but who never have HBsAg.

This leads me to a slight diversion in the area of vaccination. In the American Red Cross study, 44 percent of the recipients were vaccinated, and they have experienced, with that study and the subsequent one, that Jeff Linnen just reported, three breakthrough cases, so three cases developed A2 infection after being immunized with A2 vaccine.

In addition, they had five subtypes that were picked up of different types, F, D, and I think an E, so a key issue with blood safety, therefore, is the capacity of an assay to detect subtypes.

In the US population, the effect of vaccination has been to drive down the incidence of anti-HB core antibody positivity. CDC recently published a study showing that HB core positivity in young people dropped from 0.6 percent to 1.2 percent, and in adults it dropped from 5.6 percent to 4.6 percent, so we are reducing the antibody load in our input plasma, so there will be less

protective antibody in the feed stock that's used for plasma processing.

In Taiwan, which is probably the first and lead country that's done vaccination, the number of mutants as a percentage of total HBsAg pickups has increased from about 8 percent 20 years ago to about 23 percent now. Now interestingly, they showed very little sideway transmission of mutants, and they did show a general decrease in the total prevalence of mutants. But one of the effects of vaccine in a highly endemic country is to drive the creation of mutants and their infectivity and the ability of an A2 antibody to inactivate it in a fractionation process is completely unknown.

So one of the effects of vaccinations, then, is to drive increasing subtypes, is to drive more mutants and it will reduce the antibody levels in feed stock, raw material plasma.

It's a general truism, of course, that the lower the load of HBV that goes into any patient or into any plasma raw material, the lower your load, the less the risk days. This is a study generated by Verston and Nikolali(?) who I used to work with, looking at a weighted; i.e., an infection dose weighted risk, starting off with PRISM, moving all the way down through pools of 16, pools of 8, to Ultrio ID, to Ultrio Plus, and the main point of this slide

is to show that your more sensitive assay results in the greatest reduction of the risk.

So lastly, I hope that I've given you a sense that the ARC trial identified a number of both breakthrough cases and bypass cases, it also identified an incident case, a primary occult HBV case. I hope I've shown you that post-transfusion HBsAg negative cases do occur in occult countries and they can be fatal, that low loads can be infectious, and in fact, as Jeff Linnen just reported to you, the NAT assays are very broadly specific, and pick these variants up, and lastly, I'd like to support the position of the FDA that very high broad specificity of the assays are a major priority for public safety and for the safety of plasma fractionation products. Thank you.

DR. HOLLINGER: Thank you. Questions?

Just perhaps a little clarification; on the study he talked about in the New England Journal of Medicine about the vaccine group, it's important to understand that of the six individuals that were investigated, none of them developed clinical disease. There were no ALT abnormalities in these, followed up for long periods of time, at least 250 days or 300 days, and the levels of virus were less than 100 IU per ml at all times, so I think that's important.

Also in the study in Taiwan that he mentioned about the increase in the mutations, 23 percent, that's 23 percent of a very low number, because the number of patients who developed Hepatitis B after vaccination was extremely small, so there was no increase in infection, based on these mutations, at all.

DR. NELSON: However, I think in the Taiwan data, in those who have been vaccinated more than 25 years ago, the rates seem to be increasing. So we have experience, but in the future there may be a change in the risk.

DR. HEATON: It was interesting, in the Taiwan data, that there was very little sideways transmission of the mutants, and the point – the tide went down, it's absolutely true, there's a lot less HBV infection, and therefore there's a bigger percentage, the total number we down.

DR. HOLLINGER: Now before we close the open public hearing, is there anyone in the audience who wishes to speak to the Committee?

If not, I see no one wants to speak, so I'm going to close the public hearing and we will move into the open committee discussion, followed by some questions for the Committee. So I'm opening this up for any discussion of what was talked about this morning.

Agenda Item: Open Committee Discussion

DR. TROXEL: I have, I guess, a comment – it seems to me that there's wide agreement that the current processes that are in place result in a safe product, and that those processes include, among perhaps other things, but the things that we've focused on so far today, have been the HBsAg testing, the NAT testing, and the pathogen reduction and removal of processes as part of the manufacturing.

And the relative contributions of those things to the current safety are quite unclear, although it also seems that the NAT testing is adding marginal incremental value which is non-zero, but which is probably fairly small.

It seems to me that we're being asked about a formulization of these currently active processes from voluntary into required as part of regulations.

And I guess my big question is what is the down side to doing that, if it really wouldn't change the current practice very much? Because normally there is some cost involved, although there's been very little discussion of cost, which is a little bit odd, because we're asking about benefit, and it seems that there is some benefit, although it's likely small, and if you then translate that into cost benefit it's not so clear that the benefit part

is really going to outweigh the costs that would be involved.

I don't have a good sense of what those costs are. Maybe there are costs involved with demonstrating compliance which now are not required because it's voluntary. Presumably the actual cost of performing the testing and all of that won't change very much because that's already being incurred by the current practice. So I'm a little unclear on what the practical consequences would be of our potential recommendation to go ahead and formalize these into active regulations, and I don't know if others have some of the same questions, or perhaps answers to those questions, but it would help me a little bit to get a better sense of the relative burden that would result from all of this; in terms of actual financial cost or organizational issues, with blood centers or other things; I'm not so clear on that.

DR. HOLLINGER: But in the past, the Committee has been told, off and not to deal with cost, as an issue, although I think it's a really critical question, but that's usually been the case, is for us to look at the science and evidence of whether this is reasonable regardless of what the cost is, am I correct? Sorry; that was a good question, and good comment. Yes, Dr. Alter?

DR. ALTER: I think the main question, the question one that we've been asked, is kind of a do you love your mother question, and it's hard to say no, no matter what you really feel about your mother – there is no harm in doing what you're proposing to do. There is a theoretical increase in safety, but you cannot measure improving zero risk. We're virtually – if you look at the process we have, the donors are tested twice before they enter the system, the plasma is put on a hold so they can be retested again, the pool is retested, the sensitivity of the PRISM test is tremendous, though not as good as HBV DNA. The fractionation procedure further reduces the risk, and the inactivation brings it down, so we're talking about log reductions that haven't been seen since Paul Bunyan. Even if some mistake is made along the way, it's virtually impossible for an infectious unit to get through starting with the low titer you have at the beginning.

So I have no objection to doing this, but I think the benefit is immeasurable. I think if you follow these patients prospectively for another 20 years, you won't find a case that got through with our existing methods. And the cost isn't going to be that great; we don't talk about it but it's not going to be that great, it's being done.

So it's kind of why is it coming up, why are we thinking about it, for the volunteer system it was

important, for this system it's redundant. We're into belts, suspenders, safety pins and now maybe crazy glue protection. It's a lot, and yet it's my mother, and if you want me to like her, I like her.

DR. HOLLINGER: So Harvey, I tend to agree with you in many cases here on this, so from your standpoint, if the issue is one that – let's not deal with the question of whether it should have been done in the first place, the HBV DNA testing should have been done in the first place, that's one issue, but assuming that everybody, or most of the plasma organizations are doing HBV DNA testing, is there then some benefit of having some regulation, standardization or something like this for new companies that come in that want to do testing in this arena? Is there some advantage to that without having a lot of regulation, but having certainly some minimum standards that must be met, given the fact that – I didn't hear a percentage of plasma facilities are actually testing with HBV DNA – what do you think?

DR. ALTER: It's important to have a regulation if you think the test is important, so it's being done voluntarily for reasons that may have had to prevent the pools from having to be disposed of at the very end or something like that, so if you feel this test really adds something, then it's important to have it as a regulation

and not depend on voluntary things. If you feel it's a choice that the margin of safety is so miniscule that you can leave it up to the fractionators to decide whether they want to do it or not, I think you can make either argument – it's cleaner to just make it a regulation, say everybody's doing the same thing, the downsides are very small. I'm on the fence what to vote for, but I just – it's just kind of a principle. Do we just add a test because we have it and not because we really expect it's going to give us much?

DR. HOLLINGER: Yes, Jeanne, please.

DR. LINDEN: I'd like to just follow up on something that Dr. Alter said that pertains to picking up window period infections. This 60-day hold, it was my understanding, is not a quarantine period, that people may come back, they may not come back at all, it may be two days, it may be two weeks. They wouldn't all necessarily be tested at 60 days. Can somebody from the plasma industry clarify that? How far out do most people get?

DR. HOLLINGER: Would somebody clarify that about the 60-day hold? And my understanding is that not everyone has to do this, that that's one of the conditions, but that not everyone needs to do a 60-day inventory hold. Could you answer that one too? I think the question is, explain the 60-day inventory hold; what exactly is it and what is

required, and then secondly, does everyone, all plasma fractionators, need to do this, so we have an idea about what this inventory is.

DR. LINDEN: I would also say, if it is only a hold, how far out do most people get retested?

DR. HOLLINGER: I think there are probably going to be a couple of more definite answers for this, but I'll handle the easier one first, because that's what I'm qualified to do. The fractionator that is QSEAL certified will follow the 60-day hold. That's a part of the PPTA requirement. For another company who is not certified, it may happen if it's part of their normal standard operating procedures anyway. But from the PPTA standpoint, anyone who secures QSEAL certification is indeed doing that.

Now as far as the actual way the plasma moves through the system from collection through to fractionation?

DR. LINNEN: Well, it's not released for fractionation until you've gone through the 60-day quarantine, and at that time you've had multiple donations at that point. The donor has come back and donated again and you've got additional test results on subsequent units at that point.

DR. LINDEN: It that a quarantine?

DR. HOLLINGER: It's not a quarantine hold. You don't get the unit, then wait sixty days and then release the unit. What you do is that a person comes in today and donates today and they're negative. They come back on Monday and they're negative again. Then they wait 60 days from today to see if he ever came in again during that 60 days in order to release today's collection. And if he doesn't come in, then those are not used.

DR. RUTA: No, no, if he doesn't come in and there's not a positive donation – you need two negative donations to release today's donation, but you don't need one 60 days from now to release today's donation. They're simply held for 60 days and then released.

DR. LINDEN: So what if the person comes in again, actually doesn't change decision 60 days later, right?

DR. EPSTEIN: The hold is a quarantine in the sense that each collected unit will sit in inventory for 60 days before release, but it is not a quarantine retest in the sense that if the donor does not reappear at the end of 60 days, the units that were in the quarantine are released, so it's a quarantine hold, but it's not a quarantine retest strategy.

DR. NELSON: So the person could have an occult infection and not reappear during the 60 days and you wouldn't have any contrary evidence –-

DR. EPSTEIN: That's absolutely correct. If the donor had occult infection and did not return within 60 days, the unit would be released for use.

DR. HOLLINGER: Thank you for clarifying that. Yes, Colonel Rentas and then Dr. Gilcher.

DR. RENTAS: You know, this test, and I will say probably the reason why testing is already going on, for the most part it's already part of a multiplex testing that includes HIV and HCV, so they're going to do it no matter what, because it provides them with the flexibility to have another test already combined with other two markers out there, and I know the FDA doesn't want us to talk cost, but it goes right along those lines.

I think the biggest benefit out of making this mandatory will be on number three there, and it will be the health benefit that this will provide. I think Dr. Hollinger, you mentioned this – paid donors – sero-prevalence rates are much higher than voluntary donors, and the sooner we can get these donors off the donor pool, the better off we are, and if we can counsel them and we can seek appropriate medical care for them, again, the sooner we can do that the better off we will be.

DR. HOLLINGER: Dr. Gilcher?

DR. GILCHER: I'll reiterate what I said earlier; that I like the concept of backup redundancy, but I also want to add that I like the concept of standardizing the testing. Currently, we've heard that for almost ten years, testing has been done by the source plasma industry. However, it's not required, and if we were to standardize it, we could set the rules, so to speak, in place, and I believe that this would be a benefit, to standardize the concept of the testing, which it's not.

DR. HOLLINGER: Dr. Epstein?

DR. EPSTEIN: Yes, just in follow-up to the remark by Colonel Rentas, the investigational tests, BioLife and that of the National Genetics Institute, are in fact not multiplex tests, and those are the predominant tests being used presently by the source plasma industry. Now that doesn't mean that there couldn't be evolution toward multiplex testing, but that the current situation is that it is not multiplex testing on source plasma testing for the most part. The reverse is true for whole blood.

DR. HOLLINGER: Dr. Maguire?

DR. MAGUIRE: A different question – what element of the safety system is surveillance, and I wonder if we could hear just a little bit about what that entails and are there data?

DR. HOLLINGER: Can you explain –

DR. MAGUIRE: This is Dr. Lee's presentation; it would be slides 4 and 5; we have the different steps that are taken to improve safety, and then at the end is surveillance, and I just wondered what that was all about.

DR. HOLLINGER: Can someone answer about surveillance? Most of the things that I think Dr. Heaton talked about were in whole blood donors, not in plasma fractionation systems.

DR. LINNEN: Right, and the surveillance we're referring to is the patient surveillance, or recipients of the product surveillance, and these we have - the industry, as well as regulatory agencies, require adverse event reporting, of which that's recorded, documented, and in the event of a sero-conversion or for any pathogen, it's captured and noted and investigated, so that's the type of surveillance we're referring to. It's standard for the industry, actually.

DR. HOLLINGER: Does that answer your question?

DR. EPSTEIN: Well this probably needs a little bit more elaboration, because you know, there's a whole separate dialogue going on with HHS about improving what we call biovigilance, including hemovigilance. For plasma derivatives, adverse event reporting is required, similar

to drug reporting, and the derivatives are under the mechanism of drug reporting.

Manufacturers have to report to the FDA, but there are certain caveats, and ultimately we don't have active monitoring. That's the point that I want to bring forward, that the recognition and reporting of events still depends on a passive system, except in the circumstance where FDA may require a post-marketing study to establish validity of the assessment of safety that was done under the license review. So that's a key point.

The second key point I would make about whole blood is that currently the required reporting is only for fatalities. Now we do require reporting of product deviations, which may or may not be associated with an adverse event. Once again, though, voluntary reporting is possible through the current system of MedWatch; any physician or individual can report. So I just think that it's important to recognize that a lot of what we've learned has come out of studies, as opposed to the current system of passive reporting.

DR. HOLLINGER: Dr. Alter?

DR. ALTER: I have to preface these comments with saying that I'm probably going to vote yes, yes, yes – but I think the public health benefits are probably going to be slightly greater than the infectivity benefits in the

recipient, because the latter will be zero and the former will be something. But I think this is an opportunity; we're guessing that it's going to be a public health benefit, but it's not clear how much that would be.

I think it's an opportunity to do a study. How many of these people with occult infection will be notified and do something about it? How many will be notified before they come back and are found HBsAg positive? Probably very few of these people are going be treated with this low-level infection. I think it's not so much treatment; we don't know how transmissible they will be to their sexual partners.

So there's a lot of things that could be studied here, and I think it could be a very interesting study and it won't affect the decisions today but it's an opportunity to do something.

DR. HOLLINGER: Yes, Dr. Nelson?

DR. NELSON: That's why I asked for some data on what happened to those who were final positive, and I think that it's obviously not the only, or primary responsibility, of the industry, but I agree. Because this is a high risk population. We were having increasing immigrants from Asia and --. I think it's important. And many of them may be plasma donors.

DR. HOLLINGER: Colonel Rentas?

DR. RENTAS: I was just going to add, in regards to Harvey's statement, that if the FDA regulates this, I am sure, as part of that guidance, notification guidelines will come as well. I'm a little confused now by the comment that Jay made about the testing on Multiplex, because as I read this, it talks about the Multiplex testing for source plasma using mini-pools. Are you saying that's not what we're using at this point?

DR. NAKASI: Can you repeat the question please?

DR. RENTAS: What type of testing is being used now to test source plasma; it's not multiplex testing, I guess.

DR. NAKASI: Yes; you have to differentiate multiplexing after multiplexing testing; means three tests at the same platform, versus multiplexing pools of 512 and then pooling down 512 and then testing, and that's the difference there. So there are assays. For example, GenProbe's assay, which is a multiplex. Or cobas TaqScreen, which is –- MPX, which is also – that is, all the three, HIV, HCV and HBV are tested at the same time. But what Dr. Epstein was saying, that the test used in the pool of 512, the majority at this point is done by using either NGI or BioLife, which is a separate test, which is not in combination with HIV –- at the same time. Is that clear?

DR. RENTAS: And those are under an IND?

DR. NAKASI: They are under IND, yes.

DR. HOLLINGER: Yes, Dr. Kuzma?

DR. KUZMA: Yes, the answers to 1 and 3 are pretty clear to me as well, for all the reasons stated; inability to consider cost, so I do think there's non-zero risk reduction, which would then allow me to vote yes on 1 and 3, but number 2, to me, is more debatable, and I would like to have some discussion about why the 500 sensitivity and the definition of minipools, so if – just from the experts in the room, why 500 IU/ml and what is the difference of minipools and could the FDA be even more aggressive by suggesting a lower sensitivity, given that some of the tests actually achieve a lower sensitivity and given the state of the science when rapid genomic testing is so feasible?

DR. HOLLINGER: Yes, Dr. Zullo?

DR. KUZMA: So why not 200? Or why not 170 or why not 100, to even spur more innovation in the field?

DR. ZULLO: Again, for clarification, this is in the mini-pools, so it's the individual sample diluted in either 512 or 96 or 16. So what we have right now, these are three licensed tests, and these are the LOD and maximum pool size, so right now the capability is from 166 to 423, and for NGI, theirs is currently at 460, that they claim,

and as you saw, BioLife's is at 5,632, so it seemed to be an attainable standard, an attainable level.

DR. KUZMA: Currently attainable. So that's the rationale for that number? I understood that in the presentation; so the premise that you're operating under is that we need to recommend a standard that is attainable currently on the market, is that correct?

DR. HOLLINGER: Yes. If mini-pools –

DR. KUZMA: I just wanted to make that value explicit. From a scientific standpoint, you would want an even greater sensitivity.

DR. HOLLINGER: Well if you want greater sensitivity, then they ought to be individual donations; they ought to be tested individually, then you would get down to 411 IU per ml, and so this is sort of a compromise, if you will –

DR. KUZMA: I wanted to make that explicit, because if we are compromising on this, aren't we considering cost, really implicitly? And why can't we test individual donations to be even more protective of public health? So that's just said – scientifically it seems feasible.

DR. ZULLO: Yes, and if you decrease the size of the mini-pools, you would also increase the LOD in the pools.

DR. KUZMA: Exactly.

DR. BISWAS: I'd just like to – it's not only that it was attainable, but also we knew from the clinical trials that they were getting yields; that was also another very important consideration. It's always a balance between what you can do and does it do any good? In this regard, the good is the –

DR. HOLLINGER: - and I think that's – so they come across at 500 because they're saying can you determine the minimum pool size, based upon a sample that has a level of 500 IU per ml that is added to that pool and therefore the pool will become positive? And that will be used to determine the minimum pool size. If you can't do that then you have to have a smaller pool size, if your test is not sensitive enough for that. Like we talked about, there was one – I think one of the tests, the BioLife test, had like five thousand –- level, so theoretically, if they wanted to do that based on this, they would have to drop their pool size tenfold, down to 50 or 30, in order to meet this standard, as I understand it.

The question was fairly difficult. I must tell you, understanding this area, I know what they wanted, but the second question, I struggle with that, really, to look at it and try to figure out exactly how you would word this so it could be understood.

But from my standpoint, I had a hard time trying to decide what to do about question one, because the question says do the available scientific data, available data, support the concept that testing source plasma by HIV NAT increases the safety margin of plasma derivatives. And it's really hard to say, because for me, anyway, since there's been no report of transmissions since 1988, the risk is zero, and that was at a time when they weren't doing HBV NAT afterward, for many years, and now we have more sensitivity of assays; for example, we have better, more sensitive HBs antigen assays, and in this case, if one says is there really a risk, and maybe we've missed it; it would be a little unusual. These are lots of material that are made in the fractionation, whether it's immune globulin or albumin or other things, Factor VIII, these are lots of things, so with lots made up, you would expect several cases of Hepatitis B occurring; not just one. This is not missing a Hepatitis B case in a recipient who's received one unit of blood from a donor.

So that's one thing. The other is that we now have effective viral clearance. There had been effective viral clearance methods, both for inactivation as well as particle reduction or virion reduction. We know that there's a very low concentration of virus in HBs antigen negative source plasma, and that level is running somewhere

between two hundred to two thousand IU per ml. It's true that above that, in about seven percent of samples, can be HBs antigen negative above two thousand, but I've never seen one more than 30,000 IU per ml that is HBs antigen negative, and it's true also the reverse, that you could have samples that are below 100 IU per ml, and about 7 percent of those will be HBs antigen positive, and that all has to do with the dual pathways in the production of virions, in addition to the production of HBs antigen.

And there are two pathways; one of them, in the hepatocyte, is expressing HBs antigen alone, and the other is expressing virions that contain HBs antigen. And so those two pathways are going to differ, and that's why you have this variation in the HBs antigen detection as it relates to virions. So that's another issue.

We also have to remember that there's a neutralization effect of anti-HBs in this blood. This is blood that's not tested for anti-HBC. So it has – about 80 percent of those units will have anti-HBs, with its neutralization capacity. So you have that also in these pooled samples.

We talked about the 60-day inventory hold that is present, and I've also broached the question, I do not understand, when we have a very effective Hepatitis B vaccine, why we don't require, or why the plasma industry

does not require their donors to be vaccinated for Hepatitis B and test them after six months, or seven months, before they enter them in, before they're allowed to donate blood, that they have made antibodies, and so on? Then there's not an issue of transmission at that point at all, and they wouldn't even need HBV DNA NAT testing. So I'm not sure I would have even agreed, personally, would agree to have done HBV NAT testing in the first place.

But now it's in, now it's used, plasma industry is using it, so then the issue is, then should there be some regulation, and so I'm struggling, really, with that first question. My tendency is to vote no because I don't believe that the data shows that there will be an increase in the safety margin. That's not to say that I feel that since the cat is out of the bag, so to speak, that one should not regulate it, and have some standardization at the time, so right now, I would almost abstain from that question just because I think of the difficulties, wanting the FDA to know that I really feel that if they're going to do this test voluntarily, that there should be some regulation. But I don't believe it's going to increase the safety margin.

DR. ALTER: I think you summarize it very well. That's what I've been trying to say; it's a theoretical increase in safety margin, it's a better test, it will pick

up something, but in the end, because you have this tremendously efficient inactivation procedure, it doesn't matter. In that way, the question is ambiguous, as they always are.

DR. HOLLINGER: Is there any other comments? Celso, you've been very quiet; do you have any comments on this one or not? I give you one minute, Celso.

DR. BIANCO: I'll remain quiet, particularly after your speech now.

DR. HOLLINGER: That means you liked it, or you didn't like it?

DR. BIANCO: Yes, I liked it.

DR. HOLLINGER: Yes, Jay?

DR. EPSTEIN: I just want to make a comment; how did we get to where we are? I think that the concept that drove this really goes back to 1999, when a European requirement was put in place to test the fractionation pool for Hepatitis C. And this led to the idea, and of course there were very good reasons to do that; we didn't have pathogen inactivation, there was known transmission of Hepatitis C from certain products, and this was a means of assuring safety of the end product by assuring the safety margin.

What is the safety margin? It's the difference in fold reduction between the maximum titer and the

inactivation, or clearance capacity, of processing, of manufacturing. So if you measured the Hepatitis C level in the manufacturing pool, the plasma pool, that you were going to go fractionate, if it was below a certain level, then you knew that you had a certain margin of safety because of the known log reduction of clearance.

But in order to achieve an NAT negative pool you have to screen donors, or donations. And the reason for that is that if you wait until you screen the pool, having not screened the donations, then you have a very high risk of having pooled a positive unit, and now you're going to reject tens of thousands of liters of plasma that you've already made into a pool that you're going to fractionate. So it's the testing of the pool that drove the donation testing. Now that was only ever mandated for Hepatitis C, but I think what happened here was an extension of the concept, so if we're assuring the robustness of the safety margin for Hep C, shouldn't we be doing that also for Hep B and for HIV?

And so you end up at the same place, which is if you want to assure the safety margin and you want to do the test on the pool, if you're going to test the pool then you have to test the donations. And the NAT test was seen as the most sensitive test you could do on the pool. So that's how we got to where we are. And what we're now

debating, in effect, is that marginal difference between assuring safe end products with and without NAT, and I think we would all concede that it's a marginal difference at best. I mean, a fivefold difference, if that's real, is 0.7 log, and we believe we have good evidence of 9 to 10 log clearance. So it's marginal. We concede that. But I think we also have to understand why it's happening. It's a way of assuring that that safety margin is real by testing the fractionation pool with the most sensitive method. So that's just to provide context; it's why there is voluntary testing going on.

And all FDA is saying is, well we realize it adds a limited benefit to HBsAg, but it's adding assurance of the safety margin and fractionation; the industry is already doing it, let's apply a standard.

DR. ALTER: That's very helpful. Puts it in perspective.

DR. HOLLINGER: Yes, Dr. Bianco?

DR. BIANCO: Just to make a comment, following Dr. Epstein's very good clarification. Maybe the question should have been should we have a standard, and not necessarily in the way it was worded, and that's what got us a little bit confused.

DR. HOLLINGER: Agree. Any other comments before we go to the questions and vote?

Okay, so Susan, would you read the first question and we'll vote down the line, one, two and three.

Agenda Item: Questions for the Committee

DR. ZULLO: Question Number One. Do the available scientific data support the concept that testing of source plasma donations by HBV NAT increases the safety margin of plasma derivatives?

DR. HOLLINGER: So you have on your thing here, you have yes, a plus, you have zero, abstain, and you have a minus for no. So let's everybody vote.

DR. EMERY: The Committee has voted, and it has voted ten yes, one abstention and no nos. I'm going to read the individuals.

So, Dr. Maguire is a yes, Dr. Alter is a yes, Dr. Kuzma is a yes, Dr. Hollinger abstained, Dr. Linden was a yes, Dr. Nelson was a yes, Dr. Rentas was a yes, Dr. Troxel was a yes, Dr. Trunkey was a yes, Dr. Gilcher was a yes and Mrs. Baker was a yes.

DR. HOLLINGER: Thank you. So let's go on, then, to the second question.

DR. ZULLO: Number Two. If so, is a sensitivity of at least 500 IU per ml for the individual source plasma collection suitable for HBV NAT when testing minipools of source plasma?

DR. HOLLINGER: Okay, so vote again.

DR. EMERY: The Committee has voted, and we have nine votes of yes and we have two abstentions and we have zero nos.

Dr. Hollinger is a yes, Dr. Linden is abstained, Dr. Nelson is yes, Dr. Rentas is yes, Dr. Troxel is yes, Dr. Trunkey is yes, Dr. Gilcher is yes, Ms. Baker is yes, Dr. Maguire is yes and Dr. Alter is yes, and Dr. Kuzma is abstained.

DR. HOLLINGER: Okay. The third one's actually not a question, it looks like, it's actually just a comment. It doesn't look like it calls for a question, am I correct with that, Dr. Epstein? Yes. Okay.

So, any comments, any additional comments? Yes, Dr. Nelson?

DR. NELSON: Yes; I think this is potentially important, because clearly this is a high risk population, paid plasma donors, and we're dealing with a cancer virus; this is an important thing, it can be treated, so I think there are good potential public health reasons; now what happens after a donor is tested positive, there were really no data presented as to how many of them actually were further evaluated, et cetera, but I really think that this may carry the day in terms of the reasons for doing this.

DR. HOLLINGER: It would be nice to have had some data, wouldn't it? To know, is there a real risk to their

contacts and so on, whether they're drug contacts or other? Can you comment, though –

DR. NELSON: Maybe this is a research question; I don't know if we could fund, or if the plasma industry would collaborate on follow-up of these positive donors, but I think it should be done.

DR. HOLLINGER: Can you comment; I'd like to hear your comments, and the FDA maybe as well, Harvey sort of started it, but about how you would go about, what requirements that you would place on this, because the real issue is if you have somebody who you find to be in the seronegative window period, where it might even be the best time to look at it, assuming that the chronic carriers, who are occult Hepatitis B, so to speak, are not going to be probably ones who will have high levels and transmit sexually or otherwise, but assuming these are in a seronegative window period, who would maybe go on and become actively infected, and could transmit disease, what kind of requirements or regulations might you put on that – if you don't go see them for six months, is that going to make any difference?

What kind of things would you recommend?

DR. NELSON: I think, you know, theoretically these people are healthy adults in the window period, as you say, some of them may be immunosuppressed, some of them

may have higher viral load, we don't know that. The data are not here, they're probably not perinatal infections or they'd be surface antigen positive, but some of them may be.

DR. HOLLINGER: But should there be some kind of requirements about when they should be seen, or within what period of time? You know you have a test that's positive.

DR. NELSON: I would think one thing that would be useful is that the collected plasma, you could do viral load using the same blood, and that would be helpful. You could then sort out the ones that are at relatively higher risk. There might be some that have higher viral loads, so that's something that can be done with the available samples. There could be a requirement that at least the person be notified, and some sort of system set up.

I assume that these are centralized collection areas, that there's not everywhere around the world, but maybe it is, I don't know. But one could have a collaboration with a clinical center that would evaluate the patients and do further workup. I don't think we could require the plasma centers to do a clinical workup or notify the sex partners or anything like that, but if there were a referral to a system, a clinical system that would do this, I think that would be helpful. The only thing you could sort of require, or suggest, is that a plasmapheresis

center would have some sort of a system for a referral to a clinical center.

DR. RUTA: I appreciate the comments. So FDA regulates the blood products and we try to ensure the donors are healthy, so the products are safe, and so the requirement for the other markers, for example, HIV or Hepatitis B surface antigen, is that the donors are – if there's a confirmatory test, you run a confirmatory test and then the donor is deferred and then they're notified of the results, why you're deferred, so you're deferred because you tested positive by these tests.

At that point, our jurisdiction kind of stops, because we can't mandate treatment of the donor, but that's something that we can discuss, maybe with NIH, CDC, or if there are clinical trials, the companies can see about referring people to treatment protocols.

DR. NELSON: You could at least suggest that the viral load be measured on those samples that are positive; I don't know if that's been done.

DR. RUTA: I think from the health point of the donor and from public health point, that might be good, but I think we're trying to stretch the boundaries of how many additional tests we can require to keep the blood safe going there, although I agree with you that those might be useful medical things to do for the donor.

DR. HOLLINGER: Dr. Alter?

DR. ALTER: You know, I think you could do a very nice study that would be like a REDS2 type or REDS3 type study where you really followed up outcomes after notification, and I think that should be done, but at a minimum, I think you could require the plasma establishments to have a written counseling message letter that goes out to the donors that you could require that the date of notification be recorded, that whether or not they were able to make contact be recorded, and that the date of the next date and result of the next test be recorded, so you could see whether they were already surface antigen positive before they were actually notified. That would give you some index of whether early notification based on that was of value.

So those things could, I think, be mandated as part of the requirement. It wouldn't be the full study but it would be something.

DR. HOLLINGER: I was impressed with, when I looked at the NGI data, that they were able to follow 93 patients and I think 83 of them they picked up. That's really unusual, at least that's been my experience when I've looked back and looked at the blood banking organizations, looked back at other things. Ron, do you have any suggestions about follow-up and so on?

DR. GILCHER: I think there's very clear-cut value in follow-up. When I ran the Blood Center, we did do that. We followed up and pursued this, at least I did personally. But I took that on as a personal project. So I see value in it.

DR. NELSON: Do the plasma centers take a history of Hepatitis B vaccine that they've talked about, 40 percent or something, is this routine? If so, it might even be interesting to genotype isolates to –

DR. HOLLINGER: In fact I'd like to hear maybe from somebody from the plasma industry, why they have not, or have they thought about requiring HB vaccination in their donors?

DR. HOLLINGER: Yes, I don't think any of us really have the answer, I don't know that it's really been considered. In terms of requiring vaccination, of course, there's a whole different legal protocol that you would have to follow, in terms of an informed consent. And also, as far as being able to have a workable system, we have had many discussions, internally and with the agency, on many different issues, about donor screening, donor assessment and so on, and it's always a balance in trying to find enough donors to donate – I remember a couple years ago we were having discussions about, for example, the finger stick, and so requiring them to – understand that they're

being stuck with a needle already for apheresis, but to require a vaccination on top of that, adding burden upon burden upon burden, to a large population of people that's really fairly healthy. We have to make sure that we're getting enough donors that are committed to the donation process in a repeated manner.

And as far as a question yes or no on HBV vaccination, I don't know that it's ever really been considered by any of the working groups in PPTA.

DR. HOLLINGER: In terms of the number, you realize we have universal immunization for Hepatitis B in this country for every child that's born. In addition, OSHA requires Hepatitis B vaccination for people working in the plasma industry and maybe people in the industry are already vaccinated who are drawing bloods and phlebotomists and so on.

Most voluntary blood organizations have a designated person or persons who do notification and who do look-back and who record every step along the way; is that true of the plasma industry?

DR. BRINSLER: This is Roger Brinsler with BioLite Plasma Services. Yes, we do; not only for Hepatitis C, HIV and for Hepatitis B. We have a very robust process where we do advise the donor of the test results; we have a process where we try to initially

contact either by letter or by phone or personally, but we do have a follow-up process where we do make sure the donor is aware of the test results. We counsel them and then we advise them to go see their personal physician, or we send them to a public health service department. In addition we also notify the local state authority, or local authority. So we have a very robust process for this right now.

DR. HOLLINGER: So let's get out of here and go to lunch. We're going to break until 2 o'clock. We have a couple of people who are not going to be speaking in that first session, so we're going to meet back here, then, at 2 o'clock.

(Whereupon, a luncheon recess was taken at 12:45 p.m.)

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

Agenda Item: Topic II: Current Considerations on Use of Plasma Obtained from Whole Blood Donors for Further Manufacturing

DR. HOLLINGER: We'll go ahead and get started. I want to welcome Dr. Harvey Klein, who's chief of the Department of Transfusion Medicine at the NIH, on the Committee now. Nice to have you here, Harvey. And so the topic this afternoon is current considerations on use of plasma obtained from whole blood donors for further manufacturing. And we have two speakers; the first is Dr. Alan Williams, who's going to give us an introduction in regulatory perspective on this topic. Alan?

Agenda Item: Introduction and Regulatory Perspective

DR. WILLIAMS: Good afternoon. I'm Alan Williams; I'm Associate Director for Regulatory Affairs in the Office of Blood Research and Review at CBER. As mentioned, what I'm going to do is introduce the topic of Current Considerations on Plasma For Further Manufacturing Obtained From Whole Blood Donors.

I'll start off by saying, this is conceptually kind of a complex topic. So what I'm doing is setting a few baseline statements here which will help those of you who aren't quite as familiar with plasma collection and

pathways to understand some of the roots of what we're going to be talking about.

Fractionated plasma products, things like Factor VIII and intravenous immunoglobulin and albumin, et cetera, are manufactured from two distinct plasma pathways in the US. Ninety percent of the source material for these fractionated products comes from source plasma, and source plasma, as defined in the regulations, it's plasma collected by plasmapheresis, exclusively for use in further manufacturing, and in the United States, it's generally collected from paid frequent donors. Frequent source plasma donors must meet specific donation standards to ensure donor health, and also defined in the regs, source plasma is frozen immediately after collection to preserve labile plasma proteins, such as Factor VIII, which is kind of considered the canary, as it were, for labile components of plasma.

So, with this description of source plasma, basically, be aware that source plasma is a major contributor to the starting material, but the bulk of this discussion today is going to be about the remaining ten percent, and that ten percent comes from material currently known as recovered plasma, and this generally is plasma, it's an unlicensed product, generally obtained under whole

blood donor standards, from typical blood collection establishments, or blood centers.

Recovered plasma is obtained by conversion, at any time, of unused whole blood, fresh frozen plasma, fresh frozen plasma being a plasma component if it's frozen within eight hours, it meets the definition of fresh frozen plasma, and blood separated from whole blood within 24 hours, commonly known as PF24, is also a licensed product and it's commonly used in the United States. Additionally, other whole blood plasmas can be converted to recovered plasma. So these three components from whole blood collections.

Now again honing in on something that's going to be the major topic for today, recovered plasma may also be derived from aphaeresis; i.e., automated collection of fresh frozen plasma, frozen within eight hours, but also defined in the regulations, this conversion can only be made after a one-year outdate. I won't go into the reasons behind that, but basically with the growing use of aphaeresis, it creates inventory management issues within the blood center and perhaps stifles some of the plasma collections that could be occurring.

Once recovered plasma is produced, there is limited regulatory oversight. Product standards are defined in short supply agreements. While these are also

defined in regulations, the specifics are not reviewed or defined by FDA; they're between a blood establishment and a fractionators, and they define the standards for source material for manufactured products which can be made into either injectible or non-injectible final products.

So as mentioned, FDA and we've had several discussions now with the blood community and with this Committee, FDA is seeking improvements to the recovered plasma paradigm, and what I'm going to present are some of the rationale behind this.

Number one, the conversion of aphaeresis plasma for transfusion at any time for use in further manufacturing would enable more efficient inventory control at blood establishments. This is at any time versus holding it for the one-year outdate. It would potentially allow increased plasma collection on mobile units and potentially increase the overall supply of plasma and one reason that we need to have this discussion is doing that would be in conflict with current regulatory definitions of source plasma, because the regulations currently say that plasma collected by automated means for further manufacture is by definition source plasma.

The second rationale for seeking the change in paradigm; FDA seeks to establish standards for whole blood-derived plasma shipped for further manufacturing into

injectible plasma derivatives, to reduce variability of the starting material. Now the reason – I mean, there's a wish to establish standards for this product to increase predictability of the starting material; however FDA does currently feel that fractionated products are quite safe and there is no problem that needs to be fixed right now; it's just that the starting material would benefit from a general, more defined approach to standards.

Third, ensure that collections from whole blood donors are generally intended for transfusion, consistent with donor expectations. This was a major topic of discussion at the April 2009 Blood Products Advisory Committee. The sense that plasma is collected from whole blood donors who are often recruited as donating for the community, it was felt important that this particular aspect be considered to be consistent with donor expectations that they're donating blood product for the community, one or more blood products for the community.

Fourth, the blood community has been very supportive of this mood and may have been one of the original sources of the idea to make the change. The blood community has requested that the FDA consider defining a new plasma product with a different name from recovered plasma, that would replace recovered plasma with plasma

products that more closely resemble source plasma; i.e., licensed products with defined standards.

So our history of working on this definition of new products; defining the standards has been complex, and I think you'll begin to see some of this as Dr. Weinstein starts to go through his talk for defining some of the standards. This all started, really, with the 2004 Plasma Workshop which FDA sponsored, which included talks from fractionators to help the agency really get a picture of what was going on in the fractionation industry, what sort of source materials, what sort of standards they were looking for in short supply agreements, and essentially trying to harmonize as much as possible with these, given the fact that we felt that the final products were safe and effective, currently. There was a discussion in April 2009 with this Committee that introduced the concurrent and component plasma product concepts, and the next few slides are going to show some of the advances since that discussion.

So the first product mentioned will be concurrent plasma. This was introduced at that BPAC meeting; the acronym here you'll see used is CCP, Concurrent Plasma. It was proposed by FDA as plasma for further manufacturing, separated from licensed whole blood collection. Plasma collected concurrently with cellular components, by

aphaeresis, or a one-way conversion at any time of an existing licensed FFP or whole blood-derived plasma frozen within 24 hours that's collected concurrently with the cellular product.

The concurrent aspect is that the intent for collection for transfusion is inherent in concurrent plasma definition. A community-recruited blood donor donating more than one product – at least one of those would be used for transfusion.

At that meeting, FDA described a multi-tiered approach to product labeling which took numerous plasma handling factors into consideration, and the judgment of the Committee at that time was that the Committee recommended clarification of the product standards and simplification of labeling for concurrent plasma, and that will be the bulk of the discussion at today's session.

Mark Weinstein is going to be chairing the second discussion, and some of the factors which will come up with supporting data will be considerations of freezing temperature, time to freezing, shelf life and content of Factor VIII as kind of this hallmark of plasma stability within the product.

The second product, component plasma, is part of the consideration being presented; however there will be less of a discussion of standards related to component

plasma; in short, because the way component plasma is defined, it will inherently meet current standards that are being proposed.

In April of 2009, component plasma was proposed by FDA as plasma collected as a sole plasmapheresis product from whole blood donors, or through conversion at any time of FFP collected from whole blood donors as a sole plasmapheresis product. The Committee expressed concerns about collection of plasma for fractionation as a sole product from whole blood donors, due to the donor expectation of donation for use in transfusion, and much of the discussion at that meeting surrounded adequacy of informed consent and the need for the product, the need for two different products.

FDA's view on how to handle this situation is to retain the current pathway for that plasma collection as a sole product. So FDA's consideration for this meeting is that licensed aphaeresis FFP collected as a sole product can be converted to component plasma for further manufacturing, but after its one-year outdate.

Some of the factors related to this is it parallels current FFP conversion policy, and it preserves the concept of whole blood donation generally intended for transfusion, but it's not felt to be a major burden to the current practices within the blood community, because solo

FFP collection, while it occurs, is somewhat uncommon, at least according to discussions we've had with the blood community, and hopefully some of the statements from the blood collectors today will shed some further light on that.

Additionally, if FFP is collected as a standalone collection, it's likely to be from a male donor to help reduce the risk of TRALI in the recipient, and likely to be group AB as a universal plasma product. If it meets those characteristics, it is likely to be transfused rather than held in inventory; certainly for a year.

Regarding component plasma, the standards for component plasma are felt by FDA to be inherently met since this product is derived only, at the present time, from FFP which is frozen within eight hours, or a potential equivalent product.

Also changed from the last meeting, the proposed shelf life for these products is three years from date of collection, and I believe Dr. Weinstein will show us some data supporting that.

The third category, recovered plasma, FDA proposes retaining the category of recovered plasma as an unlicensed product, and this would be any plasma not meeting the standards for concurrent plasma or component plasma. It may still be shipped under short supply

agreement for further manufacturing, but with a limitation to use for non-injectible products.

So in these last few slides, I'm going to summarize some of the considerations that have gone into this discussion; again, just to try to round out the picture. We've had many product names proposed for these products; discussions such as why two different plasma proposed products, but currently FDA consideration that there are two potentially licensed products, concurrent and component plasma, FDA sought to define a pathway for immediate conversion of concurrently collected aphaeresis FFP collected under whole blood donor standards, and potentially a future FP24 product, and we feel that the design of this product meets that intent.

FDA wants to assure that transfusion remains the primary intent of whole blood donation, and as mentioned, this was a major subject at the last meeting. FDA wants to promote high quality starting material to make injectible plasma derivatives. Remember, this is ten percent of the starting material and the 90 percent which comes from source plasma is frozen immediately and needs to meet very high standards.

FDA has looked at all the available literature and investigated data related to the effects of time to freezing, time to separation, freezing and storage

temperature, and you'll hear a lot of this from Dr. Weinstein. We've proposed labeling and processing compatible with current blood center and fractionation operations, and have proposed a more simplified labeling scheme. Again, the intent is to try to harmonize with current practices as much as possible, so as to introduce standards but remain compatible with current practice, which we feel is acceptable.

Any additional standards which are under consideration are largely consistent with current fractionator practices as far as accepted plasma starting material, to the extent that they could be derived from current short supply agreements. There obviously is a lot of consideration with respect to the European use of US plasma, so we have taken consideration of harmonization with EU plasma standards; this is certainly desirable, but by no means has driven US policy, so it's something that's been considered in defining standards, but these would clearly be US-specific standards.

And FDA wishes to retain a regulatory pathway for plasma not meeting standards for component or concurrent plasma, and these would be then used for non-injectible products. I think it's important to note, this would also create a pathway for those facilities which may collect blood or plasma. It might not be licensed and may be

sending plasma for further manufacturing; this preserves a pathway for that product to still be sent for use.

So courtesy of Dr. Weinstein, we have these graphs which kind of puts this whole schematic into a unified picture here. For this first one, the only thing that I think I want you to focus on is right up at the top here. This left side of the group is all plasma collected under whole blood donor standards. That's important. The other group of source plasma collection, that's under source plasma donor standards, these differ slightly. There's an annual physical, protein determination and immunoglobulin determination.

So I'm going to drop out this right side, because that's not what we're looking at. So under whole blood donor standards, the current scheme prior to FDA's current considerations, is there's phlebotomy for whole blood collection, plasma taken off that whole blood collection can be used for either FFP or frozen within eight hours or 24 hour plasma, frozen within 24 hours, and other plasma products such as cryoreduced plasma. Derived from whole blood collection, these can be converted any time into unlicensed recovered plasma, which can be shipped interstate and used for plasma derivative manufacture.

Looking in at the center section, again, one of the major topics for this afternoon: collection by

automated aphaeresis. Currently, plasma from aphaeresis, from donors under whole blood donor standards, if collected with cells or in the absence of cells; i.e., plasmapheresis, requires a one-year outdate, and it can then be converted to recovered plasma and used for derivatives.

Because the term may come up included in the graph, what's known as an infrequent source plasma – this is source plasma collected under whole blood donation standards. It meets all the definitions for source plasma, but because these donors donate only infrequently, they don't have the annual physical and other donor screening criteria that are necessary for frequent source plasma donors. So this will not be discussed specifically, but we wanted to make sure that you are aware of the existence of that pathway.

Most of the discussion is going to center around this product.

So looking here, this is the conversion of the graph, and presents FDA's current considerations; sources of plasma for US plasma derivative manufacture under whole blood donor standards. So on the left side again, whole blood phlebotomy, separation of plasma, conversion at any time, that's all current practice, but this product would be known as concurrent plasma and have standards and be a

licensed product. This would then go into manufacture of plasma derivatives.

On the automated side, there would be automated aphaeresis, plasma for transfusion collected together with a transfusible component; i.e., red cells or platelets, could be converted any time into licensed concurrent plasma and used for plasma derivatives. However, plasmapheresis, i.e., collection of plasma as a sole aphaeresis product, could also be made into a plasma for fractionation, but it needs to be held a year outdate and then would become known as the product component plasma, which then could be sent for manufacture.

I made a note here at the bottom; recovered plasma option also remains available for non-injectible products from sources that typically probably would be unlicensed plasma products.

So what I hope to do is set a framework for some of the prior discussions and some of the things coming up at this meeting. The core issue for the discussion is FDA seeks the advice of the Committee on appropriate product and manufacturing standards for plasma products collected from whole blood donors or collected from donors under whole blood donor standards, to make injectible plasma-derived products.

And Dr. Weinstein is going to introduce the proposed standards and the scientific rationale that underlie them. Thank you.

DR. HOLLINGER: Any questions at this point for Dr. Williams? Let's go ahead and finish the next talk and then we can come back and ask either one of them some questions. Mark is going to talk to us about considerations for concurrent and component plasma product standards.

Agenda Item: Considerations for Concurrent and Component Plasma Product Standards

DR. WEINSTEIN: Thank you, Dr, Hollinger. Dr, Williams has given you a perspective of component and concurrent plasma from a regulatory point of view. I will be talking about the minimum standards that we wish to consider for the collection, storage and freezing of concurrent plasma. This is the product that is intended for further manufacturing into injectable products and I will also be discussing the labeling that reflects these standards. The overall objective here is to reduce the variability of plasma that is used for manufacturing purposes.

As Dr. Williams has already mentioned, component plasma inherently will meet the minimum standards of concurrent standards, so most of my remarks will be

directed toward describing the concurrent plasma standards that we are considering.

Very important point – if manufacturers have a desire to make a product that requires plasma that has more stringent conditions of manufacture than what we are describing here, they can certainly establish those conditions with a blood collector. And we will describe a little bit about that and how a product that may be considered by a certain manufacturer to require more stringent conditions than we are suggesting here, but again the manufacturer has an option to make more stringent conditions than the minimum that we are suggesting.

The topics that will be discussed are our considerations for the categories of concurrent plasma, the rationale for establishing quality standards. You know, why bother? What is the thing that we are trying to do here? We will talk about the scientific evidence that supports the categories under consideration. We will talk about industry practices as they were outlined in our workshop in 2004. We will talk about the specific rationale for each of the standards that we are proposing or that are under consideration and finally we will discus the labeling of concurrent and component plasma.

So as we already heard we have standards for source plasma. Ninety percent of our products are made

from source plasma that are plasma-derived and these standards include time from collection to freezing, freezing conditions, storage and expiration, shipping temperature and allowable deviations.

These standards do not exist for recovered plasma. So we are trying to outline the boundaries of what we consider to be acceptable as we develop concurrent and component plasma.

This table gives you the starting and endpoint of this discussion,. These are the categories that we are considering, and please keep them in mind as we develop our discussion of concurrent plasma categories. We are interested in having the plasma placed in a freezer of minus 20 degrees or less, and plasma that is collected, from time of collection to placement in the freezer be within a 24-hour period, that is have an average Factor VIII level of at least 70 international units per hundred mils, and that material with that quality indicator could be used to make labile, non-labile and non-injectable products. Twenty-four hour plasma that does not meet that quality element here could be used to manufacture non-labile and non0injectable materials. Plasma that is in liquid state for up to 72 hours before being placed in the freezer could be used to manufacture non-labile and non-injectable products, and plasma that has been in liquid

state for longer period of time beyond 72 hours can be used to make non-injectable products.

Important element here, this average Factor VIII level, we are considering that it be a process validation and possibly also a quality control testing under GMP.

Now what was the rationale for establishing quality standards? Again the question why bother? It is important to realize first of all that the term plasma quality is a relative term, that the nature of plasma that is used for the production of labile products may be different from that which is acceptable for non-labile products. When we talk about non-labile we are talking particularly about immune globulins and albumin that are more resistant to proteolysis and denaturation than let's say Factor VIII. This Factor VIII – this is an important point. Historically this has been the common indicator of plasma quality. When people talk about plasma quality they are usually saying what is the level of Factor VIII? This of course, because there is this commercial interest in obtaining Factor VIII in high yield for simply economic reasons. It also is a surrogate, thought to be a surrogate for other processes that may be occurring in plasma, other denaturation processes so that we may not be measuring, say, protein S or some other materials that may be also subject to breakdown in plasma over time. But looking at

the Factor VIII level one is thinking at least that this is a model of the canary in the coal mine.

It is also important to recognize that plasma for injectable products should not contain substances that, if not removes or neutralized during the manufacturing process, could adversely affect the safety or efficacy of the final product. This gets to the heart of the idea that we want to have plasma that has a certain degree of stability, that we are not introducing materials, unknown materials that can be carried through the manufacturing process and end up in the final plasma derivative.

We know that there are a number of parameters that can affect the quality of plasma, a whole host of things – the method of plasma separation from cellular materials, whether or not a leukocyte reduction filter is used in the preparation of the plasma. We know that surfaces can affect the activation of certain coagulant proteins. The time, the temperature that plasma remains in a liquid state can affect the quality, the nature of proteins in plasma, the cell content, the anti coagulant used, the rate of freezing, the storage and temperature time are all elements that can affect the nature of the product.

So we are again looking to at least limit some of these elements here that we are aware will affect the

quality and the heterogeneity of proteins in plasma.

Plasma in contact with cellular components can undergo spontaneous proteolytic activity over time. This is an experiment that demonstrates that feature. Here we have a platelet concentrate that has platelets and leucocytes in it. In this experiment a chromogenic substrate was introduced and the material was incubated over a period of time at 22 degrees. And we see here that in the plasma that contained a high concentration of cellular material we see a fairly robust development of proteolytic as determined by this chromogenic substrate. You might notice here that it is sort of maybe a nonlinear process. With reduction of cell contact here there is less proteolysis going on and in control material we see in this particular experiment, with this particular indicator of proteolysis, we see that there was not a detectable level of activity.

This is an important element here in our considerations here, that the observation of proteolysis or heterogeneity or other conditions is very dependent on the material, the substrate, the analyte that you are examining here. And although this particular study does not show proteolysis – I'll demonstrate that there are other studies that in fact do indicate that things are going on in plasma when there are not cells present.

So coagulation factors, inhibitors and other plasma components can change over time, become proteolyzed, aggregated, activated or inactivated in liquid plasma, leading to increased heterogeneity of constituents of poorly understood or controlled physical properties. This is an example of that kind of proteolysis or heterogeneity that can occur over time. The data for this particular – that I have graphed here comes from a study by Yazer et al. The information, the graphical representation of the data that was in his paper was something that I produced and here you see that over time, with 18 samples of plasma that were examined, that there was an average increase in the level of expression of Factor XI activity. This means that Factor XI-A is being generated in plasma, this thawed plasma, over time. Look at, say, the protein S content of this plasma. There was a decline over this time and here we see a five-day period.

The data in this paper shows that there are a number of other plasma proteins that had apparent increases in activity. Her is Factor IX, again the Factor XI, the Factor XII all increased in activity until there is some indication of a proteolytic function going on here while other proteins decreased in activity, Factor V, VII, protein S and some of Factor VIII. Again the whole notion here that, in this case, after five days we have evidence

of activation and inactivation of proteins over time.

SO activation factors could potential become concentrated in certain plasma factions leading to adeverse events.

This is a complicated slide, very difficult to read, but this is the Cohn Oncley blood plasma fractionation process. The take home message from this slide is that one step of the fractionation process is dependent on the output of the previous step. So if you take plasma and you add some alcohol and change the pH and the temperature you can get a precipitate and a supernatant. Form that precipitate you can make, say, a product here is fibrinogen. That supernatant is then further treated under certain temperature and alcohol concentrations and so forth and you get a whole series of steps here, one dependent on the other until you get to, say, immune globulins or plasma protein fraction, albumin, so forth.

There is also an element here that if you introduce a step in this plasma fractionation process – say a manufacturer decides to make a new product, say, a Factor XI complex. They might introduce a new column, a new step here that pulls out material from that earlier supernatant, pulls it out, changes the quality, the nature of proteins that are in that supernatant and because there are 4,000

proteins in plasma, at least here, you don't know what all of those changes can do to the supernatant. And so you can end up in a situation where you are concentrating down elements in plasma that you had not originally recognized or though would be there and end up with material that might have, say, thrombotic potential.

We know that there has recently been an indication of a high concentration of Factor XI-A in immune globulins. I am not saying, and this is very important, I want to emphasize this point – we don't know that this came as a cause of the quality of plasma that we started with. However, there is this idea, this potential for unknown changes in plasma occurring in the raw material that could be concentrated and end up in your final product here and cause adverse events.

So what are some of the types of plasma that can presently be distributed as recovered plasma? There are a whole host of material and Dr. Williams has already aligned some of these – the idea that fresh frozen plasma can be used for manufacturing purposes, plasma that is paced in the freezer within eight hours of collection. It is stored at minus 18 degrees or lower, We have cryoprecipitate, reduced plasma, we have platelet rich plasma. The liquid plasma is an interesting situation. This is plasma that is separated no later than five days after the expiration date

of whole blood, and the expiration date of whole blood can be up to 35 days. So one could have plasma sitting with cells for up to 35 days, at a temperature of one to six degrees. Now manufacturers do not use this material routinely. But the idea that it is currently within our current framework would be an allowable material to be used for fractionation. So the constraints that we are describing here, the standards would eliminate the potential of this kind of material to be used in products that are licensed in the US.

Again, different kinds of plasma, fresh frozen plasma described in an AABB circular here, includes apheresis and whole blood collections. Plasma frozen within 24 hours, another one is thawed plasma, which is derived from FFP and PF24. And again this can sit for up to five days in the liquid state as a thawed material. This potentially could be used now for the production of plasma derivatives.

SO what are some of the scientific considerations for standards for concurrent plasma? These are the standards that we are considering, that we would like to establish for concurrent plasma. Considerations for establishing time from plasma collection to freezing, cell contact time and Factor VIII yield for plasma used to produce labile versus non-labile products are the things

that we are focusing on in this discussion.

These results are a study of apheresis plasma in whole blood that was placed in a freezer within three hours after donation. The point here is that looking at apheresis plasma you can see that levels of protein are always in fact higher that what one sees in whole blood plasma. Importantly one has to remember that apheresis plasma is less diluted with anticoagulants than whole blood plasma, but even if one takes not account this dilution effect in whole blood plasma – maybe seven or eight percent – we still get lower levels of these factors compared to what one gets in apheresis plasma, which to remind you again is what the component plasma would be, except that it has an eight hour after donation time limit.

This is just an indication that changes in protein content can occur relatively quickly after donation. If you look at some of the coagulation activation and proteolysis markers here you will see that there is an activation, say, of prothrombin. This is a fragment from the prothrombin molecule. There is an increase in the whole blood plasma compared to apheresis plasma over a relatively short period of time. These are cellular enzymatic indicators here and we see that they are increased in whole blood plasma compared to apheresis plasma. The idea here again cellular contact can affect

the nature of factors of proteins that are in the whole blood.

This study or this chart is a literature review. The references for these various experiments are in the packet that the Committee members have. One study, for example, if you look at the time when plasma was in contact with cells, time without cells over this 24 hour period at this particular temperature – and if you recall we are looking for the quality element of our proposal or consideration for labile products to be 70 units or greater. In this particular study we see that this plasma fell below that level.

Here we see under another set of conditions similar in cell contact time but different temperatures that the Factor VIII content would have met the considerations that we have for Factor VIII levels, and again different studies show different levels depending – very dependent on the conditions under which these studies were done.

So our conclusion is that most studies suggest that holding whole blood for up to 24 hours from collection to freezing under a variety of temperatures and cell contact time will yield plasma containing an average Factor VIII level of at least 70 units per hundred mils. And other studies that the Committee has references to indicate

that this is also true of apheresis plasma.

Regarding the freezing rate, we know amny studies have shown that rapid freezing helps to reserve the activity of Facto VIII. This is an early study that shows that plasma frozen at minus 40 degrees, very quickly, there is a loss of about eight percent of the Factor VIII activity, while at a slower freeze and higher temperature, minus 20 degrees, here the loss of Factor VIII activity in the thawed material, in the liquid state after you take that plasma and thaw it out completely that the Factor VIII activity was higher in the rapid freeze than the slow frozen plasma.

And the European Pharmacopoeia takes into account this notion of rapid freezing increasing the apparent level of Factor VIII activity. These are the specifications for plasma in the European Pharmacopoeia that are used for production of labile proteins for fractionation and you can see again the time from collection to freezing is within this equal to or less than 24 hours, that plasma had this rapid freeze condition here – it should be frozen to a core temperature of minus 25 degrees of less within a 12 hour period, and that the average Factor VIII level be yo units or greater as examined in QC and testing under GMP conditions.

At the same time, and recognizing that these

standards exist for this idea of controlling the rate of freezing using this minus 25 degree and freezing within 12 hour, is something that one should be aware of and this study by Bravo et al in 2006 suggests that in fact the yield that one gets of Factor VIII in cryoprecipitate to manufacture the finished product does not necessarily follow these stringent freezing conditions. We placed plasma in a chamber at minus 30 degrees, minus 25 or minus 20 degrees, froze it and then thawed it completely and looked at the Factor VIII recovery, one finds that in fact the material frozen at minus 20 degrees had a lower recovery than material frozen at these lower temperatures, which is sort of what one would expect.

However, looking at the cryoprecipitate produced under these conditions did not show that the yield of Factor VIII under these manufacturing conditions was much different, the freezing rate did not seem to affect the level of product, of Factor VIII.

So our conclusion – rapid freezing increases Factor VIII yield in thawed plasma compared to slower freezing, but may not in fact increase Factor VIII yield in cryoprecipitate, or the final yield of other plasma proteins made under various manufacturing conditions. And in this particular study it turned out that Factor IX level in the thawed material was actually a higher level of

material frozen at the minus 20 degrees than the minus thirty degree.

So manufacturing conditions – exactly how it is done, exactly how the plasma is used, may make some of these considerations somewhat moot with regard to the rate of freezing. So at this time FDA is not considering specifying the rate of freezing in establishing minimum quality standards for concurrent plasma.

With regard to storage freezing temperature and time of storage, the data that was obtained by a study by Kotitschke in 2000 really is the basis for our considerations for appropriate storage temperature and the length of storage. These results were also backed up by a number of other studies. The idea is that plasma stored at minus 20 degrees versus minus 40 degrees over a three-year period did not show a decline in activity for many of the proteins examined.

This information really is the basis, the foundation for our standard of storage at minus 20 degrees and the time of storage lasting for three years, for 36 months.

What is industry practice? What do they actually do and would our proposed standards fit within the framework of what industry currently does? This was the information that we received in 2004 from a number of

manufacturers. We see here that there was one manufacturer that used exclusively plasma collected within eight hours for production of a particular product. I should also mention that the manufacturer specified that it be frozen at minus 30 degrees. Again, what we are suggesting here for concurrent plasma would not exclude this specific condition as desired by a given manufacturer. WE see here that plasma that is in a liquid state for up to 24 hours is routinely used by all the manufacturers for the production of non-labile and labile products, including Factor VIII, albumin and immunoglobulins and so forth.

We have only one manufacturer that had used plasma, or was allowed to use plasma for the production of non-labile products here that was in a liquid state for up to 120 hours. Virtually all the others were using plasma that was a maximum level in liquid state for 72 hours, or within 72 hours. So again this is the sort of concurrence of our standards with what the practices are that industry is actually doing.

So let’s look now at standards under consideration for concurrent plasma to be used for injectable products. Again, labile and non-labile products that include Factor VIII, immunoglobulin and so forth, would have an average Factor VIII level equal to or grater 70 units per hundred mils, and this would be determined by

process validation, possibly QC testing under GMP. The time from donation to placement in the freezer would be within this 24 hour period; the temperature of the freezer minus 20 degrees or less storage, and shipping temperatures minus 20 degrees or less. For non-labile products the maximum time in liquid state would be less than or equal to 72 hours, freezer at minus 20 degrees or lower, and shipping and storage at minus 20 degrees or lower.

Taking each of these suggestions in order here, labile products made only from plasma held for 24 hours or less at specified temperatures from collection to placement in freezer, and the rationale for this reflects the available data and is in accordance with current US industry practice.

Non-labile products, the standard would be plasma held for less than or equal to 72 hours at specified temperatures from collection to placement in freezer. The rationale – this addresses the concern that we have about the increase in protein heterogeneity that can occur over time and is within the current practice of most manufacturers.

Plasma that has been thawed and refrozen would not be used for injectable products. The rationale is that there is a concern about the quality of plasma that has been thawed and refrozen multiple times based on potential

for changes in some proteins. It is notable that source plasma has similar limitations.

We are considering replacing the minus 18 degrees or lower with the minus 20 degrees or lower for all conditions of freezing, shipping and storage. The rationale for this is the temperature limit of minus 20 degrees or lower for all conditions is the current industry practice and is supported by the data that I have already shown.

Allowable shipping and storage temperature deviations can exceed minus 20 degrees for less than or equal to 72 hours total, never greater than minus 5 degrees, never refrozen. These are the current FDA standards for source plasma and are known to assure protein stability.

The limit for plasma storage would be up to three years after collection. And again the data we have already discussed here by Kotitschke supports that period of time.

The average Factor VIII level, 70 units or greater per hundred mils for plasma used to make labile products as determined by a process validation and possibly also quality control testing under GMP. The rationale for this – this element of plasma quality is the same as that specified in the European Pharmacopoeia so it indicates that it can be done. The Factor VIII activity of 70 units

or greater per hundred mils for whole blood and apheresis plasma is an achievable benchmark, is a desirable level of activity for manufacturing purposes and is one marker of plasma molecular integrity.

And just to indicate how this procedure is carried out under the European Pharmacopoeia guidelines, it is not intended that the determination of Factor VIII is to be carried out on each unit of plasma. It is rather given as a guideline for good manufacturing practice, the test for Factor VIII being relevant for plasma intended for use in the preparation of concentrates of labile proteins. The aim of good manufacturing practices to conserve labile proteins as much as possible. The method used, at least according to the European guidelines, they carry out the test using a pool of not fewer than ten units. The samples are thawed and examined at 37 degrees against an international reference standard.

SO taking into account these various considerations for manufacture of component and concurrent plasma, the labeling will reflect these various conditions. The labeling for concurrent plasma, injectables for labile products, caution for manufacturing use only, placed in a freezer within 24 hours, may be used for labile or non-labile injectable products, and the Factor VIII level of greater than 70 units per hundred mils would be a process

control that would assure that this average level would be met.

For non-labile productions, caution for manufacturing use only, placed in a freezer within 72 hours or less, may be used only for non-labile injectable products. It is notable that this label would encompass the plasma that met the 24 hour in liquid state here, but not the Factor VIII level. Factor VIII would be lower than 70 units in this 24-hour liquid state plasma.

Labeling for non-injectable use, caution for use in manufacturing non-injectable products only, and this is plasma that is frozen greater than 72 hours after donation.

As far as the labeling for component plasma, for labile products – caution for manufacturing use only, placed in a freezer within 8 hours, may be used for labile or non-labile injectable products. And in the future we would consider for other apheresis products that may be developed in the future.

So in summary, currently the storage freezing conditions for recovered plasma vary widely and are specified in short supply agreements between collectors and fractionators or manufacturers of IVDs. The variations in freezing, thawing, time in contact with cells and time in liquid state affect the preservation, activation and inactivation of known and unknown plasma proteins, which

can potentially affect the consistency and safety of the finished products. The manufacturing conditions specified for concurrent plasma will help to assure the manufacture of safe and effective plasma products. Component plasma, that is, apheresis FFP, already meets these standards. These candidate specifications are generally consistent with current manufacturing practices. The standardized categories for labeling of concurrent plasma and component plasma for key conditions of storage or freezing will inform purchasers in the US and abroad about the salient characteristics of each product and establish minimum standards of processing and handling. The standards for concurrent plasma will enable the FDA to provide regulatory oversight that will increase consistency and limit the extent to which plasma with unknown or inferior properties could be used for manufacturing. Other categories may be established based on further evidence showing that safe and effective products can be produced from plasma manufactured under specified conditions.

Thank you.

DR. HOLLINGER: Okay, questions for either Dr. Williams or Dr. Weinstein. Dr. Gilcher?

DR. GILCHER: Maybe I am missing something. Is there a scientific reason why you don’t want to allow the

conversion of apheresis fresh frozen plasma from an infrequent donor to occur in less than one year?

DR. WILLIAMS: Thanks for that question, Ron. Again it is a complex story. One of the considerations – let me preface by saying fractionated products are life-saving critical products. There is no question about that. But they are made by commercial for profit manufacturers who receive raw materials from both commercial plasma collectors of largely sourced plasma and from whole blood collection centers.

At two levels, one is the donor and one is the larger blood supply issue. At the donor level the typical blood recruitment message or appeal is community use, i.e., a sickle cell baby who needs a transfusion, an injured fireman or policeman, military personnel injured in theater. The donor is typically recruited for the idea of providing lifesaving transfusions who need, maybe in their community or maybe elsewhere in the US because I make sure donors realize components are shipped around.

The blood establishments currently are not for profit and do not collect plasma as a sole component and hold it and ship it for fractionation as a rule. It is generally collected as a transfusable, fresh frozen or PF24 transfusable product. If it is not used it is considered excess inventory material and shipped for fractionation.

I think one cannot rule out the possibility that if a pathway were created for collection of plasma as a sole product, and it could immediately be put into the stream for commercialization into a fractionated product, that would potentially, both at the single donor level and the overall blood supply level create some discord in terms of the reason that some of these donors are recruited to donate at the blood establishment in the first place.

I think FDA not only looks after the safety of its products but issues of availability also can become safety issues. The blood supply – I am amazed at the volume of blood collected every day and use, and while supplies have generally been maintained at adequate levels, it is fragile. If there was attention raised to a potential issue that would compromise the ability to recruit donors, there is a potential to jeopardize supply and I think that is one of the concerns under consideration.

DR. GILCHER: I would like to comment because you do remember that we had a transfusable apheresis fresh frozen program at OBI. That program, that plasma was aimed at the therapeutic area, which we did a lot of, and used that in lieu of using whole blood derived fresh frozen plasma. But at times we would have, in a sense, too much of that plasma, that is, apheresis fresh frozen plasma

collecting a 500 ml fixed aliquot. The donors very clearly wanted to donate. That is my point. And if we told them not to they got turned off. They really wanted to donate. That would increase our inventory. That was the real reason for my question.

DR. WILLIAMS: Sure, and I think the regulatory structure provides pathways for that sort of activity to occur through variances to current regulation. So that in a well constructed program like that, where clearly the best interests of the patients and the donors have been considered, there are mechanisms to run that sort of program. But in the larger scale I think there are just concerns about sticking with the intent of the donor coming in on the basis of a recruitment message that has their donation being used for transfusion purposes.

DR. KLEIN: The current blood bank freezers are both specced and QCed at minus 18 degrees. I am assuming that there is no problem in moving that to minus 20 degrees. Is that correct?

DR. WEINSTEIN: As far as our knowledge goes most centers now that provide plasma for fractionation do have the minus 20 degree or lower temperatures. Clearly there would be a period of time once this consideration perhaps was enacted here that there would be a period of time that there would be a phase-in of the minus 20 degree level.

But our current understanding is that the minus 20 degrees is quite within current practice in the industry.

DR. HOLLINGER: But if you had a minus 20 degrees and you think that is a minimum, knowing that the FDA often likes to have a space, a level of safety – so why isn't it then at minus 25 or minus 30?

DR. WEINSTEIN: Because the idea is the set point actually would be lower. Routine practice, good manufacturing practice would say, yes, minus 20 is the upper limit here, but the actual set point in order not to exceed that level, if the freezer door opens or other sorts of things happen, routinely the actual set point is lower than the minus 20. Also we had this discussion at the workshop – why not have everybody blast freeze to minus 25 degrees or lower. This is a whole different, very expensive conversion, as I understand it, of freezers to these lower temperatures. The other element that I was bringing out here, it is not entirely clear, at least in our minds, that this lower temperature necessarily is going to lead to a product that is of inferior quality compared to material frozen at this minus 20 degrees or lower level.

DR. HOLLINGER: What do the source plasma manufacturers freeze their product?

DR. WEINSTEIN: It is the minus 20 degree or lower temperature, upper limit here. But they generally,

as I say, have freezer chambers that are lower, have set point lower so as not to exceed the upper limit here.

DR. HOLLINGER: And there are so many – I am confused about the number of freezing times. It is relay confusing from the data. The source freezes immediately. I guess that is within what period of time? Immediately is what?

DR. WEINSTEIN: It is usually within an hour. Immediately – there is always this idea what is immediately mean? But I think for most plasma collection facilities that idea is translated to within an hour or so of collection.

DR. HOLLINGER: So then we have the plasma that is frozen in less than 8 hours, we have plasma that is frozen at 24 hours or less and so on. Are all of these necessary? The data that you showed seemed to suggest that the time at which it might be separated from cells particularly is important.

DR. WEINSTEIN: The idea is again we are trying not to deviate from what the current practice is. We do believe that our products are safe and effective. Manufacturers, in general, can use plasma that is obtained let’s say within 24 hours to make their products, labile products, the factor VIII in particular. Manufacturers, in general, do not want to make labile products from plasma

that is older than this because of the very considerations that we have discussed here about degradation, lower yield of the factor VIII material. But again, this plasma is acceptable for the production of less labile products – immunoglobulin, albumin.

DR. HOLLINGER: But is factor V, for example, is that much more labile in terms of –

DR. WEINSTEIN: Factor V, in general, has not been found to be as labile as factor VIII. Protein S turns out to be something that is fairly labile. But the point is here that factor VIII, at least historically again and for commercial interest and for its lability is the commonly recognized indicator of surrogate for protein degradation and heterogeneity that can occur over time. So the idea that – the slides that I was trying to show here say that up to 24 hours most studies show that you have factor VIII that meets that level or indicator of so-called quality. It is not a perfect indicator by any means. One can test that notion and the idea that apheresis plasma automatically by its concentration you get a higher level simply because there is less anti-coagulant in the apheresis plasma. So that is an element to consider when we talk about factor VIII as a surrogate indicator of proteolysis or lability. On the other hand, this is what we have now. This is about as good as we get at present.

DR. GILCHER: Under the current considerations then cryo-poor plasma that is not transfused would still remain for non-injectable use only?

DR. WEINSTEIN: We had not come to a resolution about that. That is still under consideration here exactly how we will handle that.

DR. BIANCO: There are several issues. One, I think it would be useful – there is some information that is going to come out during the public hearing from industry on collection practices that I think will answer some of these questions.

After that I would like to make some comments.

DR. HOLLINGER: Okay, thanks, Celso. Yes, Colonel Rentas?

DR. RENTAS: We have been talking a lot about 24 hour before we freeze. I don't think we have said much about what the storage temperature will be before we actually freeze. I think you showed a slide there showing room temperature and four degrees having about the same levels of factor VIII after 24 hours. Could you say something about that, please?

DR. WEINSTEIN: I think currently, our current licensed products, plasma that can be as warm as 25 degrees or so up to 8 hours and then it is cooled down to a lower temperature. Clearly what I was really expressing on those

slides – the scientific evidence is not perfectly straightforward about the level of factor VIII that you get out of this kind of material for manufacturing purposes. This is the important point. We are talking about plasma for manufacturing purposes and it appears that the level might not be lower for plasma held at these other temperatures. But these are still areas here – we are looking at the license, the applications that we have for plasma held are various times and temperatures and so fort. The data doesn't say we have to exclude that material in our considerations, that is, material that is held at these different temperatures right now.

MS. BAKER: You mentioned a couple of times the Europeans and their guidelines. To what extent do they have guidelines that are similar to what the FDA might be proposing? Have you looked at that?

DR. WEINSTEIN: Yes, that is the slide that I showed, yes. That was the chart that contains the European guidelines taken from their manual.

DR. HOLLINGER: Instead of taking a break at this point I would like to go into the open public hearing.

Agenda Item: Open Public Hearing

DR. HOLLINGER: There are three people who have asked to speak and then when we finish with that we will

take our break and then we will come back for the committee discussion.

I have to read the announcement again. It says both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee meeting FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or a group's payment of your travel. Lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement to advise the Committee if you of not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statements it will not preclude you from speaking.

So with that as a background, the first person who has asked to speak is from the AABB, Ms. Allene Carr-Greer.

MS. CARR-GREER: Thank you for the opportunity to provide input to this discussion, I am the director of regulatory affairs and today I am speaking on behalf of the AABB inter-organizational plasma task force. The task force membership includes representatives from AABB, the American Red Cross, America's Blood Centers, Blood centers of America, Blood Systems, Incorporated, Department of Defense, Hema-Quebec, Plasma Protein Therapeutics Association and manufacturers' representatives from Baxter BioScience, Octapharma and CSL Plasma. You have that on the screen.

Since 2002, members of the blood banking and plasma community have interacted with FDA in various venues in an effort to establish a pathway to licensure for the product, recovered plasma that is currently distributed under short supply agreement. There is a brief description of the interactions that we describe in this written statement that have occurred over the past several years. Then I would skip down and say that the issue summary published in preparation for this meeting today describes the structure for licensed product, rather than the current

one that has minimal oversight in the Code of Federal Regulations.

The opportunity to manage these products through biologics license applications, rather than contracts and short supply agreements, is indeed a great improvement and is greatly appreciated. Should FDA develop a regulatory pathway we wholeheartedly endorse the consideration for variances to allow blood establishments to implement changes at a time prior to publication of final regulations.

We do note several items that we believe would benefit from additional discussion or would facilitate implementation of this new regulatory pathway. Even though it was not talked about much in the previous presentations, the FDA considerations that were published in the topic summaries include unidirectional labeling of the plasma product from use for transfusion to use for further manufacturing. And the task force agrees that this is likely the predominant direction that labeling would take. However, there are events that affect inventory management and could result in a deficit of transfusable product where the need could be filled by relabeling the plasma for further manufacturing to its original plasma for transfusion product, the product name code.

This need could arise if the establishment loses the contents of a freezer through malfunction or disaster, or if a hospital customer has an unexpected need for large volumes of plasma for transfusion or therapeutic purposes. The age of the plasma and the freezing and storage condition would have to be suitable for the transfusable plasma product for this to be allowed. Current CFR requirements for recordkeeping and computer controls for these parameters do exist and we think that it could safely happen. There is no biologic or scientific rationale not to allow bidirectional labeling of conforming plasma and given the amount of time it takes to revise regulations once they have been create, we believe it is unwise to create a barrier to effective inventory management by determining through regulation that labeling can occur in one direction only. We again agree that we do believe that the predominant direction that labeling would occur would be in the direction of transfusable product to product for further manufacturing.

The proposal to differentiate the products for further manufacturing that are described as concurrent and component plasma - - this creates a dichotomy for two products that in reality are the same component. They are collected from donors qualified under the same set of regulations, processed and stored under the same condition,

and the products, the transfusable products, that is, are used the same in transfusion practice. Blood establishments cannot collect standalone plasma from donors any more frequently than is allowed under the guidelines for infrequent plasmapheresis that have been in place since 1982.

The European Union and others do not differentiate between apheresis plasma collected in these two different circumstances and creating two different products would lead to further disharmony with the EU. AS there is no scientific or biologic basis for setting limits for when a product is converted to plasma for further manufacturing, we reiterate our belief that it would be unwise to create a barrier to effective inventory management by arbitrarily assigning a waiting period before allowing a product to be relabeled. The component product is biologically the same as the concurrent product.

The proposal to differentiate these products through use of labeling as concurrent and component has also created a GMP error-prone process when apheresis FFP products need to be relabeled for further manufacturing. In the topic summary there is a figure 2. It provides a visual of the products that could be collected manually or by automated methods. The amount of time involved before the product could be converted to a plasma for further

manufacturing and what the product for manufacture would be called. When looking at the automated apheresis products it appears that the FFP product collected with a cellular product is called by a different name than the FFP product collected as a standalone product. In just looking at the figure this is what it appears. But both products are labeled and placed in the freezer as apheresis FFP. This is true even for products labeled with ISBT 128. There is no information on the apheresis FFP label, either in the name or in the code, to note the difference between the two. Establishments will have to introduce additional computer controls or reports to insure that a standalone plasma is not labeled prior to expiration. The inherent GMP challenge is in the proposal are an additional reason it is best to have one product name for plasma for further manufacturing.

Language from the European Pharmacopoeia concerning factor VIII levels for plasma used to make labile products was cited in the summary and a parenthetical statement was added reflecting indecision about the frequency of the testing and which establishment should perform the testing.

This test from the monograph does not reflect mandatory requirements of the Pharmacopoeia and it is variably applied by fractionators in Europe. Recent

conversation within the task force, including representation from fractionators indicates that this test intended to demonstrate adequate quality of the starting material for fractionation could either be done by the blood establishment or by the fractionators as part of the end process QC on starting pools for fractionation. Responsibility for testing should be left to the fractionators to define in the contract with the center.

We note the blood establishments do not perform factor VIII levels in FFP or plasma frozen within 24 hours. Factor VIII levels are performed for purposes of QC on cryo manufacturing and these data will be presented here today, I believe.

Freezing at minus 20 will require modifications for some establishments, as Dr. Weinstein said, and sufficient time should be allowed in the implementation of new product standards for establishments to make the modification. As a comment we note that FFP collections at mobile sites are primarily constrained due to the need to get the product into the freezer within timelines required by the directions for use for the blood collection processing and storage systems and while we hope that these changes that are proposed will give us increased ability to create some FFP, that it is really the increased

flexibility to manage existing inventories that we are looking for.

Again, we thank you for the opportunity to participate in the discussion and I would like to emphasize that these comments today are intended to facilitate implementation of the new regulatory pathway. The task force appreciates the time that has been spent moving this issue forward and we look forward to having this licensed product for further manufacturing.

DR. HOLLINGER: Thank you, Allene. Any questions of the AABB representative? If not we will move on to the next person, from America's Blood Centers, Dr. Gay Wehrli.

DR. WEHRLI: Good afternoon. I am Gay Wehrli and I am from Virginia Blood Services and the University of Virginia Health System. I am just realizing that you probably all are able to be here today because, like me, you did not receive an invitation to William and Kate's wedding of tomorrow. Okay, on with the show.

America's Blood centers is a network of 74 non-profit, community-based FDA-licensed blood centers that provide about half of the volunteer US blood donor supply. Hema-Quebec, our Canadian member, supplies about a quarter of Canada's blood supply and is licensed by Health Canada. The Blood Centers of America and Blood Group Alliance are group purchasing organizations for members of ABC that

manage the contracts for shipment of plasma for further manufacture, the fractionators. All are represented in the AABB Interorganizational Plasma Task Force.

I will be presenting today the survey on plasma for further manufacture. This survey was designed to respond to questions that have been raised by CBER's Office of Blood Research and Review about the impact of the proposals for, one, licensure of recovered plasma currently shipped for further manufacture under short supply agreements, and two, conversions of plasma collected concurrently with infrequent apheresis of whole blood donors to plasma for further manufacture before expiration.

These proposals have been the subject of a 2004 workshop, 2009 BPAC review and ongoing discussions between the AABB Interorganizational Plasma Task Force and the FDA.

This 18-question survey was conducted between April 19 and 25, 2011. Thirty-seven of the 74 US America Blood Center members responded, representing 4.6 million whole blood and apheresis collections per year. All respondents prepare recovered plasma. In 2010 they shipped over 640,000 liters of plasma for further manufacture.

The survey asked about the proportion of plasma for further manufacture that met the manufacturer's requirement for maximum time between venipuncture and freezing. In the first row, our centers shipped plasma for

manufacture of solvent detergent plasma, which carry the blood type and is frozen within 8 hours. Over 60 percent of the plasma prepared by many centers is frozen within 8 to 24 hours of venipuncture for manufacture of labile plasma protein, such as factor VIII. A smaller proportion is frozen up to 120 hours for the manufacture of stable components like IV Ig. Some of the plasma for the manufacture of stable components is cryoprecipitate depleted. The cryoprecipitate is distributed by the blood center for transfusion purposes. The time to freezing is in general determined by collection facility and, in particular, is dependent upon the distant between a collection site and the laboratory, which will be separating and freezing the plasma.

A substantial number of our member centers meets the European Union requirement for freezing to minus 25 Celsius within 12 hours, and for storage at minus 20 Celsius. A few small centers do not have this ability. Over 80 percent of plasma shipped by 19 centers must meet European Union requirements in order to be accepted by the fractionators. Additionally a substantial amount of the centers meet the European Union requirements voluntarily. Depending on fractionators requirements, some centers will perform some type of QC, mostly the qualification of the raw materials to the manufacturer.

Centers preparing cryoprecipitate need to perform QC. In general, they do this by sending specimens to coagulation laboratories to measure factor VIII levels. This is an example from the Mississippi Valley Regional Blood Center and shows two years of their QC performed on cryoprecipitate. Similar data has also been provided by Blood Systems.

In the survey they were also asked about the impact of preparing plasma for further manufacture within 72 hours. Twenty-two of the 26 centers said that this is feasible but are concerned about cryoprecipitate-poor plasma. About 60 percent of the respondents collect apheresis plasma for transfusion, although they limit the volumes collected and they focus on collecting group AB to avoid outdates.

Twenty-nine centers collect concurrent plasma during apheresis for red cells and platelets. They adjust the volumes and types again to what can be distributed for transfusion.

So, they also reported on advantages to relabeling a plasma for transfusion as plasma for further manufacture. Certainly it provides inventory flexibility, greater ability to manage group O and group A units. It prevents wastage of a valuable resource, in particular, when we have female donors, when there is a problem between

the distance between the collection site and the center which will do the processing, post donation information, which would qualify the unit and also expand automated concurrent plasma collections to like groups other than AB. For example, O and A platelets or double red cell collections.

What are some of the disadvantages of the unidirectional labeling, meaning plasma for transfusion being labeled to plasma to further manufacture but no backwards? This prevents the use of plasma for transfusion after conversion. It restricts inventory management options. It discourages selectively relabeling when fresher inventory is available, and need to store – you have to store this until there is enough product available for shipment and you must pack it separately from whole blood derived plasma. It discourages a blood collection center from asking donors to give for transfusion or for further manufacture according to what the current need may be.

While respondents indicated that they would like this option to re-label and go backwards and forwards units for transfusion to units for further manufacture, they also felt that it really was not necessarily the most critical issue.

So why would you want to re-label plasma for further manufacture as plasma for transfusion? In particular, if there is a patient in need and this plasma meets the requirement for transfusion, let's make it available to the patient. The ability to use AB plasma or product from first-time donors for transfusion if the donor meets criteria, and certainly other patient needs whether it is due to a mass casualty situation or there is a shortage of a particular ABO group plasma, or an acute patient needs, such as a patient undergoing plasma exchange for a TTP. Again, it increases the flexibility to manage inventory.

That is all I have to report from this survey. Thank you very much for providing me this opportunity and I am here to take any questions if there are any.

DR. HOLLINGER: Any questions?

DR. KLEIN: Do you have any idea how long you might be storing plasma once it is re-labeled before it is shipped?

DR. WEHRLI: I will have to turn to Celso for some help here.

DR. BIANCO: You are talking about the recovered plasma?

DR. KLEIN: Should you re-label it unidirectionally would you then hold it for a month?

DR. BIANCO: No, in general centers don't even have storage capacity for so much. In general, every two weeks the plasma will be picked up and shipped.

DR. KLEIN: I guess the point I am trying to make is going backwards would probably be on an emergent basis and very unusual.

DR. BIANCO: And I think that is why the majority of the responders said that this would be nice but it is not a critical issue.

DR. HOLLINGER: On the same question, is the problem with availability one of fresh frozen plasma or one of red cells and platelets?

DR. BIANCO: I think you are relating to the question of why the restriction in terms of the shipment of plasma obtained by apheresis for further manufacture and the different with source plasma. I think this is an old concern that FDA has had for many years. I don't think there is a basis today for that in terms of availability or distribution. The structure of blood centers – blood centers are driven, the voluntary sector is driven by the collection of red cells and platelets. The plasma that is shipped for further manufacture represents financially and economically is not more than five percent of the total revenue of a center. But in these days, with health care

reform and everything, it is a very important source that balances everything, and balances what happens.

Also is the idea that a plasma that is good for transfusion is good for further manufacture. The second concern that has been always, again in terms of FDA, was that even within this environment would blood centers voluntary systems change their model and transform themselves into plasma collecting facilities? We would never have the structure to do that or necessarily the desire. They are volunteer donors. The maximum plasma that we can collect from them maybe is once a month in apheresis for an AB plasma. But rarely a donor who is under the infrequent plasma collection rule, rarely a donor will do that.

The third concern there has been is the concern that the plasma would be shipped to a commercial facility. These days I believe that as the hospital chains move, I believe that a substantial number of hospital chains are for profit chains. They are getting our red cells, they are getting our platelets – I think the focus of our donor is the patient, and that is how we recruit and that is what moves them to donate is to help patients. And if we tell them we are going to help patients with plasma or manufacture of immunoglobulins, or manufacture of other factors, they understand that and they accept that. It

depends also on the quality of information that we give them.

I must say that, in general, and you heard some from the task force, from Allene from AABB, we are very happy that finally FDA is moving in this direction. And there are two fundamental things. One is the licensure of recovered plasma. We don't even like the name "recovered plasma." It seems to be a second rate product that is going to be used for something. It is very important, and if this plasma is good for transfusion, as I said before, it is good for the manufacture of a product, that it will still help people and save lives.

And the second thing is to allow, within certain limits that are being imposed, the conversion – if we collect a unit of platelets we can collect simultaneously from a donor, from a male donor particularly, that we are interested in that plasma since we are trying not to ship plasma from females for transfusion to reduce the risk of TRALI. That becomes very important.

So I think that those will be small issues if the big issues are resolved and finally we move in that direction. So I am exulted with the fact that we are discussing this today and we are addressing the issue today. These smaller things are not going to stop us from moving. The most critical issues are those – the licensure

of the recovered plasma essentially, the controls, and the conversion of the concurrent plasma collected with the platelets or with the double red cell apheresis for transfusion that will increase, because we lost that. Before those were all whole blood collections and today more than ten percent of the red cells distributed come from double red cell collections. And we don't collect plasma almost from these donors because we can't really control, to focus on the right types and the right things. If we can have that outlet, that will improve things for all of us and w will be very happy.

DR. HOLLINGER: Thanks, Celso. I want to just finish up the open public hearing and then we will get back later on with the questions. SO we have one last speaker here. It is Miriam Goldstein from the Committee of Ten Thousand.

MS. GOLDSTEIN: Thank you. My name is Miriam Goldstein. I am appearing today on behalf of the Committee of Ten Thousand, a grass roots advocacy and support organization for people with HIV, most of whom contracted HIV from tainted blood products.

Corey Dubin and Dave Cavanaugh, who would normally be here, are out of town and send their regrets. They are also not at the royal wedding. I have no financial interests or relationships to disclose.

COTT appreciates the opportunity to comment on the proposal to revise the classification of recovered plasma. COTT is in favor of bringing plasma that is included in manufactured products within the scope of effective FDA licensing and oversight, including standardized requirements for freezing, storage and shipment. But we have some questions about the proposal and its practical consequences for end users of plasma products.

One is that unlicensed products still exist. We still have a category of unlicensed recovered plasma. We support the restriction against using that in injectable products, but are concerned about what use could be made of that, aerosol medications or something else.

Second, the proposal gives industry broader leeway to collect and to include concurrent and component plasma in manufactured products unless it is, in fact, a stated goal. But it leads to questions about what effect this would have on manufacturers' existing source plasma collection programs. Connected to that, as the use of concurrent or component plasma expands, is there going to be an upper limit on how much can be included in manufactured products. Now, in practice, ten percent is recovered plasma. Could a final manufactured product consist of 50 percent or more? What is the meaning under

these circumstances of industry certification programs? Can industry continue to say it is following standards that relate to the collection of source plasma if a growing part of its product comes from concurrent or component plasma?

Finally, what is the ultimate effect on product quality and will there be an active and effective post-market monitoring of that impact?

In conclusion, as the Committee discusses today's proposal, COTT urges you to keep at the forefront the interest of plasma end users for whom plasma and plasma products are vital lifesaving resources.

Thank you.

DR. HOLLINGER: Any questions to the speaker about her presentation?

DR. BIANCO: I don't have a question. I have just a couple of comments. I understand the concern and I believe the concern comes more from actually the main recovered plasma than anything else. Today it is a product that we collect under the same standards as we collect whole blood donors for transfusion under FDA license, under AABB accreditation, CAB accreditation and others. That is what is transfused. And that is the product that is used for manufacture.

But there are no regulations regarding these products. It is all just an agreement between the company

that fractionates and the blood center that collects. What this change will do, it will bring FDA regulation to that product. So it will be a better product in terms of your point of view, the point of view of COTT, because it will be a regulated product the same way red blood cells are regulated today, the same way that a platelet is regulated today.

There is only one question that I don't know how to answer, is the question about the aerosol. I don't know if aerosols use plasma. I know that there are certain products that are derived from plasma, that is, the eye drops for people with problems with dry eyes. But I don't know of other products. Maybe somebody from FDA can help us, Dr. Weinstein or Dr. Epstein.

DR. EPSTEIN: There are five that can be used topically, including internally. There is aerosolized proteinase inhibitor. I think we take this comment and probably what we really had in mind was products for in vivo use as opposed to in vitro use, and we can clarify that. I think for the purposes of today's discussion with the Committee let's assume we are distinguishing in vivo from in vitro rather than injection versus aerosol versus topical.

MS. LINDEN: Sort of related to that, this issue about the amount of oversight and regulation – is there

something particular that causes your group to have concerns that blood cells, blood transfusion, apheresis or whole blood do or don't do that would render the recovered plasma less safe than source plasma?

MS. GOLDSTEIN: As a consumer I can say that I have been present -- I have two sons with hemophilia – at a number of very detailed presentations about the safeguards that now exist to assure the purity and quality of plasma-based factor. Some of these were discussed this morning in terms of stringent donor qualifications and inventory controls and so on. I think many people do not realize that that is true of 90 percent of the input, that it goes into fractionated products, and no it sound like maybe that percentage is changing. I understand that those programs are voluntary industry certification, but the end users are being told that the product that they are using is one thing and perhaps it isn't.

DR. HOLLINGER: Thank you. I just want to ask is there anyone else in the audience who wants to speak during this open public hearing? If not, we are going to take a 15 minute break.

(Break)

Agenda Item: Open Committee Discussion

DR. HOLLINGER: So let's just see if there are some questions among the Committee members about this topic

today, on the standards for concurrent component plasma, et cetera, comments about it, directions, unidirectionals, bidirectionals, et cetera. So yes, Ron, why don't you start off, Dr. Gilcher?

DR. GILCHER: These are my personal thoughts, but also I've talked to a few members, and that is that I felt that unidirectional labeling is appropriate, and that bidirectional labeling is not. My personal concern, when I ran the Blood Center, was that every time we labeled, we ran the chance of an error, and so continuing to make labeling changes introduces the risk of error. So I would be not in favor of bidirectional labeling, but continue to favor the unidirectional labeling, so I wanted to share that.

DR. HOLLINGER: Can you tell me again, on what's been called, recovered plasma, that can be anti-core positive only, is that right? Is much of the anti-core positive blood - I mean, the source plasma uses blood that's not been tested for anti-core, and the whole blood industry does not. So the question is, blood that is anti-core positive but is not positive for anything else, is that blood set for further manufacture, by and large, by blood banks? Can you tell me?

DR. GILCHER: No, all core-positive blood was not labeled in our blood center because it could not be a

transfusible product, obviously, and then be relabeled to become recovered plasma.

DR. HOLLINGER: I know it can't be used as a transfusible product, but it cannot be also shipped to a source, a plasma manufacturer for further –

DR. GILCHER: It could be used for non-injectible use, I think that's correct.

DR. HOLLINGER: It can be. Yes, Jay?

DR. WILLIAMS: FDA standards, regulations and guidance do not prohibit converting an anti-core positive plasma to recovered plasma. Of course, it cannot be used for transfusion.

DR. HOLLINGER: So it could be used for further manufacture. But I guess my question is do the blood banks in general do that or not? Ron?

DR. GILCHER: What Jay is saying is, you have recovered plasma but then you have types of recovered plasma; recovered plasma fresh frozen, recovered plasma non-injectible. This would become recovered plasma non-injectible. It never was labeled as a transfusible product, then let's say fresh frozen plasma that became recovered plasma fresh-frozen, if you understand what I'm saying.

DR. CARR-GREER: Could I just clarify – as of a couple of years now, the fractionators have not wanted the

core-positive plasma, so there seems to have been a shift, and so even though it is allowed, as Dr. Epstein said, by the regulations, the core-positive plasma is allowed for further manufacture, and so it could bypass the transfusion label and go directly to be labeled for further manufacture, for the past few years it simply hasn't been because the fractionators do not want it, so the contracts have disallowed it, if that's helpful.

DR. HOLLINGER: I wondered if that was maybe something that the person from the Committee of Ten Thousand had some concerns about initially and that was one of the reasons I asked that question. Celso, you had a –

DR. BIANCO: I had a comment about one issue that is prominent in the questions to the Committee, but that we didn't discuss, is the question of the measurement of the Factor VIII levels in a product? I didn't think that it was as – I didn't read it in the way that I'm reading now, that it would be a requirement to measure the average Factor VIII for the plasma. Whose responsibility is that, because until now, that is, we do it for the cryoprecipitate, because it's a requirement, but we don't regularly do it for the recovered plasma that we ship? We see this as a requirement of the manufacturer as they qualify the raw material that they are going to --.

DR. HOLLINGER: And Mark, would you also comment – just to clarify, I think, about the number – it's not every unit that needs to be tested like this, but it's a pool; so could you clarify that too?

DR. WEINSTEIN: Right. It is this notion of being a pool, as I mentioned, for the European pharmacopeia they require at least ten units to be part of that pool that they're examining for the average Factor VIII level. I did actually inquire to our European colleagues about who does this for the products that are manufactured in Europe, and apparently it is the collection centers who would be doing this measurement for the products shipped there.

I think that again, we're talking about process validation, or we're talking about that we're not necessarily looking to – this has to be worked out, it isn't entirely clear how we're going to go forward with this, but it's potentially a consideration that we would think that if you can establish that you can do this in a routine manner, and there might be some quality control element, periodic, to ensure that you actually are accomplishing this, that this may be a path forward?

And how large the pool is, that question, but interesting consideration here. In order for one to make FFP and qualify that, it turns out that the plasma – one can demonstrate that they can make a cryoprecipitate from

FFP; in fact, that FFP has to meet the 70 units per 100 ml element to it, because you can't make cryoprecipitate that has the 80-unit average per cryoprecipitate, so there may be some thinking about exactly what has to be done for FFP in relation to this qualification of assuring that the 70 units per 100 ml is attained.

DR. BIANCO: However the concern that I have, and others have, is the plasma that goes for cryoprecipitate; that is, the one that we measure, is a plasma that is collected and frozen within eight hours, and so what happens with the plasma at 24 hours or at 72 hours, that is going to go for the –

DR. WEINSTEIN: We're not measuring the Factor VIII levels for the non-labile products. But for the 24-hour, if you want to, again, use that plasma that is collected within the 24 hours for labile products, it should meet that Factor VIII level, that 70 unit per ml average level – and that can be achieved, as we saw from some of those studies here, it can be achieved in non-FFP plasma.

DR. HOLLINGER: Yes, Dr. Kuzma?

DR. KUZMA: I had a question going back to the issue of bidirectional labeling. What is the rate of errors in labeling if you have those numbers versus the frequency of shortages of transfusible plasma? I'm just

looking for the ramifications of error-prone versus shortages; do we know those rates at all?

DR. BIANCO: I don't have numbers that I can pass to you; it's very, very low because today, labeling is all computer controlled. Labels are printed on demand as you go back and forth, unless the product qualifies according to tables that were created and validated. The rate of errors is – that's not where the errors occur.

DR. KUZMA. Okay. So that would support bidirectional labeling?

DR. BIANCO: It would support both ways, yes. It's also all controlled by bar codes, so it's not just somebody entering a number into a little keyboard.

DR. HOLLINGER: Go down through some of the comments that they want us to make here and see if anyone has anything to say in this regard.

They've asked us to comment on the current considerations on standards for concurrent plasma, and the first is label products made only from plasma held at equal to or less than 24 hours from collection to placement in freezer. So the labile products would be made only from those. Are there any comments about that?

DR. KLEIN: I think that by and large it assures that you're going to have a better quality of plasma, and I have not heard from the public or anyone else that that

would, in any way, impede the current supplies, so that it's certainly true that you can make all kinds of labile factors from plasma that's older than that, but of course it's less efficient, so by and large manufacturers don't want it now anyway. So this really regulates a better quality of plasma. I don't see much of a downside.

DR. HOLLINGER: Any other comments about that – again, I'm still trying to struggle with why the fresh frozen plasma at 8 and 24, in terms of transfusible product, when a physician asks for a transfusible product and he asks for fresh frozen plasma, I'm sure the physician doesn't know that one is frozen at 8 and one is frozen at 24. He might –

DR. KLEIN: Thank goodness.

DR. HOLLINGER: I can understand that. So is there any difference between those two products in terms of any of the factors, any of the labile factors?

DR. KLEIN: Practically speaking, Blaine, the reason for this is so that you can't take plasma that's on units of whole blood used for other purposes, where you have to store, for example, blood that's on a mobile or blood that's being used for platelet production, and still salvage that plasma and not have to throw it out because you can't freeze it within eight hours. Practically speaking, as you know, every one of us has different levels

of labile factors of Factor VIII. The loss that you have between 8 hours and 24 hours is relatively small, and probably doesn't make much difference in terms of what you give, since ordinarily you don't, or shouldn't be, giving a single unit of fresh frozen plasma, or plasma frozen within 24 hours, to anyone except a baby.

DR. HOLLINGER: So the second comment is about – again, we've talked a little bit about average – the Factor VIII levels are equal to or greater than 70 IU per 100 ml for plasma, used to make labile products as process validation and possibly also quality control testing under GMP. Any comments about that or who would do it? Or anything in general? No comments? Okay.

The next one is non-labile products made from plasma and held for equal to or less than 72 hours from collection to placement in the freezer.

Then replacing the temperature from equal to or less than 20 for the equal to or less than 18 degrees for all conditions of freezing, shipping and/or storage.

And the next one, I thought was kind of interesting; this allowable shipping and storage temperature deviation, which can exceed the minus 20 degrees for up to 72 hours total, but never greater than minus 5. I guess what they're really saying is you could

ship something, and the temperature could fall to minus 5 degrees for up to 72 hours and that would be okay.

Anybody have any problems with that – we talked a lot about how – well I guess this could be for labile fractions also. Is there any data about this – Mark, do you have any data on what happens when you have a sample like that?

DR. WEINSTEIN: Well first of all, this has been the standard for many years, and this is the thing for source plasma, and I have to say that I don't have – I can't cite a literature source that says that nothing would happen under these conditions, but it is important to remember that the plasma is not in the liquid state under these conditions. It's always going to be frozen.

Now there is a process of – they call it – where they hold plasma for a certain amount of time at a somewhat higher temperature – conditioning, I think, for plasma manufacturing, when you can change the quality of cryoprecipitate, say, if you raise the temperature of plasma for a certain period of time and you'll get perhaps more proteins when you thaw it out – or you make cryoprecipitate, you can change the quality, but as far as any indication of inferior quality to a plasma that undergoes that particular variation. I don't have information directly to be able to cite as demonstrating

that this would be okay, on the other hand there is history, I guess, and the fact that this is the standard that is used and recognized both in European and in our regulations.

DR. HOLLINGER: And I presume, in shipping, there are mechanisms set up, regulations or so on, where the temperature is recorded and monitored, or either known whether things might thaw and then refreeze? Yes, Don?

DR. WEINSTEIN: Yes.

DR. TRUNKEY: I'm curious, we've got down to this one – are all of these in sync with the EU standards?

DR. WEINSTEIN: No, not entirely. It mentioned here, for example, the EU standard for this rate of freezing; in other words, getting your plasma frozen to reach a core temperature of minus 25 degrees in 12 hours is not something that we are considering at the present time. However it was very interesting to hear the information just now about what, in fact, is done for plasma that is being shipped. In fact, people are able to achieve those temperatures; I guess a large majority of collectors are able to ship plasma to Europe under those quick-frozen conditions, and that was interesting to us.

DR. TRUNKEY: But it seems to me it would be desirable, if possible, to match up EU and US standards.

DR. WEINSTEIN: There's nothing to prevent folks from doing that. Again, our consideration was, was it really going to yield a better product, and that's what I discussed here in this whole idea that even though you do this quick freezing, you don't necessarily in the end derive products that are of higher yield, for example, in the Factor VIII, when you make your cryoprecipitate when plasma is frozen quickly, compared to the minus 20 degree issue here.

So we thought perhaps, we were imposing more of a burden on collectors than apparently would be the case; again, learning just now about the routine practices that apparently are being done.

DR. EPSTEIN: I just want to comment that these issues are linked in a certain way. Why we're talking about process validation and possibly quality control for Factor VIII level is because we recognize that we aren't, in this consideration, seeking to control all the possible variables, and we know that they would be different from blood center to blood collection center. So what we're saying instead is well, we'll set minimal standards for the process variables; namely, time to freezing and freezer temperature, but we're not going to control time of cell contact, rate of freezing and surfaces and many other things. Instead, what we're saying is well, you need to

validate that the way you make the plasma produces a plasma suitable to make labile factors, and the way to do that is to show that it meets the Factor VIII standard.

So by having a functional standard where, in effect, substituting that for more stringent conditions of processing, which we're leaving open, recognizing that they may vary from place to place. I hope that helps somebody.

DR. HOLLINGER: Okay, the next one is storage for up to three years. I understand that the plasma industry, the source plasma can be stored for up to ten years, is that right?

DR. WEINSTEIN: That's the current rate.

DR. HOLLINGER: So storage up to three years. Any comments? And the last one, we sort of dealt with a minute ago, about thawed and refrozen should not be used for injectible products with the possible exception of cryo-poor plasma. What's the last section in there? Why is that okay?

DR. WEINSTEIN: I think that because it is, in fact, being done now to make suitable immune globulin and albumin products, there is somewhat of a track record here, so we have to be cognizant of that.

DR. HOLLINGER: This is the last chance – anybody with any comments about concurrent plasma and component plasma, the designations?

And the same thing goes with the bidirectional issue. We want to be sure that we've covered all the bases on that. I thought there was actually a reasonable suggestion from the task force, suggesting that possibility and capability to do the bidirectional, anyway.

Yes, anybody else?

Okay. Then we do have a vote, I guess. Yes, thank you. Put in the numbers you think are the best. No, they not asking us that, they just say does the Committee agree with the FDA's current considerations on labeling categories for concurrent plasma? We'll have a similar one for component, but this is for concurrent plasma.

And I guess these are – perhaps you might want to explain. I think they're asking for each one of these levels; that is, if plasma has been frozen within 24 hours and has an average Factor VIII level of equal to or greater than 70 IU per 100 ml, that there should be considerations or standards for labile, non-labile and non-injectible products made from it. And then the same thing is true for the other conditions that are listed, but which ones that will be labeled, is that correct?

DR. BIANCO: Dr. Hollinger, I want to raise again, a little bit of concern about average Factor VIII, higher than or lower than 70.

What is average? Do I have to measure all the units that are in the batch that I'm shipping? And it says on the bottom, with the star, process validation possibly also quality control testing under GNP. But this, I think, is rather vague. What Europeans do is they'll take, a couple of times a year, ten units from their supply, and they'll send to a clotting lab, and measure the Factor VIII, which is different than under CGMP. Most blood centers, some do, don't even have a clotting laboratory. They ship it to a reference lab or to a university. How often will we do that? How do we define the average? It could become very burdensome, and that's something that I'd like very much for us to emphasize, that during process validation, probably, you are correct, you've documented that the process is working as was predicted. But after that, that this be a reasonable process.

DR. HOLLINGER: Mark, could you give us a –

DR. WEINSTEIN: Again, it may be clarification for me here, but how you do your qualifications for cryoprecipitate, you know, you do have standards for cryoprecipitate that you have to demonstrate, and I forget exactly what the frequency is here, but it has 80 units on the average in your cryoprecipitate. Somebody's doing that measurement, somebody is – you do have a process now for people who make cryoprecipitate from plasma here, that

there is a procedure that's going on now, I just don't know exactly how much more burdensome what we're suggesting here might be, you're looking again at an average and you're sending it to a laboratory to do that measurement.

DR. BIANCO: It's a question of volume. The amount of cryoprecipitate that is prepared by a center is rather limited as compared to 50 percent of the plasmas that are prepared are from females.

DR. WEINSTEIN: Again, we're talking about when the Europeans are here, they talk about European pharmacopeia, they have this pool of 10 units that they are looking for the average level of Factor VIII. I think that these are considerations that we can take into account when we get more specific –

DR. HOLLINGER: Does that mean that the pool is less than 70, that it could not be used? Is that basically what you're saying?

DR. WEINSTEIN: Well perhaps it would be indicating that the process which the particular blood collection system is using might not be giving you this level at a predictable occurrence, and there are various ways that one can adjust that, you know, the different donor populations have different levels of Factor VIII and posing, or trying out, this more rapid freezing condition would raise the level that you're measuring – these are all

potential ways that one could adjust and assure that that level was being reached in your pools.

DR. HOLLINGER: So again though, just from a practical standpoint, I guess I'm also a little puzzled: If a blood bank, an organization sends to a manufacturer five thousand units of the plasma, they theoretically could take out ten of those units and test them. Therefore, they're going to make a decision based upon those ten units of what the other – might have been collected under a variety of ways, and so on, of where they're going to throw out the – I mean, not be able to use the rest of them for labile products?

DR. WEINSTEIN: I think they may be asking the blood collection organization unit, whatever to do to assure that the product they're sending to the manufacturer has this level of activity, so it's responsibility. At least again, this is being done. Somehow it's being managed in the European context, and we're making it – I think our suggestion is, in fact if this is done through a process validation consideration here and there's occasionally QC testing here under GMP that this may allow for a perhaps easier way to comply with this consideration for achieving this level of activity.

DR. HOLLINGER: Does that resolve that for you, Dr. Bianco?

DR. BIANCO: Well my impression is that Europeans do not do it very frequently, but again, it is just talking to people. I think that we need a little bit more information about their experience with the process before I could tell you something more concrete.

DR. HOLLINGER: Yes, Dr. Klein?

DR. KLEIN: I think you may be concerned that regulation will then put some burdensome type of mechanism in place, but this is not unknown to blood centers. We already do process validation for -– we do process validation for white cells in leuko-reduced blood, so the concept is there, but I guess it's the consideration of the detail – is it going to be so much demanded that it will be burdensome, and again, I think a reasonable process validation, which that's the concept, is something that we've commented on; I think the FDA has heard it now, and are aware of the possibility of doing in a reasonable fashion, the possibility of doing it in a burdensome fashion. The level of 70 really isn't easily achievable –- if you're not doing that, you're doing something wrong.

DR. KUZMA: I had a procedural question and then a substantial question.

Can we propose amendments to the question? Like for example, I think what's concerning you is the quality control language under there, which is different than

process validation, so could we propose an amendment to delete and possibly under quality control? Or just for the time being? That's just a procedural question, whether you allow amendments to the questions.

DR. WEINSTEIN: Well sometimes, I think it's useful. Other times, it may be equally as useful to give your opinion about it, because the FDA will listen to this and they'll utilize it in making these decisions. So do you have a specific - ?

DR. KUZMA: Well I was going to suggest we delete the quality control, and possibly quality control because quality control implies a greater frequency to me than process validation. But that's just a friendly amendment.

DR. HOLLINGER: So Jay, could you respond to that?

DR. EPSTEIN: -- that there's a concern about an excessive burden if we were to routinely require quality control. I think that the way the FDA is looking at it is that we're actually talking about a lot of different manufacturing processes, some of which may require control and others of which may not. We're just not prepared at the present time to rule out a quality control approach. We understand that a one-time process validation as along the process is then not changed, may suffice. So we got that idea.

But it's what do you do in the face of variability.

DR. KUZMA: Thank you, that clarifies it for me. My second question is what's the difference substantially between two and three, rows two and three, and why would they be labeled differently. This is perhaps just an industry feature that I'm not aware of – why would you want to label one differently than the other? They're both – they both have the same end uses, and so why?

I may have missed that in the presentation, I'm sorry.

DR. WEINSTEIN: Let me make sure I understand what you're saying. So the 24-hour you have liquid state, so less than 70 units per mail. And the 72-hour plasma would actually have the same label; that is both of these are being used for non-labile products, that would actually have the same label – the same label would appear on them.

DR. KUZMA: Oh, okay. I thought they were going to be two different labels.

DR. WEINSTEIN: No, we just wanted to make it clear, that clarification.

DR. KUZMA: Thank you.

Agenda Item: Questions for the Committee

DR. HOLLINGER: Let's go ahead and vote on this concept here, without specifics, but the concept of how

this might be set up. So again, a yes vote is that you agree with that concept for this table, abstain, appropriately, a negative, that you do not agree with this concept.

So let's go ahead and vote, and while we're finishing the vote up, Celso, I know you're a non-voting member, but how would you vote for this?

DR. BIANCO: I would vote yes, because I really am happy to see this project of many years moving ahead.

DR. HOLLINGER: Thank you. Can we see the response please?

(Pause)

It's illegal to vote over there on the next one next to you also. (Laughter)

(Pause)

DR. HOLLINGR: Yours is not working? I guess, if there's not a problem, I guess you just vote on that one over there. They're going to have to set it up. It's not a big deal.

So yours is not recorded? And his vote is a yes. Are we square with this? I think we're square. Now we're square with it. So go ahead and read the vote.

DR. EMERY: The Committee has voted, and it is unanimous yes. So Dr. Hollinger voted yes, Dr. Linden voted yes, Dr. Rentas voted yes, Dr. Troxel voted yes, Dr.

Trunkey voted yes, Dr. Gilcher voted yes, Judith Baker voted Yes, Dr. Kuzma voted yes, Dr. Klein voted yes, and Dr. Maguire voted yes.

DR. HOLLINGER: Thank you. You're the final table, and it's a similar table. But – well it's not a similar table, it's about component plasma, and it's divided up into equatorial less than 8 hours, fresh frozen plasma, to be placed in either labile, non-labile or non-injectible, and these are products, my understanding, products prepared specifically for plasma, aphaeresis products for plasma. Is that correct?

DR. WEINSTEIN: The component plasma is initially for plasma aphaeresis – outdated aphaeresis plasma for transfusion.

DR. HOLLINGER: Yes, for transfusion, thank you, and then what's the future products?

DR. WEINSTEIN: We may end up, in the future, having products that are longer period of aphaeresis plasma held in the liquid state for a longer period of time but we are not considering that at the moment.

DR. HOLLINGER: Any comments about this table? If not, let's go ahead and vote again, yes, acceptance for the concept of this table and abstain, and then no. So go ahead and vote.

DR. EMERY: The Committee has voted.

DR. HOLLINGER: Any comments, Celso, on your part? You would have voted -

DR. BIANCO: Well just a comment that I regret the lack of trust, that we wouldn't transform ourselves into plasma houses, but otherwise it's acceptable, it's a small fraction of what we do. The other part will help us tremendously.

DR. EMERY: Question number three. The Committee voted unanimously yes, and that is Dr. Hollinger yes, Dr. Linden yes, Dr. Nelson yes, Dr. Rentas yes, Dr. Troxel yes, Dr. Trunkey yes, Dr. Gilcher yes, Judith Baker yes, Dr. Kuzma yes, Dr. Klein yes and Dr. Maguire yes. I said earlier that Dr. Nelson voted yes, but Dr. Nelson is not here, and please scratch that from my statement.

DR. HOLLINGER: Okay, well we're not supposed to adjourn until five, so that's nine minutes, so we all have to stay here for another nine minutes until we adjourn. So we've going to adjourn early, and tomorrow morning we'll start at 8 o'clock and the topic is on the written statement of understanding for blood donors.

Thank you all for your participation today.

(Whereupon the meeting adjourned at 4:51 p.m.)