BLOOD PRODUCTS ADVISORY COMMITTEE

56TH MEETING

Thursday, September 18, 1997
8:15 a.m.

Quality Suites Hotel
Potomac Ballroom 1, 2, 3
3 Research Court
Rockville, Maryland
PARTICIPANTS

Blaine F. Hollinger, M.D., Acting Chairperson
Linda A. Smallwood, Executive Secretary

MEMBERS

Charles S. August, M.D.
Benjamin Cheng
Corey S. Dubin
Jerry A. Holmberg, Ph.D.
Rima F. Khabbaz, M.D.
Jeanne V. Linden, M.D.
William J. Martone, M.D.
Beatrice Y. Pierce, R.N.
Jane A. Piliavin, Ph.D.
Joel I. Verter, Ph.D.

NON-VOTING CONSUMER REPRESENTATIVE

Reverend Violet C. Little

NON-VOTING INDUSTRY REPRESENTATIVE

Paul M. Ness, M.D.

TEMPORARY VOTING MEMBER

Paul R. McCurdy, M.D.
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statement of Conflict of Interest</td>
<td>5</td>
</tr>
<tr>
<td>Welcome and Opening Remarks</td>
<td>8</td>
</tr>
</tbody>
</table>

### INADVERTENT CONTAMINATION

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of Previous Discussion and Introduction to Topic: Edward Tabor, M.D.</td>
<td>12</td>
</tr>
<tr>
<td>Definitions and Operational Practice: Boyd Fogle</td>
<td>19</td>
</tr>
<tr>
<td>Donor Risk Factors, HBV and HCV: Robin Biswas, M.D.</td>
<td>30</td>
</tr>
<tr>
<td>Donor Risk Factors: HIV Kimber Lee Poffenberger, Ph.D.</td>
<td>47</td>
</tr>
<tr>
<td>Significance of Risk Factors Revealed by Surveillance: Miriam Alter, Ph.D.</td>
<td>70</td>
</tr>
<tr>
<td>Illustrative Case Studies: Alice Godziemski</td>
<td>94</td>
</tr>
</tbody>
</table>

### OPEN PUBLIC HEARING

### OPEN COMMITTEE DISCUSSION

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation of Question: Edward Tabor, M.D.</td>
<td>112</td>
</tr>
<tr>
<td>Committee Discussion and Recommendations</td>
<td>113</td>
</tr>
</tbody>
</table>

### DISCUSSION ON IPPIA PROPOSAL

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction and Background: Mark Weinstein, Ph.D.</td>
<td>167</td>
</tr>
<tr>
<td>Presentation of Proposal: IPPIA Representatives</td>
<td></td>
</tr>
<tr>
<td>Douglas Bell</td>
<td>171</td>
</tr>
<tr>
<td>James Reilly</td>
<td>174</td>
</tr>
<tr>
<td>Dr. James Waytes</td>
<td>181</td>
</tr>
<tr>
<td>Douglas Bell</td>
<td>190</td>
</tr>
<tr>
<td>FDA Commentary on Proposal</td>
<td></td>
</tr>
</tbody>
</table>
CONTENTS (Continued)

OPEN PUBLIC HEARING

Kathy Miles Crews 212
Bruce Ewenstein, M.D., Ph.D. (by Pat Collins) 217
Val Bias 221
Christopher C. Lamb 224
Wayne Swindlehurst 232

OPEN COMMITTEE DISCUSSION

Presentation of Questions:
Mark Weinstein, Ph.D. 234

Committee Discussion and Recommendations 234
PROCEDINGS

Conflict of Interest

DR. SMALLWOOD: We will proceed with the meeting at this time. Good morning and welcome to the 56th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. At this time, I will read the conflict of interest statement as it pertains to this meeting.

This announcement is made a part of the record to preclude even the appearance of conflict of interest at this meeting of the Blood Products Advisory Committee on September 18 and 19, 1997.

Pursuant to the authority granted under the Committee Charter, the Director of the FDA Center for Biologics Evaluation and Research has appointed Paul R. McCurdy, M.D., as a temporary voting member.

Based on the agenda made available and all reported financial interests as of this date, it has been determined that all interest in firms regulated by the Center for Biologics Evaluation and Research which have been reported by the participating members present no potential for a conflict of interest at this meeting.

The following disclosures are presented: Dr. Charles August has an unpaid association with the Medical
Advisory Board of the American Red Cross, South Florida Division. The Agenda approved a waiver on June 11, 1996 for his association.

Mr. Benjamin Cheng's employer has received an educational grant from two different regulated firms. Both grants are unrelated to the committee discussions.

Mr. Corey Dubin has an Agency-approved Appearance Determination on December 11, 1996, regarding his suit with several regulated firms.

Dr. Blaine Hollinger will serve as the Acting Chairman at this Advisory Committee meeting. He served as the principal investigator on an unrelated grant awarded by a regulated firm.

Dr. Jerry Holmberg has an Agency-approved Appearance Determination regarding the use of test kits from regulated firms in relation to his official government duties. In addition, he provides technical expertise on platelets for an NIH contract for the American Red Cross. Dr. Holmberg consulted in the past with a regulated firm on unrelated products in which he received a fee.

Dr. Rima Khabbaz's employer, Centers for Disease Control, Division of Viral and Rickettsial Diseases, has unrelated CRADAs with two firms which could be affected by the general discussions.
Dr. William Martone is a Federal Government employee detailed to the National Foundation for Infectious Diseases, a nonprofit organization. The Foundation receives grants and/or donations from regulated firms. The grants and donations are unrelated to the committee’s discussions and Dr. Martone receives no personal remuneration from these grants and/or donations.

Dr. Paul McCurdy is employed by the National Heart, Blood and Lung Institute. As part of his official government duties he reviewed proposals submitted to the Cord Blood Program for the collection, process, storage, and transplant of cord blood stem cells from two firms that could be affected by the committee discussions.

Ms. Beatrice Pierce has reported that she spoke at the National Hemophilia Association and the Kentucky Chapter of the NHF. The Agency approved a waiver on June 11, 1996, regarding her association with the National Hemophilia Foundation. In addition, the Agency approved an Appearance Determination on December 14, 1996, regarding a class action suit.

Copies of all waiver statements addressed in this announcement are available by written request under the Freedom of Information Act.

In the event that the discussions involve any
other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

In regard to the FDA's invited guests and speakers, the Agency has determined that because the services of these guests and speakers are considered essential, any information provided by them will be included in the public record to allow meeting participants to objectively evaluate any presentation and/or comments made by the guests and speakers.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Are there any declarations to be made at this time for the record?

[No response.]

Welcome and Opening Remarks

DR. SMALLWOOD: At this time, I would like to introduce to you the members of the Blood Products Advisory Committee. As I call your name, would each member please raise your hand.
Dr. Blaine Hollinger, who will be Acting Chairman for this meeting. Dr. Jerry Holmberg. Ms. Beatrice Pierce. Mr. Benjamin Cheng. Dr. Rima Khabbaz. Mr. Corey Dubin. Dr. Jeanne Linden. Dr. Charles August. Dr. Paul McCurdy. Rev. Violet Little. Dr. William Martone. Dr. Jane Piliavin. Dr. Joel Verter. Dr. Ness.

As I mentioned before, Dr. Blaine Hollinger will be the Acting Chairman for this meeting. I would also like to make the public announcement Dr. Scott Swisher, who was formerly the Committee Chair, has resigned from the Blood Products Advisory Committee.

At this time, I would like to call on Dr. Jay Epstein.

DR. EPSTEIN: Thank you very much, Linda.

I just want to take a moment to give personal thanks and thanks on behalf of the Center for Biologics Evaluation and Research to those committee members who are completing a two-year term of service, some of whom will be leaving our committee.

Really, I want to thank these individuals for their public service. We recognize that being a special government employee and serving on an advisory committee does entail personal sacrifices. We recognize that the awards are not material, however, we value greatly the
contributions that you have made to decisionmaking, and we assure you that the Government takes seriously its need for outside inputs and for balance in the effort to reach sound decisions in the public interest.

Also, I would just note that we have been operating in the last two years under a new charter and that this has represented a change in the dynamics of the committee. Additionally, with the creation of a Public Health Service Committee to advise on issues relate to blood safety and availability, there has been also a need to revise how we think and what our scope of concerns is and how we articulate issues, as well as the broadening mandate as we deal with new technologies, such as expanding our scope of concerns into the area of tissues and cellular therapies.

So, let me just mention the names of these individuals: Dr. Charles August, who we thank; Dr. Susan Leitman, who I guess hasn't quite arrived yet; Beatrice Piece, Dr. Piliavin, Rev. Little, and Dr. Paul Ness.

We will of course be reconstituting the committee and it has not yet been decided what the membership will be. I should mention, just so people are aware, that it is possible for members to serve two consecutive two-year terms, so some of you perhaps may not be off the hook just
yet, but we certainly recognize your efforts in the last two years, and I just want to thank you.

DR. SMALLWOOD: Thank you, Dr. Epstein.

I have just a few administrative remarks to make here. For the record, I would like it to be known Dr. Carol Kasper and Dr. Gary Friedlaender will be absent from this meeting.

Also, I would like to bring to your attention that on the outside table, there is a listing of the tentative dates of the Blood Products Advisory Committee for 1998. I will read them now, and I would like everyone to acknowledge these tentative dates with respect to planning, so that we can successfully have a coordinated schedule for next year.

March 12th and 13th, 1998, will be the first meeting in 1998; June 18th and 19th; September 17th and 18th; and December 10th and 11th. Again, these are tentative, but we are trying to adhere as close as possible to our regular schedule during these months.

Also, I would like to invite any speakers that are presenting this morning to please come forward and be seated in the seats to my left in the first two rows here.

That concludes my administrative remarks. At this time, Dr. Blaine Hollinger will preside over the proceedings.
Thank you.

DR. HOLLINGER: Thank you, Linda.

I also want to thank the committee members who are going to be leaving here. I know how much effort it takes for these committee members to spend time and come to these meetings, and while it is very beneficial to them also, they really lent a great importance to this group, as well as to Scott Swisher, who also was the Chairman of this committee before, and I think we will certainly all miss him also.

We have a very busy session today and tomorrow. Today, the sessions will be on the Inadvertent Contamination. It is sort of carryover from what we discussed last time, but this time we will be discussing some donor issues, which I think are real important issues, of what to do when blood may be contaminated with somebody who may have a risk factor that they didn't admit in the first place.

The second issue this afternoon then is going to be on the IPPIA proposals and to discuss a little bit about some of their suggestions and some of the responses from CBER and others to their proposal.

With that as an introduction, we do have a busy schedule. By the way, I am also appreciative of all the
efforts that the FDA puts into providing us with background information on these issues here, so that we can sort of get up to speed, if you will, about trying to resolve some of these very important issues that we are facing.

We will start off with Dr. Tabor.

INADVERTENT CONTAMINATION

Summary of Previous Discussion and Introduction to Topic

Edward Tabor, M.D.

[Slide.]

DR. TABOR: Good morning and welcome to the discussion of inadvertent contamination of Phase II.

[Slide.]

As you will recall from your discussion in June, inadvertent contamination is the presence in a plasma pool or plasma product derived from a plasma pool of the unit of plasma from a donor who was subsequently found to have an exclusionary risk factor or a reactive screening test. These are donors who were thought to have met all donor acceptance criteria including negative tests on the donated unit, or an inadvertent contamination can be a situation in which a plasma pool is found to have an unexplained reactive test on the pool itself, and this is a situation that is arising more and more now that groups are interested in pool testing.
I think it is important to reiterate that inadvertent contamination is very different from an adverse reaction. In the case of an adverse reaction, the event is defined by something that happens in the blood or plasma recipient, and in that case, the material is recalled.

In the case of an inadvertent contamination, it is really a situation involving information that is obtained after the fact, either on the donor or the unit, the pool, or the final container, and we are here to discuss another aspect of what to do in that situation.

Now, at the June BPAC, we limited our discussion to the viruses HIV, HBV, and HCV, and we limited the discussion to situations where the test for one of these viruses is found to be positive after the fact.

This issue of inadvertent contamination is very broad, we felt it would be necessary to limit the discussion in some way. So, what we did was limited it to the discussion of those viruses for which tests are available and those for which effective inactivation steps are available.

The recommendations that you, the committee, made
in June, the first recommendation was when notified of inadvertent contamination of a fractionation pool with units reactive for HBV, HCV, or HIV, FDA should immediately and uniformly quarantine or recall all products as a first step, and then determine regulatory action based on an assessment of product risk, for instance, the impact of virus removal or inactivation on the product in question.

Further, BPAC recommended that in such circumstances, FDA should not modify its actions on the basis of product shortages.

Finally, you recommended that in such circumstances, FDA should not make any distinction between in-process and final products.

The situations that we were talking about in June were what we have chosen to call "unit issues." That is, inadvertent contaminations in which the information relates to the unit that has been collected, and really, that essentially means a test result that is called into question after pooling.

These unit issues could include situations where a test was performed incorrectly or was recorded incorrectly
due to human error in the laboratory; a situation where a donor sample was tested again later or at another location or by another method; a situation which is becoming more and more common now where a pool sample was tested later or at another location by another method; a situation where a more sensitive test becomes available after pooling has occurred; or a situation in which the red cells from the same donation have been found to transmit disease after pooling of the plasma has occurred, but before the plasma derivatives have been fully utilized.

[Slide.]

Well, today, we are going to talk about donor issues that define inadvertent contamination, and again we are going to limit our discussion to the viruses HIV, HBV, and HCV.

We hope that at a future BPAC, possibly in December, we will be able to turn our attention to some other infectious agents.

[Slide.]

Donor issues really involve the 23 donor questions that are asked of donors at the time of donation. We intended to have a copy of this in your packet. It apparently was not included and you should receive one sometime in the next hour or so.
These donor issues involve a number of situations in which a risk factor or some causative donor history that should have been picked up by the donor questions, is not picked up, but is later revealed, and the situation might be that in which a donor calls up the center later and says I forgot to tell you, but I did have a history of such and such a risk factor.

It could be a situation in which a donor develops disease symptoms indicating that he or she has a risk factor after the time of donation, and it could be a situation in which a prior donation by the same donor transmits infection after the current unit has been pooled.

There are several principles that I think we should keep in mind during our discussion today. First of all, there do exist validated procedures to remove or inactivate HIV, HBV, and HCV during the processing of plasma derivatives.

Secondly, marker-negative donors, those donors whose plasma has been tested with the FDA-approved tests, who also have no known risk factors, can still be infectious for these agents, but nevertheless, the inactivation procedures provide safety for the plasma obtained from them.
Third, we believe that if we can determine the range of viral load or risk associated with a specific donor risk factor, that we can then determine what the risk is associated with a specific inadvertent contamination episode from a donor with that risk factor.

The questions we would like to ask the Committee to consider today -- and you will get a chance to see these again later, as well -- are:

First, do you agree that, when notified of inadvertent contamination of a pool consisting of units negative for markers of HIV, HBV, and HCV, but nevertheless containing one or more units from a donor with a subsequently discovered risk factor, FDA should determine regulatory action based on an assessment of product risk?

What we are talking about here, as we were last time, is whether FDA should have the flexibility to make decisions based on the amount of viral contamination that might be present and the inactivation that is available and applied.

The only difference between this time and last time is now we are talking about the same flexibility when inadvertent contamination is due to donor issues as opposed
to unit issues

[Slide.]

The second question. Does the committee agree that an assessment of product risk should take into account an estimate of the maximum level of contamination that could be associated with the risk factor and the capability for virus removal and inactivation?

[Slide.]

Third, if within 48 hours or within any other time frame that the committee recommends of an incident of inadvertent contamination it can be determined that it raises no new scientific issue and the manufacturer has an excellent recent record of GMP compliance, can a quarantine of distributed product be dispensed with?

This is a question related primarily to distributed product since we would ordinarily require that material that is still in-house not be distributed until the issue is resolved.

[Slide.]

Finally, as you know, there has been a great interest in PCR testing and other types of nucleic acid testing, particularly with their applications to pools and mini-pools of plasma, and we would like to ask whether the committee feels that a negative nucleic acid test or other
additional assay applied either to the donor sample or to the pool, or to the donor himself can be used to eliminate the need to destroy a pooled product.

Examples would be PCR testing on the donor or the pool, subsequent test-negative donations that the donor comes in again, is tested and is negative, and then also follow-up testing of the donor when the donor is called back specifically for that purpose.

Thank you.

Definitions and Operational Practice

Boyd Fogle

MR. FOGLE: Good morning. I am Boyd Fogle and I was asked to present to the Committee definitions and an overview of what we see operationally within the context of GMPs, so that for the discussion we have, one, a reorientation to the terms that are involved, also, to give you a sense of what is within the scope of GMPs, because as Ed mentioned, one of the questions relates to compliance with GMPs, and also other issues where risk assessments are performed to give you an overview of some of the steps that are followed in some of these situations.

[Slide.]

We will start with the definition again of recall. Recall is defined by the Agency in 21 CFR Part 7, which are
formal guidelines for conducting recalls. These are used by industry and the Agency. The definition is a firm's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which the Agency would initiate legal action, for example, seizure. The point here is that the product is violative and we would take action against the product.

[Slide.]

Definition of market withdrawal is a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the FDA or which involves no violation, for example, a normal stock rotation, routine equipment adjustments, and repairs.

The difference here is that with the recall, the Agency would be prepared to take action if the firm did not. A market withdrawal is there is a violation, but it may be a minor violation where, according to policies and practices, the Agency may not be prepared to take a formal legal action against the product. Remember, seizure was a key element of the definition of recall.

[Slide.]

There is also a definition of stock recovery. Again, it is found in Part 7. This is a firm's removal or
correction of a product that has not been marketed or that
has not left the direct control of the firm, i.e., the
product is located on the premises owned by or under the
control of the firm, and no portion of the lot has been
released for sale or use.

Now, in situations where a product is viewed to be
violated based on new information, we find varying degrees
of where that product is located. For example, if the
product is still within the distribution channels of a firm,
then, an attempt to retrieve that product could be viewed as
a stock recovery.

However, if it is out of that firm's control,
still in distribution but at a wholesaler, if it is at that
wholesaler, still hasn't gone to full commercial use, it
could be viewed as a market withdrawal or recall, because it
is out of the control of the immediate manufacturer. It
still may not have gone to the public, but the fact that it
is out of the manufacturer's control, it could still pivot
to a market withdrawal or recall classification, if
appropriate.

[Slide.]

Now, those terms are defined, as I mentioned, in
our formal guidelines. In previous discussions, there have
been terms brought forward, such as quarantines and holds.
These are not defined within the context of the GMPs. They are also not defined within the context of our recall guidelines, but commonly accepted definitions for quarantine include to exclude, to detain, or isolate, a strict isolation imposed to prevent the spread of disease.

[Slide.]

With respect to hold, it is defined as to set aside reserve or retain from use, to keep back from action, hinder, restrain, interdiction. Now, we see these terms being used interchangeably, but I think the concept is, is there some information that indicates that a product should be held at some state based on some new information. It may or may not be suitable for its intended uses. So, the concepts, whether the terms are used interchangeably indicate that a hold should be placed on this product.

[Slide.]

Operationally, within the context of GMPs, there are the general principles of withholding from use unsuitable products. This may also be based on the fact that unsuitable components may have been used in products that would pivot decisions within the context of GMPs for testing and examination, retesting or reexamination, so that decisions can be made as far as release for use in distribution.
This may be initial distribution. It also may be for redistribution, for distribution initially or something is already in process, but yet you now have information, and you may have placed a hold on it, so you may want to do additional reviews.

Now, these functions are conducted within the context of GMPs. For your reference, I have provided three particular cites which are 211.84, which relates to testing and approval or rejection of components, drug product containers and closures.

There is also 211.192, which has specific requirements for product, record reviews.

There is also 211.204, which related to returned drug products.

Looking at these three regulations collectively, there are principles that require manufacturers to assess information about the suitability of products prior to release decisions. Also, if there is information that comes after a product has been released, and they should do a review of product records to determine if other associated lots have been affected by new information where quality of the product may have been affected, and it requires full investigations with formal reports of these activities.

[Slide.]
Also, operational within the context of GMPs, we believe that the actions of voluntary hold and quarantine are voluntary on the part of the firms, according to GMPs, and they are the first people with this information, they are obliged to initially take the action as appropriate to hold or quarantine a product.

These efforts may also include a form of notification that is voluntary from the firms, which may include an in-house hold, a notification for distribution centers within house. It may also include going to the distributor wholesaler level, which may include establishments that are outside their control, and it may also include notifications for hold and quarantine to the user level, and we have seen that happen recently, initiated by the manufacturers.

These efforts -- and it will be at varying degrees -- case-specific, permit the firm additional time to further investigate and evaluate the situations and other associated lots, as we have mentioned, within the context of the GMP requirements.

[Slide.]

These evaluations customarily include reviewing batch production records, which give the manufacturing history of the particular lot or other associated lots. It
may also include reviewing the history of source material, which may include unit testing histories and donor testing histories if there is a donor-specific issue.

It may also include reviewing adverse experience reports associated with distributed products. It will also include review of customer complaints and service reports. to gather any information that may be within their system that would indicate a quality issue with respect to the product.

[Slide.]

Also, with respect to batch production records, there will be reviews of viral inactivation processes to determine if those processes were established and followed and also that they had been properly validated.

There is also review of SOPs and procedures to make sure that they have been properly followed and there have not been any changes that would affect previous acceptable validation.

There is also review of quality control records to determine if there were any deficiencies in testing with respect to the history of the product.

[Slide.]

We are also seeing that there may be additional testing on a case-specific issue that would go back to
additional testing of donors or individual units or segments from units that are available. There also may be additional testing of pools and also final containers. There are customarily medical evaluations and risk assessments that are performed in these situations.

[Slide.]

With respect to risk assessment factors, these generally include also looking at information, if there are any disease or injuries that have occurred, any other relevant contributing factors.

There is an assessment of the hazard to various segments of the population. There is also an assessment of the degree of seriousness of associated hazards, assessment of the likelihood of occurrence of a potential hazard or risk, and an assessment of the consequences of occurrence.

These risk assessment procedures are performed by the industry and also by the Agency on case-specific issues. These also include specific procedures that are followed by the Agency as we evaluate recall or market withdrawal situations.

[Slide.]

The conclusions that the Agency attempts to reach is a determination of if a violation exists with respect to the product and its manufacturing, a determination if the
violation is actionable. As you may recall, it goes back to
the basic definitions of recalls, market withdrawals.

Also, a determination if a health hazard exists
because of the existence of the violative conditions, and
also if there is notification that is required and also
based on the distribution patterns and the history of
distribution of the particular product or associated lots,
and what level of notification is appropriate for that.

I hope this helps to refocus us and reorient us to
the definitions and also concepts within the 211 GMPs.

DR. HOLLINGER: Do any of the committee members
have any specific questions about these definitions, they
want to ask Mr. Fogle? Yes, Reverend Little.

REV. LITTLE: The use of the word "user," are you
using that to mean the consumer?

MR. FOGLE: It could go down to the consumer.

REV. LITTLE: The end user?

MR. FOGLE: Yes. As you may recall, in the recall
procedures, there are identified levels, the retail level,
the wholesale level, the consumer user level, and depending
on the features of the product, it may be the ultimate
patient user or it may be physicians depending on what the
indications are.

DR. HOLLINGER: And the risk assessment factors
and conclusions are perhaps what the FDA might request or
might do regarding an issue?

MR. FOGLE: The risk assessments will include
FDA's assessment, yes, but in other situations it may
include working with the particular manufacturer, gathering
additional information, historical data.

It may also include other public health agencies,
such as CDC, depending on the specific example, and we will
pull in whatever expertise we need to do a comprehensive
risk assessment.

DR. HOLLINGER: Mr. Dubin.

MR. DUBIN: My voice is a little gone, so you will
bear with me.

At both the December '96 and March '97 meetings, I
requested that everybody on the committee be given a copy of
the recall market withdrawal regs, look back, a lot of it is
in the '78 package, at least how I have it, and I am not
sure that has been done.

It would seem to me, it is obviously very helpful
in the middle of this discussion to have it up on the
overhead, because it gives us a chance to listen and think
about it, but I know, since I have read it, and reread it
regularly, usually, I go back to it before every BPAC
meeting, I think it is pretty important that the members of
the committee have regular access to that in their deliberations because so many of the questions we are asked to answer somehow relate directly or indirectly to those regulations.

So, I would restate my request that the members of the committee each be given a copy of that. I think it would be immensely helpful.

Thank you.

DR. LINDEN: I have another question on a separate subject.

Mr. Fogle, could you please clarify the difference between quarantine and hold? I am still not completely clear on that.

MR. FOGLE: That is a very good question. The terms have been used interchangeably, and it is like quality control/quality assurance, where does it start, where does it stop, but people start using the terms interchangeable, and we see that in practice, quarantine and holds have been used interchangeable.

In the absence of a formal definition, it is hard and difficult in certain situations to draw a line, but if you look at the basic definitions, I think with a quarantine, it gives a higher level of concern that there may be some possible condition that could be transmitting
disease. I think quarantine gives a higher sense of urgency versus a hold, but we have seen in practice that they are used interchangeably.

DR. LINDEN: Thank you.

DR. HOLLINGER: Thank you very much.

**Donor Risk Factors, HBV and HCV**

Robin Biswas, M.D.

[Slide.]

DR. BISWAS: This morning we are discussing the inadvertent contamination of plasma pools by units that test negative for HIV, HBV, and HCV using required or recommended tests for source plasma, but that were collected from a donor who has a risk factor.

My portion of this task is to cover the areas of Hepatitis B and Hepatitis C in this record. My object this morning is to present to you the small amount of data showing the concentration or level of virus in a unit of blood that tests negative, negative for either HBV or HCV, but that is collected from a person who, nevertheless, is infected either with HBV or HCV.

I will compare this data with again the small amount of available data showing the amount of virus in a unit of blood that tests positive for HBV and HCV.

[Slide.]
Now, how do HBV/HCV negative donations from a donor who should have been deferred get into the plasma pools anyway? Well, after donating, the donor admits belonging in one or more deferral categories, and the plasma, collected, tested negative and is already pooled, and in fact, intermediates and final products may have already, and quite often are, already been manufactured.

According to a study by Alan Williams, the Red Cross, about 2 percent of donors who deny deferral criteria at donation subsequently admit risk.

[Slide.]

Well, what sort of risk factors are we talking about? This slide lists the blood donor deferral criteria addressing certain risk factors, and is by no means comprehensive.

There may be intravenous drug use in the history, certain sexual behaviors, certain geographical-based exclusions, recipients of blood and blood products excluded for a time, and previous history of clinical viral Hepatitis.

The et ceteras, there is several there. One that one could mention is a previous report of having tested positive for a viral marker.
Now, let us talk about HBV/HCV test-negative donations from HBV/HCV infected donors. What sort of units are these?

Well, they may be window period donations, may be infectious, but in the pre-seroconversion phase, or they may be units from long-term infected donors with low level viral markers. Both of these two, the window period donations and infected donors with low level viral markers, are functions of the viral marker serum load and also test sensitivity.

As far as donors infected with viral variants are concerned, the test might only pick up a rather narrow band of circulating viral markers associated with the disease.

Now, this data has been assembled by Mike Busch and shows the estimated number of infected HBV and HCV test negative units per million units. What I should say is this, is that this data has been collected for whole blood donors, so there might be some differences as far as plasma donors are concerned, but I still wanted to show it to you anyway.

For HCV in the window period, there are about 8 HCV test negative units per million units; for HBV it is 15. As far as variants are concerned, at least using currently
licensed tests and in the U.S. setting, variants don't play a role.

As far as atypical seroconversion is concerned, atypical seroconversion refers to the long-term infections in which the viral marker is not detected.

For HCV, there is data to support that some HCV carriers are not detected by current anti-HCV tests, however, it has been difficult to establish the relative importance of chronically infected antibody-negative donations, and those figures up there, 1 to 100, is a compilation of several studies.

[Slide.]

Now, the reported window periods for HCV and HBV are, for HCV, about 70 to 160 days from infection until anti-HCV is detected, and for HBV, it is about 30 to 60 days from infection until HBsAG is detected. In some cases of HBV, it might actually be a bit longer.

Now, keep in mind, though, that for HCV, as I said in discussing the previous slide, anti-HCV negative, chronic HCV cases, that never seroconvert, play a role in regard to inadvertent contamination of the pools.

[Slide.]

What I wish to do now is to discuss comparative viral load by which I mean comparing the viral load in test-
positive units from infected individuals versus viral load
in test-negative units from infected individuals.

[Slide.]

Before that, however, we must briefly discuss the
problems associated with assessing viral load in HBV and HCV
infections.

Firstly, there are no usable cell cultures
available for HBV and HCV, and what I have up there only
quantitative nucleic tests available to assess viral load.

More accurately, one should say only nucleic acid tests used
in a quantitative fashion are available to assess viral
load.

[Slide.]

Now, there were some problems with estimating HBV
and HCV viral load using nucleic acid detection tests, and
these are being dealt with.

One item is, is that the tests are not
standardized or validated. They were not standardized or
validated when the studies on viral load were done.

They are rather difficult to perform. It is
difficult to confirm positive results if the system is very
sensitive.

Most available tests are qualitative, not
quantitative. There are some tests that do specifically
address quantitative HBV DNA and HCV RNA, but there are really very few. Most of the quantitative viral studies analyze therapeutic efficacy only. Therefore the literature that is available and useful to us is very, very limited indeed.

Another issue is the quantitative correlation of nucleic acid load versus infectivity load. Now this has been demonstrated but on a rather limited basis using chimpanzees.

[Slides.]

The next few slides are the result of the very extensive literature search to find useful visual illustrations of serial testing of persons with HBV and HCV infections with some form of quantitative nucleic acid testing.

The first two slides depict HBV infections from a study that my group did some years ago with J. Hoofnagle's lab, and I am not showing them actually for lack of modesty, of course, but because these were really the only slides that I could find.

[Slide.]

In any event, all I want to show you is that when you have a positive HBsAg test, the DNA load is more than when the HBsAG test is negative.
All I want to show you is, is that when there is no HBsAG, when the HBsAG here, and also back here, is negative, there is really very little or no HBD DNA compared with when you have detectable HBsAG. There is HBV DNA.

Also, note that there is HBe DNA, there is e antigen, which sort of comes together, peaks together with the HBsAG load and the HBV DNA load. The importance of that is that e antigen is a sign of HBV DNA replications.

What I want to make quite clear is that I am not saying that there is no infectiveness or no virus, there is no infectiousness or no virus here or, for that matter, possibly here. I am only saying that when the HBsAG is positive, that there is more HBV DNA, more of a viral load than when it is negative.

I should say that the more sensitive HBV DNA PCR tests do detect HBV DNA within one week after exposure. Our test was a hybridization test.

This slide of chronic Hepatitis B infection is just meant to demonstrate the same thing, that when HBsAG is positive, over here, there is more HBV DNA shown here compared when the window period, where the HBsAG is negative.
In contrast to this, this depiction of a chronic Hepatitis C case, from a review article by Harvey Alter, shows that before the serologic test becomes positive, here, before that becomes positive, in the window period, which is this area here, in the window period, there are higher levels of HCV RNA than after the seroconversion.

So this is HCV RNA peak here in the window period, and here are peaks of HCV RNA which are somewhat lower after the antibody has developed. These shadows here are the ALT peaks.

In this acute resolving Hepatitis C case, in Dr. Alter's review -- and this does occasionally occur in perhaps about 10 to 15 percent of cases of Hepatitis C -- again, the HCV RNA in this case occurs some weeks before the seroconversion.

This is just meant to show what I just showed you more graphically with numbers, and it is a study by Rawal, et al., and it shows the relative viral load in 17 HBV infected donors. What you see here is that the mean of the HBV DNA genomic copy numbers, the mean in the seronegative window is considerably lower than then mean in the
seropositive units. However, do note that there is some overlap here and here.

[Slide.]

For HCV, the situation is the other way around, and this is from Dr. Alter's review article. Here, the seronegative units do show somewhat higher HCV RNA copy numbers than in the seropositive units.

[Slide.]

So, this slide really summarizes my talk. In HBV, the viral load is lower in the window period than in seropositive units. With HCV, it is possibly the other way around, the viral load is higher in the window period than in seropositive units.

In regards to the viral inactivation and removal efficiency, which Dr. Tom Lynch showed you in June, using marker viruses, chimpanzee studies, and epidemiologic data, clinical data, clinical study trial data, the evidence indicates that steps used in the manufacture of licensed plasma product provides a clear margin of safety of the so-called "unavoidable" contamination of the window period units and the non-seroconverting units, and the processes that are used, I am referring to solvent-detergent treatment, heating treatment, and some viral filtration.

I would like to end by repeating what I indicated
earlier. Nucleic acid copy number by RNA or DNA amount, and degree of infectivity, has been shown sort of on a limited basis, and studies are really needed to validate this, and with the improvement in PCR, let's hope that that happens.

I would also like to thank Drs. Lynch, Mei-Ying Yu, Finlayson, and Dr. Tabor and Janet Claggett for helping me very much in preparations.

DR. HOLLINGER: Thank you, Dr. Biswas.

Questions from the committee for Dr. Biswas in regards to this important data he has presented?

[No response.]

DR. HOLLINGER: Robin, I have several questions about this, because I think it is important to point out. First of all, let me start this by saying I think the inactivation procedures is what is really critical here, and the rest of it becomes of more scientific interest.

I think we need to always consider a couple of things, and that is, we don't know that much about the replicative cycles and what is produced during the normal replication in terms of infectious and noninfectious particles. All we are measuring is virus, nucleic acid. That doesn't necessarily correlate to infectivity, although we think it does in many cases.
If you look at different viruses, for example, the real viruses, the real viruses can have anywhere from 1 to 1 infectious particles to noninfectious particles -- I think that is actually too low -- to maybe 1 in 5 during early stages of infection.

For most other viruses, that rate can be 1 in 50,000 to 1 in 100,000, that is, 1 infectious particle to 100,000 noninfectious particles, some of which will not have nucleic acid in capsids that are empty, or they will have nucleic acid, but they will be defective.

So, we have to be I think careful, particularly with these viruses, and saying, look, the nucleic acid is really high here in the beginning part, does that necessarily equate if we did infectivity studies to the fact that there is a large amount of infective virus. There may be actually higher nucleic acid in some places and lower in others, and yet it may be more infectious.

DR. BISWAS: That is correct.

DR. HOLLINGER: And during cycles with mutations and changes -- we know this with HIV -- that all of these things can occur. So, that was one thing that I wanted to comment about that we always have to bear in mind.

The other is can you comment a little bit -- I know there is some information in which there seems to be,
at least anecdotally, I don't know if it has been reported or not, but there seems to be some information about individuals who are HCV/RNA-positive and anti-HCV-negative, but do not seem to be in the window period.

That is, I think some individuals have followed these patients along for a long period of time, perhaps even up to a year, and they have remained HCV/RNA-positive and anti-HCV-negative. But what I don't know is whether or not they have been shown, in animal studies or others, to be infectious.

Can you comment a little bit more about that or do you have any information on that?

DR. BISWAS: No. I looked at that for both HBV and HCV, that particular question, and I could not come up with any published information on that. I did, up until yesterday, I was looking for precisely that, and I haven't really come across it in the published literature.

DR. HOLLINGER: Dr. Alter, you had raised your hand. I know there is some data about that, and I just don't know. I know it is not probably published yet.

DR. ALTER: [Off mike.]

DR. HOLLINGER: The other thing, Robin, I want to comment about -- which I appreciate all this information, it has really been good -- just again for the committee to also
realize that most of the studies you present, at least the ones with HBV DNA, were done with hybridization technology, and that is why the DNA looks like it comes later.

If you look with PCR --

DR. BISWAS: Absolutely.

DR. HOLLINGER: -- you will see it earlier.

However, having said that, because it is more sensitive, you still can get the same information, that is, that the highest concentrations still come later, after the HBs is positive, so I don't want people to sort of leave thinking that HBV DNA is not found early. It is almost invariably found earlier, and there is infectious material even before the HBs antigen becomes positive. The difference is, is that the highest concentration of nucleic acid does come after HBs antigen is positive, which is somewhat different than what is seen in HCV --

DR. BISWAS: Right.

DR. HOLLINGER: -- in which the highest concentration comes earlier.

Those are my comments. Yes, Dr. August.

DR. AUGUST: I think this point may have come up in the June meeting, but it bears on I think ultimately clear products or clearing units, and that is, that if you take the most conservative assumption, and that is that
one particular equals one infectious unit, if you were to find no viral RNA in a product or DNA, as the case may be, could you then confidently assume that there was not going to be infectivity and that you could release the product? Is that a fair conclusion to draw?

DR. BISWAS: I think that in a well-validated test, you can be assured, if it has been well validated --

DR. AUGUST: And repeatedly negative.

DR. BISWAS: The lower that at least the lower limit of detection that at least in the item that you are testing, the pool that you are testing, the amount of RNA or DNA will be at least lower than the limit of detection of that test. It depends on the sensitivity or the test that you are using.

DR. HOLLINGER: Did that answer your question, Charles? I am not sure.

DR. AUGUST: Well, it does. It says beware, and you can't conclude what I said, and that is that it would be uninfected and guaranteed uninfected and therefore safe, completely safe.

DR. HOLLINGER: Outside of the inactivation procedures, which of course we have to remember are present now in most cases, you are right. I mean these tests at the very best will still miss perhaps as many as 100 to 1,000
copies or more per ml of sample, and while you can
cconcentrate large amounts to look at it, you still might
have infectious particles present.

   DR. BISWAS: There is another issue. I don't know
   if Tom Lynch is somewhere in the audience, but apart from
   the viral inactivation, there is also a dilution factor when
   you make these pools.

   DR. HOLLINGER: Yes, Jay.

   DR. EPSTEIN: Just a clarification. When you gave
   the DNA or RNA titers post-seroconversion, there really are
   two cases. You have chronic carriers and then you have
   resolved infections, and are these numbers averages, in
   other words, have you lumped --

   DR. BISWAS: Which one are you referring to?

   DR. EPSTEIN: Both, in both Hepatitis B --

   DR. BISWAS: In Hepatitis B, that data came from
   Rawal, and what I showed were means.

   DR. EPSTEIN: Yes, but are they in people who are
   chronic carriers or are they combining carriers with
   resolved infections?

   DR. BISWAS: The HBV data comes from for the
   seronegative portion, they were acute. These were acute
   cases.

   DR. EPSTEIN: Okay, so HBV --
DR. BISWAS: I am sorry. For the HBV, they were acute, right, and for the HCV it was for the chronic.

DR. EPSTEIN: Also, let me ask, the data would suggest a difference in pathogenesis of Hepatitis B and C, but in fact, is it not true that the apparent low level of HBV DNA in Hepatitis B is because we are directly detecting antigen? In other words, you have clipped off the high titers because you picked them up as seropositives?

DR. BISWAS: Using the antigen test.

DR. EPSTEIN: Yes. I mean were you to compare antibody to antibody, you might not see such a dramatic difference in B and C.

DR. BISWAS: That is correct.

DR. EPSTEIN: It is just because you can detect antigen that you therefore call seronegative only the lower titers.

DR. BISWAS: Right.

DR. EPSTEIN: Because otherwise they would be antigen-positive, they would be called seropositive. So I am just pointing out that when you say seropositive, you mean antibody or antigen.

DR. BISWAS: Right. I should have clarified that. That is correct.

DR. EPSTEIN: I would just comment to Dr. August I
do not think we could assert that PCR-negative means no possible infectivity. That would be false reasoning. On the other hand, I would say that what we would assert is that it establishes an upper limit of the possible infectious titer. In other words, if you know you have negative PCR, infectious titer cannot be higher than some value.

DR. HOLLINGER: Dr. Busch.

DR. BUSCH: First, to respond to Jay's question, the Rawal data is from my group, and he is correct about two things. One is that if you actually compare in primary seroconverters, the DNA levels in the pre-antigenemic versus the primary antigenemic or pre-antibody phase, the pre-antigenemic levels are much lower, in fact, there is a very clear cutoff above which when you begin to detect antigen, the DNA levels are at a particular high level, something like greater than 25,000.

The data with respect to the antigen concentrations in chronic infections were in any course antigen positives, and the DNA levels were restricted to the antigenemic -- the mean copy numbers were among the DNA-positive group, so these were the chronic carriers, if you will, and DNA-positive chronic carriers.

Just another comment with respect to the question
of chronic HCV in non-seroconverters to these so-called atypical seroconverters, I think Marian Daulter's [ph] work was the first to point these out back four or five years ago, but the first confirming and disturbing data is actually coming from the pilot pooled PCR studies, particularly those going on in Germany, where they are picking up in the range of 1 in 20,000 donations -- and this is with an n now of a million -- that are being found to be PCR-positive and anti-HCV-negative.

Importantly, they have done a moderate amount of followup of these donors, and the majority of these donors, 95 percent -- and their numbers now are in the hundreds -- are not seroconverting at approximately 6 to 12 months of followup, and yet remain viremic, and these don't appear to be contamination in terms of sequence analysis. It looks like they are discrete sequences that are consistent over time, but not consistent with contamination.

So, it looks to me to be real, but on the other side of the coin, the look-back studies that have been done, which number in the 30s or 40s, of recipients of prior red cells from these donors have to date been consistently negative. So, these people do not appear to have infected. Now, whether they, in fact, were viremic at those earlier time points is unclear.
So, these do seem to exist, but whether they are infectious and whether they are just delayed seroconverters versus atypical virus versus atypical seroconverters is still unclear.

DR. HOLLINGER: Thank you, I appreciate that.
We will go on.

**Donor Risk Factors: HIV**

**Kimber Lee Poffenberger, Ph.D.**

DR. POFFENBERGER: Good morning. I am Kim Poffenberger and I am going to talk about what I hope is maybe a slightly simpler topic, which is HIV.

[Slide.]

What I am going to talk about, to review real quickly, is inadvertent contamination. That is when a plasma pool containing a unit from a donor who has subsequently reported a deferrable risk factor. This donor unit is marker negative. For HIV, that means it is nonreactive by screening assays for HIV p24 antigen and for antibodies to HIV.

[Slide.]

To look at what the risk is to the pool that contains this unit with the donor risk factor, there is two questions to be looked at - what is the risk that the implicated unit is HIV infected, that is, what is the
likelihood of occurrence that there is virus in this unit, and what are the estimates of viral load in that unit and in the plasma pool that it is in.

[Slide.]

Both of these questions lead us to look at the possible sources of risk. When these units are marker negative, that means either there is no virus there or there is virus, but it is undetected.

If there is virus which is undetected, it will come from several sources. It could be from a donor who is in the window period of infection, that is, they are not yet reactive by the assays that are used to screen.

They could be in the middle of an immunosilent infection in which case they would not be reactive by antibody testing.

They could be viral variants, which none of the current screening tests can detect.

[Slide.]

These sources of risk have been evaluated in a study called the REDS study, in which there is long-term surveillance of over a million random whole blood donors each year. The incidence rates of the markers of actually converting to a confirmed HIV infection in donors is where we can get an estimate of what the risk would be that a unit
from a donor who has some sort of risk factor, that that unit may be infected.

The REDS study data, as you know, comes from random donors. There is a good bit of data from that study. There is also some limited data on source plasma donors.

[Slide.]

As has been reviewed previously, in the publication from Mike Busch, et al., when the REDS study was evaluated to see how many donors actually did seroconvert, the number per million units, as is blocked out by the risks categories, is 1.5 unit per million were found in the window period, less than 0.6 units per million for variants, and less than 0.01 units per million for atypical seroconversion.

What we are really looking at when we are considering a pool that has a unit from a donor who has a risk factor, is probably most of the risk comes from the window period unit, and that rate, if you want to convert it to a percentage, is 0.00015 percent of the donors.

[Slide.]

Information for source plasma, I have really not been able to get an update on this information. This is a summary of data that was presented in the 1994 Workshop to the Advisory Committee.
The topmost line summarizes the numbers from --
they were gleaned by Mr. Riordan in our group from license
application submissions. This is covering the time from
1984 to 1990 for donations screened by HIV-1 EIA. Thirteen
were confirmed positive out of -- let me make a correction
here -- 11,214.

The middle set of data comes from Dr. Rodell.
These are from 1991 donations which were screened by HIV-1,2
COMBE test, and 5 out of 100,000 were confirmed positive.

The bottom set of data is from Dr. Sue Stramer.
This is for donations in 1992 to 1993, and in this case I
have an asterisk by the data because this is the repeat
reactive rate. These are not confirmed. So, this would be
higher in number than the actual confirmation.

But this is to give you an idea of what the actual
rates are. They are still relatively low.

[Slide.]
What does this tell us about the risk when a donor
reports having a risk factor? It tells us that the actual
rate of occurrence of conversion to becoming seropositive is
low.

Dr. Biswas referred earlier to a study by
Williams, et al., in the Journal of the American Medical
Association in March of this year, in which what they did
was sent out questionnaires to a subset of the REDS donors, and they asked them a lot of different questions in this questionnaire. The n for this, that is, the total of people responding was 34,000. It was a good response.

What I want you to note is that 1.9 percent of those donors did report having a risk factor at the time of donation. This is coming from a very similar population to the population that is showing 1.62 confirmed seroconversions in 1 million donations.

So, I think what you hear here is that a lot of people who have risk factors do not go on to seroconvert. This rate may be different in source plasma donors. We are just beginning to pull that data together.

[Slide.]

Now that you have a little perspective on what I would say is very preliminary data on how many of these donors with risk factors actually go on to convert, I want to look at how you evaluate the viral load if a unit actually does have virus.

Just to go back, you can see that when donors who have been shown to seroconvert are detected, most of them come from the window period phase.

[Slide.]

That is where I focused my data collection
efforts. So in order to ask how to determine the viral load in a marker-negative unit, I got the help of the staff at Boston Biomedica, Inc., and Mike Busch also contributed data, and what we have done is to review the viral load in seroconversion panel samples, and in particular, the load in p24 antigen negative, antibody negative seroconversion panel samples.

[Slide.]

To give you a brief review, I am going to have to apologize for my graphic slides, I just switched over to IBM and I did these in Power Point and Excel, and I am not very good at getting some of the axes to work out yet, ask me questions as we go along.

The scales on the left, which are the logarithmic scales for viral, those are good. That is the good scale. The bottom scale is sometimes not linear. This is just a history slide showing the natural history for HIV infection, and what I want you to see is that when the RNA levels are peaking after infection, the p24 antigen levels are peaking also.

[Slide.]

In data that I have collected from numerous sources, in particular, data presented at the AABB meeting, Mike Busch et al., also data from screening of the BBI...
seroconversion panels, from seroconversion panels from some infected individuals who were not donors, and in all publications I could find about viral loads measured in units from seropositive blood donors.

The numbers in nucleic acid copies per ml in a window period unit typically will range from $10^3$ to $10^7$, and I have an asterisk here because there have been rare cases of $10^8$ copies per ml reported.

The seropositive units in blood donors have ranged from $10^3$ to $10^6$ nucleic acid copies per ml. I should point out that the reason $10^3$ is the lower limit is because at the time most of these studies were done, that was considered the lower level of sensitivity for the test, and certainly I am just talking about viral load in units which actually have detectable virus. A lot of these window period or pre-seroconversion units would have no virus in them.

[Slide.]

Just to give you the next reminder, which has been repeated several times, these units are from individuals whose blood has tested negative for antibodies to HIV and negative for p24 antigen.

[Slide.]

I am going to show you three profiles from three different seroconverting individuals. This is actual data.
In order to incorporate all the data on one slide, I used a logarithmic scale to show viral load, and I am also talking about signal to cutoff here. P24 and EIA reactivity is not usually presented on a logarithmic scale, but anything over a value of 1, this line here, is considered a positive reaction in the assay.

As you can see in this case, when viremia kicked in and viral load increased, p24 antigen followed and the antibody reactivity is just coming up at the end. What you should note from here is that from day 16 onward, these units would have tested as marker positive. So, that means the donation from day 14 would have indeed gotten through as marker negative and does have a viral load is 2 times 10^4 nucleic acid copies per ml.

[Slide.]

Another example, you see a similar profile, the viremia, the RNA load is going up, p24 load is following, and the antibody reactivity is lagging but coming up. Here, you can see that from day 12 onward, the unit would be considered marker positive and would be eliminated from the pool. At day 7 and day 5, it would be marker negative, and here the viral load is on the order of 10^2 or 10^3 nucleic acid copies per ml.

[Slide.]
The last profile I am showing, once again you are seeing a similar profile. In this instance, possibly because of the length of time between the donations, for whatever reason, all of the units given in this profile would be RNA negative when they are marker negative. That is, the first day in which there is viral load, which is day 86 here, is also the first day at which there is p24 reactivity and antibody reactivity.

[Slide.]

Now, instead of going through a lot of these profiles, I summarized this data. This represents 66 samples from about 22 seroconversion panels, and what this is, is a scatter plot with p24 value across the bottom, and viral load on the vertical axis.

Once again, if you have a 1 or greater value here, the p24 would be considered a positive assay. So, if you think of an imaginary line here, all the ones to the left of this line here, all those donations would be p24 negative, and as you can see, most of them fall at 10^5 copies per ml or lower. As you go up in p24 reactivity, you go up in viral load.

In this case of the 66 samples, which I managed to crunch the data for, we go up to about 3 times 10^6 as a peak viral load.
I want to emphasize I have got the label on this wrong, that these are antibody negative units, and what I did was go through all the panels and pull out any sample which had either a p24 reactivity or a detectable viral load or both.

[Slide.]

Mike Busch has provided data from -- this is an overlapping set of plasma donor panels, what I presented is a subset of this data. Once again, this is from work with the help of BBI.

What we are showing here, this is the vertical access, once again is viral load, and this is grouping the reactivity for different seroconversion panel members. In this case, the leftmost panel are those samples which have no reactive assays, that is, they are EIA for antibody negative, they are p24 negative, and their viral load ranges from about $10^2$ to $10^5$ copies per ml. That is an n of 19 there.

The next panel shows p24 positive donations. They are still antibody negative, but they do have p24, and you can see a dramatic shift in the viral RNA levels. They range from $10^4$ to $10^7$ copies per ml, and from then on, I represent those samples that are EIA reactive. In this case, they are almost all p24 reactive, too.
As you can see, the viral load stays about the same, goes up just a little bit as EIA reactivity kicks in, and then sort of follows what you would expect as the normal curve during the peak viremic phase of infection.

[Slide.]

To summarize the data that I just talked about, what you have seen is that during the natural history of HIV infection, the window period levels can be higher than the levels after seroconversion. However, one of our screening assays, the p24 antigen screening assay, correlates very well and identifies units which have a high viral load. It will eliminate those units from being entered into plasma pools.

As sort of an aside, those donors who have a high viral load may be too ill to donate, and that concept is getting more attention now as the p24 antigen assay has been on the market longer, and there have been very, very few donors who are coming in as p24 positive, antibody negative. One of the possibilities is since we know they are so viremic during that phase, it is possible they would be feeling too ill to donate. So, there is different factors which will affect how much virus is going to be in a unit coming from a window period.

[Slide.]
This is the slide that summarizes all the data. I need to apologize to the committee. This was on Microsoft Graph, and I could not figure out how to make it print, so that I could give you a handout. I have a handwritten version that we will be getting out to you by the end of the day.

What I am showing here is sort of a combination of what is the risk and what would the load be in a unit and in a pool for which a donor has reported a risk factor. The least risk, in my opinion, is what is the predominant. That is, the majority of cases these people who have a risk factor are not going to be seroconverting. They will have no virus and will not introduce any viral load or any risk into the pool.

If these individuals are indeed in the process of seroconversion or are infected, their units are marker negative, they don't have p24 antigen that is detectable, they don't have detectable antibody. As you have seen from the previous data, the viral load ranges from $10^5$ nucleic acid copies or less.

If you take a typical source plasma donation of 800 ml's, that would lead to an 8 times $10^7$ copies per ml load going into the pool, which comes out to 8 copies per ml in, for example, a 10,000 liter pool.
The worst case scenario is where someone who has a risk factor, actually is seroconverting. I made it the worst case by taking the highest possible peak load that we have seen, which is $10^8$ nucleic acid copies per ml.

The only way I can imagine this occurring is that this person does indeed have a risk factor and possibly they had a test error, their p24 antigen test was negative, it should have been considered positive, but came through as negative. In any case, this is the worst that could go into the pool. $10^8$ or less nucleic acid copies per ml times 800 ml's gives you a load, input load of $8 \times 10^{10}$ nucleic acid copies into the pool. In a typical 10,000 liter pool, that would 8,000 nucleic acid copies per ml.

[Slide.]

One thing I want to emphasize is that because there is a possibility that you would have viral variance or some sort of immunosilent infection that might have gotten through, if you do have what would be considered actually to be in the phase of post-seroconversion, the viral load there doesn't generally go as high as that $10^8$ value that you see in the initial peak of viremia, so this worst case scenario would certainly capture any of those units.

[Slide.]

To end, coming back to the point that was made
earlier, the real issue then is how much clearance do we get from these products. HIV is fairly well inactivated by the solvent detergent process and by certain points during the fractionation, and this provides a summary of data that Tom Lynch discussed a little bit at the last meeting, which essentially shows that if you pool all the plasma products into one kind of group, your range in log reduction factor for removal of HIV during production ranged from $10^{11}$ to $10^{17}$ log reduction factors.

As has been pointed out before, we are not actually comparing apples to apples here. I am talking about nucleic acid copies when I gave you the previous information. Log reduction factors tend to come from multiple sources, from tissue culture infectious dose reduction, but more and more, a lot of the validation of these procedures is done looking at viral load.

This gives what I would consider to be a reasonable margin of safety considering what the possible input would be into the virus. Then, it remains to make sure that the manufacturers are indeed performing their fractionation and inactivation procedures as they have validated.

I think that is all.

DR. HOLLINGER: Thank you, Dr. Poffenberger.
Questions from the committee? Yes, Beatrice Pierce.

MS. PIERCE: Is there information if the reduction during fractionation and inactivation, that log reduction factor, is that the same for the different strains of HIV?

DR. POFFENBERGER: Well, for the different subtypes within HIV-1, is that what you are talking about? I think probably since HIV-1 is our primary concern.

It will depend on how things are screened, and I would say in general that is the case, however, when you are looking at using PCR to detect this, the probes have to be designed to look at the different strains.

Our screening assays detect a lot of the strains. The Type O is really the only outlier, which is rapidly coming under cover now. Most of the kits are detecting most of them, the ones that have been found so far.

Now, when you do the inactivation processes, the limitation for Type O will probably exist, in other words, the viral load for an O, I couldn't tell you for sure whether that had been properly validated. Those tests will be being brought on-line for inactivation processes.

Possibly Tom Lynch or Mark could address that a little better, I don't know.

DR. HOLLINGER: Dr. Poffenberger, what is the
longest time in a person who is known to seroconvert,
actually been shown to be infected, what is the longest time
period it has been between when the HIV RNA becomes
positive, what is the longest delay that you know of?

DR. POFFENBERGER: In infection?

DR. HOLLINGER: A person who is actually known to
be infected, ultimately found out to be infected, what has
been the longest delay between when they have been found to
be HIV RNA positive?

DR. POFFENBERGER: So from essentially the time of
infection --

DR. HOLLINGER: From time of infection until they
have become infected.

DR. POFFENBERGER: I really don't know. I mean we
can probably surmise where infection occurred, but, Mike, do
you know you would know that from these seroconversion
panels? I know there is an average time that has been
deduced, but not the longest time.

DR. BUSCH: It really doesn't come from the
seroconversion panel. The best data -- and this requires
the known date of exposure and then serial samples to assess
seroconversion -- the best data is recently compiled by CDC
from health care worker infections where about 55 health
care workers over the last six or seven years have become
infected from needlestick accidents, and in analysis of the
sample data from those cases, the median is about 30 days
from exposure to seroconversion, but there were two cases
that did not seroconvert until after six months, at six and
seven months, and both of them were virologically confirmed
as the virus being identical between the source and the
subsequent infections that evolved in the seroconverters,
and there was actually a survival curve that showed, you
know, a consistent sort of declining rate of time to
seroconversion.

So, although the average is still a month, it is
clear that there are a subset of about 5 percent of people
who will not seroconvert until after six months, and then
there are these handful of I think well-documented cases of
non-seroconversion. Those cases typically progress
clinically to AIDS and death very quickly if you don't
control the primary viremia, but those outlier cases like
the Utah plasma donor and a few others do exist, but in
addition, there is a tail of delayed seroconversion.

DR. POFFENBERGER: Is there viral load data on
that?

DR. BUSCH: There is data from a small number of
the -- well, from these non-seroconverters, these really
rare cases, they do appear to have high-titer viremia for
the duration of infection, and probably that is why they progress so quickly in terms of CD4 decline in symptoms.

In a couple of the cases of health care workers -- and there was one published case from Europe also -- that had samples available prior to a delayed seroconversion in the cases that took about six months or longer, and what was interesting is these individuals, in testing back to their prior bleeds, were only viremic on the bleed immediately prior to seroconversion, so they are actually non-viremic for this period of four or five months. Then, the virus bursts in the bloodstream and they seroconverted, so it is consistent with a sort of a restricted replication for this delayed seroconversion probably in the region of inoculation, you know, the virus enters the mucosa or whatever and is replicating just in that local lymphoid tissue and then disseminates and induced seroconversion in a fairly typical fashion after a delay, and that has been documented in animal model studies, as well. If you inoculate, you know, submucosally, you can in some animals have a delayed seroconversion, but that delay is not usually associated with a prolonged viremia. Viremia usually just precedes seroconversion.

DR. HOLLINGER: Thank you.

Dr. August.
DR. AUGUST: I am sure we are going to be asked questions based on this kind of reasoning, so I thought I would try to anticipate it, and that is that if you have a marker-negative individual that again the very conservative estimate of that person's potential viral load is that it may be as high as $10^5$ particles, and the fractionation inactivation process, by your estimate from the slide on the screen, the lower limit is $10^{11}$.

Now, can we conclude that we therefore have a cushion of $10^6$ in terms of assessing the safety, and if in fact that is the case, we would be very confident and very comfortable that the processing in fact is going to sterilize products that may contain an inadvertently contaminated unit.

Now, is this reasoning correct or is there something that tells us that really shouldn't be that confident or we can't be that confident?

DR. POFFENBERGER: I would say that you really have to take the rational approach. That is what we are doing here, what is the risk, and this is the scientific data. What I would like to say is what would bolster up our confidence in following this rationale is the history of transmission from products for HIV, and when you look at the products that have, say, that lower level of $10^{11}$. log
reduction factor, how do they in fact transmit it over the
millions of doses that have been given, and I think the
safety record there is very, very good and does indeed
support the fact that this rational approach is giving us
the real facts. I would not say you can determine this to
an absolute black and white, yes, this is absolutely safe.
You can take your most rational approach.

So, I can't give you a definitive answer. I can only say that the clinical record supports that assumption.

Did you want to say something, John?

DR. FINLAYSON: Yes, not to put too fine a
logarithmic point on it, but I would propose that it's even
better than Dr. August says, because if you took not the
$10^5$, which would the usual worst case, but the $10^8$, which
would be the worst worst case that Dr. Poffenberger showed up. By the time that went into a pool, which would be not a particularly large pool, one was down to 8,000, and the logarithm of 8,000 is going to be 3.9, and so that one has a
10 million-fold cushion there.

DR. HOLLINGER: Yes. Please state your name and
association.

DR. GOLDING: Dr. Golding from the Division of Hematology at CBER.

I have two caveats that I think we should
remember. One is -- and I think it is related to a question that was asked -- the viral validation studies, to my knowledge, are always done with lab strains, they are not done with isolates from patients.

There is no reason that I know to believe that those envelopes, for example, would be more resistant to solvent-detergent or any other treatment, but because we are dealing with a serious problem, we need to remember that.

The other factor that came, and others have brought up, is that the level of detection of these viruses has a lower limit, so when you do a viral validation study, they are always done with very high loads of virus, and what you get as an answer is non-detectable virus often in the test, and then you say -- if you started out with 10⁷ and you went down to non-detectable levels, and the non-detectable is 10³, then, you can say, well, it is greater than 10⁴ viral removal, log removal, but that doesn't mean that there is absolutely no virus there. There is a possibility that with low levels of virus in there, especially to start out with, that some of these methods may not be as efficient. We are always looking at these validation studies with high levels of virus.

The reason I am bringing this up is not because I think there is a serious scientific chance that we are not
removing all the virus, but there is some chance and that
to ensure the maximum safety for the system.

DR. HOLLINGER: Thank you.

Yes.

MS. PIERCE: I have a question that maybe you can
answer, and that is, when the inactivation studies are done,
you said there is a strain used. Also, let me see if I can
phrase this, so it is understandable, are viruses used from
different periods, say, early on the onset versus later on
to answer the question of different infectivity at different
stages of the process?

DR. GOLDING: The virus, when it was initially
isolated, and then passaged in the laboratory of Gallo and
all those other people was done a long time ago, and those
were the 3B and then LAV strains, and those viruses are
possibly very different in many respects from primary
isolates that are taken from patients.

There is a lot of scientific evidence that
suggests that they are different in terms of the infectivity
and other properties and in terms of the antigen makeup.
So, these viruses, as far as I know, that are used for the
validation are all these stock viruses that have been
passaged for a long time, and I don't think in any way
relate to acute infection or chronic infection, and I don't
think you can make that relationship.

But as I said before, I don't know of any reason
to believe that their envelope is going to be different in
terms of the viral validation studies. These are different
in terms of its antigenicity, and they are different in
terms of how they can infect people, but in terms of the
viral validation study that we have, it has never been
tested to see if all the viruses are equally sensitive.

I would say from just the physical/chemical basis
of the steps that are taken, that there is no reason that I
know of to believe that this is a problem, that we should
just keep it in mind that it is different from the viruses
that are out there infecting people.

DR. HOLLINGER: Yes.

DR. BUSCH: The problem with trying to use
"primary isolates" or these plasma panels to assess
inactivation is that the viral titers in fact are
exceedingly low. In order to rigorously measure the $10^{10}$
levels of inactivation, you need to bump up viral titers up
to $10^{20}$, $10^{22}$, which requires extensive in-vitro
amplification of these isolates.

We have recently done with Bob Coombs, cultures,
panels, and you can't even get a positive culture from these plasmas until you have over 100,000 copies of RNA.

So, in these typical panels, only the two or three bleeds at the peak of antigen viremia are culture-positive. Prior to that, all of the RNA only and into the low level antigen RNA-positive samples, and subsequent to seroconversion, these plasmas are culture-negative, and even at the peak viremia, you never have more than 1 log or 2 logs of dilutional sensitivity in terms of plasma culture isolates.

So, you have so little virus in terms of the culture system, I mean it is partly a limitation of the sensitivity of the culture systems, that you simply can't take those products through any inactivation and talk about log reduction because just spinning it down, if you will, will reduce it to negativity.

Another point is that all of these panels that we are looking at, these plasma donor panels, are actually derived from historical, you know, screening of large numbers, millions of plasma donors, and the truth is that all of these high-titer antigenemic samples that we are showing you in these panels in fact were in pools, were fractionated for the last decade.

The truth is that there has not been an HIV
transmission since '86 in the United States, so I think the proof is in the record that enormous numbers, well, hundreds certainly, of high-titer antigenemic viremic plasmas have been fractionated into pools, and have not resulted in infectivity over the last decade.

DR. HOLLINGER: Thank you.

We will move then to the next speaker.

Significance of Risk Factors Revealed by Surveillance

Miriam Alter, Ph.D.

DR. ALTER: Thank you.

Don't look too hard in your packets for hardcopies, they are not there. Unfortunately, I can't give you the excuse that I upgraded to a new versions of Power Point or I couldn't figure out how to make my latest version of Microsoft print out. They are just not there.

[Slide.]

I think that my task today is to attempt to put the risk factors for acquiring Hepatitis B and Hepatitis C in the United States in some perspective.

There are variety of exposures that can be associated with bloodborne virus transmission. For Hepatitis B virus and Hepatitis C virus, these include blood, blood products, organs, and tissues from infectious donors.
Obviously, for Hepatitis B, this has really not been an issue for a very long time. The opportunity under most circumstances for HBV infection to be transmitted from an infected donor are extremely remote given the sensitivity and accuracy of long-time testing for HBV infection.

For HCV, it is only recently that we have been able to substantially reduce the chances of transmission in this setting.

On the other hand, injection, particularly injection drug use is a major risk factor particularly for HCV transmission. For the most part, there has also been some reports of an association between non-injection drug use, primarily cocaine use, and the transmission of HCV, and I am going to go into that a little later, but certainly injection drug users have one of the highest prevalence rates of both HBV and HCV infection than any other group studied.

Other potential sources for HBV and HCV transmission include contaminated instruments, equipment, and supplies used for procedures involved in traditional medicine, folk medicine, percutaneous procedures, such as tattooing, body piercing, and even the use of commercial razors, or even the use of razors in commercial establishments.
For the most part, associations between these types of activities and the transmission of HBV and HCV have only been documented in countries outside of the United States. There have been occasional episodes, clusters of cases, of HBV infections associated with tattooing and acupuncture in the U.S, and there have been no such associations with HCV transmission.

We have been unable to associate these types of procedures with sporadic cases of either Hepatitis B or Hepatitis C in this country.

[Slide.]

Other potential sources for Hepatitis B and Hepatitis C virus transmission includes exposure to infected contacts. For Hepatitis B, this is much more clear than it is for Hepatitis C. Such infective contacts include exposure to an infected sexual partner, exposure to infected household members, perinatal transmission from infected women to their infants at the time of birth, transmission from patients to patients or patients to health care workers in hospital settings, and transmission from infected health care workers to patients, which fortunately is a very rare event.

Transmission of HBV from infected sexual partners or as the result of high-risk sexual activities involving
multiple partners is extremely well documented. In fact, as you will see, sexual transmission of HBV or sexual exposures account for the majority of the transmission of HBV in the United States today.

Transmission from chronically infected non-sexual household members is also well documented for Hepatitis B, and vaccine, of course, is recommended for both sexual partners and household members of persons who are chronically infected with HBV.

Perinatal transmission of HBV is also a substantial risk or a substantial risk for Hepatitis B. Infants born to infected women have a 90 percent or greater chance of becoming infected at the time of birth, and again, there is well-substantiated prophylaxis that is extremely effective in this setting and has been recommended for many years.

The transmission of HBV from infected patients either to other patients or to health care workers also does occasionally occur. It, fortunately, is very rare now, not only because of appropriate precautions and disinfection and sterilization procedures used in this country, but also because of widespread vaccination of health care workers against Hepatitis B.

Finally, infected health care workers fortunately
rarely transmit Hepatitis B to patients, although this has been documented in the literature in the United States maybe eight or nine times here in this country, but again it is extremely rare and we do have recommendations for that setting.

In terms of HCV, as I mentioned, the transmission from infected contacts is much less clear. There is a great deal of controversy about the transmission from infected sexual partners or the risk of transmission if you are exposed to multiple sexual partners.

In the United States, there have been so few studies that, in essence, the data are insufficient to draw any conclusions, and I will go into that a little bit more.

Household members again are potential sources, but not well documented here in the U.S. In terms of perinatal transmission, the average rate of transmission is about 5 percent. Breast-feeding has not been implicated in transmission of HCV. We appear to have patient-to-patient transmission of HCV in dialysis units, but we have not documented it in other settings.

Patient to health care worker transmission has occurred in the setting of accidental exposures to needlesticks and other sharp injuries at a rate of about 2 percent, and finally, there has been one report of an
infected cardiovascular surgeon transmitting to his patients from Spain. We have not documented such transmission in the U.S.

[Slide.]

The overall prevalence in the United States of either past or current infection is about 4 or 5 percent. This slide summarizes the overall prevalence by age from the National Health and Nutrition Examination Survey conducted from 1976 through 1980. We have recently completed analysis of NHANES III, which are the data collected from 1988 to 1994, and interestingly, there was little change in the age-specific prevalence of even by racial/ethnic group.

Regardless, you can see that the overall prevalence increases with age, with blacks having a substantially higher prevalence than whites, and with an increase starting actually in early adolescence.

The chronic infection rate is much, much lower, but corresponds to about 1 to 1 and a quarter million HBV infected Americans.

[Slide.]

The most variation in the prevalence of HBV infection is based on a variety of either ethnic, behavioral, or lifestyle risk factors in the population.

Individuals who have immigrated from areas of high HBV
endonicity into the United States have extremely high rates of HBV infections, 70 to 85 percent, and very high rates of chronic carriage with HBsAG positivity actually as high as 20 percent.

This is also true for Alaskan natives and Pacific Islanders who are American citizens with chronic infection rates of between 5 and 15 percent.

In individuals in institutions for the handicapped have also experienced high rates of HBV infection in the past with prevalence rates as high as 80 percent and again chronic carriage rates of 10 to 20 percent.

Injection drug users have high rates, have had high rates of infection as have men who have had sex with men, and as I mentioned, all of the other categories of individuals who are at risk for HBV infection.

This slide summarizes fairly old data on HBV infection and it does not reflect the effect of high rates of vaccination among many of these groups, so that we could expect that the rate of chronic carriage in these individuals has declined dramatically as vaccine coverage has increased in most, but not all, of these groups.

[Slide.]

In looking at the trends in acquisition of HBV infection in the last decade or so, we can see that while
the incidence of Hepatitis B reached a peak in the mid-eighties, it has declined dramatically since then.

You can see that there has been a dramatic decline in the incidence. I would like to say that this is due to vaccine use, and you can see a variety of recommendations for Hepatitis B vaccination that have occurred over these years, but in fact, most of the decline has occurred because of decreases in two of our previously highest risk groups.

These include a decline among men who have sex with men and a decline in disease among injection drug users. The decline among homosexual men is the result of changes in high-risk sexual behaviors to prevent HIV infection, and this occurred in the last half of the 1980s and showed the effect of intensive educational efforts in community-based prevention programs.

The decline among injection drug users is actually very poorly understood, and we don't really know why there has been such a large decrease in that risk group.

[Slide.]

Here, you can see the dramatic decline among homosexual men in the mid-to-late 1980s, while there was an increase in the number of cases among injection drug users and among men and women who had either infected sex partners or who were exposed to multiple partners.
The number of cases in all of these risk groups has declined during the 1990s, and we certainly hope that it continues. Again, we are focusing our vaccination efforts on both injection drug users and other high-risk adults in order to continue to achieve this downward decline.

[Slide.]

Currently, as I mentioned, sexual exposures account for the majority of HBV transmission in the U.S., almost half, with most of it being transmission between men and women, and most of this, interestingly, the result of exposure to an infected sex partner, meaning that these individuals are not aware that they should receive post-exposure prophylaxis in this setting.

Injection drug use accounts for about 15 percent of new cases today, household contact for about 3 percent, employment or exposure to blood in the health care setting for about 1 percent, and about a quarter of patients deny a specific exposure during the incubation period of their acute disease.

As you can see, most of these have a history of high-risk exposures: 5 percent are drug related, and that these individuals said they injected drugs in the past, but not during the incubation period; 8 percent denied having multiple partners, but have a history of other sexually
transmitted diseases; 1 percent have been in prison or jail; 1 percent have characteristics associated with low socioeconomic levels, which suggests that they in fact may have been exposed to high-risk behaviors or which they may have failed to acknowledge or they had unrecognized contact with an infected individual. So, all but 5 percent of the recently acquired Hepatitis B in the United States can be associated with high-risk behaviors or lifestyles or occupations, most of which could be prevented with Hepatitis B vaccine.

[Slide.]

If we look at the risk factors for Hepatitis C in the United States, I covered these when I first introduced sources of infection for transmission of both of these viruses, and these are the factors that we know to be associated with transmission in the U.S.

I think what, as I mentioned before, is the most controversial is the role of sexual and household transmission in the transmission of this particular virus. In the U.S., most of the studies have shown no evidence of infection in sexual partners of chronically infected individuals, however, none of these studies have included more than about 50 or so partners, which would not be a sufficient sample size to demonstrate a risk in a setting
where we have a very low frequency event.

Transmission has been shown in case control studies between sexual partners and among partner, steady partners in STD settings. Exactly what this risk is and what factors influence its occurrence is unknown. Certainly particularly in comparison to other sexually transmitted and bloodborne viruses, the risk in these settings is extremely low, and may occur 1 percent or less of the time.

Unfortunately, at the moment, we just do not have the data to determine the exact risk.

Individuals who have multiple sexual partners are at high risk for acquiring a variety of bloodborne viruses, and have been shown again in case control studies, as well as zero prevalence studies, to be at risk of acquiring Hepatitis C. Again, the extent of this risk is unknown, and is much, much lower than that, not only for other bloodborne viruses like HBV and HIV, but also in contrast to direct percutaneous exposures.

[Slide.]

If we look at the overall prevalence in the U.S. population of anti-HCV positivity, we find it to be 1.8 percent, which corresponds to an estimated 3.9 million infected Americans, most of whom are viremic.

The prevalence does vary by racial/ethnic group
with the lowest rates among non-hispanic whites and the
highest rates among non-hispanic blacks and Mexican-
Americans.

[Slide.]

This prevalence varies considerably by age, as
well as by racial/ethnic group with the highest rates in
young adults between the ages of 30 and 49, and with the
highest rates among blacks between the ages of 40 and 49,
reaching almost 10 percent for black men in this age group.

However, as varied as this might appear, the
greatest variability in the population is by risk factors
for infection. As I mentioned before, injection drug users
have one of the highest rates of any other group studied
along with hemophilia patients who received factor
concentrates prior to viral inactivation.

Other individuals with moderate rates include
hemodialysis patients, lower rates among homosexual men, and
individuals with multiple partners, as well as health care
workers. Again, volunteer blood donors have the lowest
rates, even lower than the general population, but do not
reflect actually the general population in the U.S. since
they are a highly selective group screened on the basis of
risk history, as well as serologic markers.

[Slide.]
If we look at the recent trends in the acquisition of Hepatitis C, we can see that they mirror somewhat the trends in Hepatitis B in terms of decline in cases among injection drug users. While the incidence of Hepatitis C was fairly stable during the 1980s, we note that there was a more than 80 percent decline since 1989.

Most of the decline among transfusion recipients actually took place prior to the introduction of first-generation testing and really had very little impact on the overall incidence of disease since this group represented less than 20 percent of the newly acquired cases in the 1980s.

The decline that occurred since 1989 has been primarily among injection drug users, and the reasons for this decline actually, just like for Hepatitis B, are not clear.

Here, you can see the trends in the three most common, what are thought of as the three most common risk factors for Hepatitis C, and you can see that in terms of the amount of disease associated with each of these factors, there is very little associated with transfusions in the last five years, and in fact, we have failed to detect a case of transfusion-associated Hepatitis C in our surveillance systems since 1994. It doesn't mean it doesn't...
occur, it is just that it is at such a low frequency that we can't detect it, whereas, the two most common risk factors are associated with injection drug use and high-risk sexual exposures.

[Slide.]

I want to spend a moment on illegal drug use because perhaps among plasma donors, this is one of the risk factors that is of greatest concern. As I mentioned, they have one of the highest prevalence rates of any other group studied with about 60 to 90 percent of users of persons with a history of injection drug use testing positive for anti-HCV. It is the most common exposure among HCV-infected persons in many geographic areas and certainly in the United States, and it is rapidly acquired after initiation of drug injection behavior with one study showing that 50 to 80 percent of injection drug users tested positive for anti-HCV within 12 months after they said they started injecting behavior.

There has been one study in the U.S. which has reported an association with a history of intranasal cocaine use. This study was actually published from the NIH group and was among volunteer blood donors who had denied any of the risk factors on the history, had subsequently donated and turned out to be anti-HCV positive, but, one, we don't
know what its contribution to transmission is and we don't
know whether the history of intranasal cocaine use is a risk
factor itself, such as through sharing of contaminated
straws, or whether it is an indication that both injection
drug use and non-injection drug use were actually practiced
by that individual. It is very rarely reported by newly
acquired cases of Hepatitis C in the absence of any other
percutaneous risk factors.

[Slide.]

Currently, injection drug use during the
incubation period is reported by 43 percent of newly
acquired cases of Hepatitis C, whereas, sexual exposures in
the absence of a percutaneous risk factor is reported by 15
percent.

Two-thirds of these individuals have an anti-HCV
positive sexual partner, and the other third acknowledge
multiple sexual partners during the incubation period.
Transfusions account for a very small percentage and again
none since 1994.

Occupational exposures account for 4 percent.
Having an anti-HCV positive household member accounted for 3
percent. Then, about 30 percent, 31 percent denied a
specific exposure during the incubation period. All but 1
percent of them could be associated with some high-risk
characteristic.

   Note that 16 percent were drug related. They either admitted to injecting drug use, but not during the incubation period, or 5 percent of them said that they snorted cocaine. Four percent denied having any multiple sexual partners, but had a history of other sexually transmitted diseases. One percent had been in prison or jail, although they denied having any high-risk behaviors, and as with Hepatitis B, 9 percent reported low socioeconomic status which may be indicative of a failure to acknowledge a high-risk behavior or failure to recognize contact with an infected individual.

   So that if one were to add up these high-risk factors, 60 percent of the recently acquired cases of Hepatitis C would be associated with illegal drug use and 20 percent with high risk sexual exposures.

   [Slide.]

   These are factors that have not been associated with acquiring sporadic Hepatitis C in the United States, and include a variety of those types of exposures that I mentioned early on in my presentation.

   Again they include a variety of health care procedures, a variety of percutaneous exposures, such as tattooing, acupuncture and ear piercing, as well as male
homosexual activity or foreign travel.

[Slide.]

In my last two slides, what I have tried to do is put all of this in perspective - what is the prevalence of the behavior in the population and among those individuals, what is the risk of having been infected with either HBV or HCV, and I had to use a variety of sources to do this.

These are all estimates. It is a very rough attempt to again put a perspective on the chances of an individual actually having this risk factor and being infected.

The prevalence of injection drug use in the population is probably unknown. The National Institute for Drug Abuse estimates it out about a half a percent of the population, whereas, the study by Allen Williams, published in JAMA, of donors, estimated it at about 5 percent who had said that they had ever injected drugs in the past even though they were actually negative for markers, but the infection prevalence in this population is extremely high, from 50 to 80 percent for B, and from 50 to 90 percent for C. Even though the infection rates have declined dramatically in this group, these individuals still experience, those who are still susceptible, still experience a high incidence of disease.
A history of transfusion is a little harder, it is even harder to estimate. Again, there was a study published by Murphy and colleagues in JAMA from the REDS group, looking at the prevalence of these factors in the volunteer donor population, and this again may be very different, as pointed out by other speakers in the plasma population, 6 percent have ever had a history of transfusion. In the current donor screening procedure, donors were only excluded if they have had a transfusion in the prior 12 months. I have no idea what the prevalence of HBV infection is in this group. In the Murphy study, the prevalence of HCV infection was 1 percent, and this was done among donors who were identified during 1992 to '93, so I assume their transfusion was before that.

Tom Zuck, in doing a sort of public lookback or public notification program in Cincinnati, found that among individuals who came in to be tested as a result of sort of this public campaign to get people in to be tested for Hepatitis C, found that about 20 percent were positive. So I think it is going to vary greatly depending on the population that you are testing.

About 9 to 10 percent of the U.S. population is involved in health care employment. About 6 percent of them are infected with HBV, have had HBV in the past. The vast
majority actually have now been vaccinated, and about 6 percent are infected with HCV.

Cocaine use, which may be an issue, which is an issue that has been discussed I know among the blood collection agencies in terms of whether or not to add that as a risk factor, the prevalence of this behavior is about 14 percent in the population as estimated by NHANES III. Again, 9 percent of these individuals have been infected with HBV and about 10 percent with HCV.

We have no idea of the prevalence of tattooing, having pierced body parts, acupuncture, et cetera, is in the population, nor do we have any prevalence estimates of infection in individuals who have had those particular procedures.

[Slide.]

We look at sexual risk factors. An estimate of male homosexuals in the U.S. population is about 10 percent. Unfortunately, they are not well vaccinated and 20 to 40 percent of them have been infected with HBV and about 4 percent with HCV.

The prevalence of having an infected sex partner in the population is also unknown. If we look at some of the older studies published in the seventies and eighties of the sex partners of volunteer blood donors, we find that
about 40 percent of them were infected with HBV. We don't
now what the prevalence of HCV is among the sex partners of
chronically infected individuals.

In the U.S., it has been anywhere from zero to 1
percent in studies that have looked at 50 or fewer of them,
but if in fact this does occur maybe 1 percent of the time,
then, we would not be able to determine what the prevalence
is based on those particular studies. Regardless, it is
extremely low. The risk of transmitting HCV to a steady
partner is extremely low.

Then, if we look at those with multiple partners,
we see that the prevalence of having more than one partner
in the U.S. population is extremely high, and the prevalence
of HBV infection ranges from 4 to 12 percent in those with
multiple partners, and for Hepatitis C, from 2 to 9 percent.
I actually do have hardcopies of these last two slides and I
will leave them with the group, so that you can get copies.

I hope that provided some perspective on the
frequency with which the particular high risk exposures are
associated with acquiring both Hepatitis B and C in the U.S.
today. Again, the plasma donor population is very different
from either the volunteer donor population or the U.S.
population as a whole.

Thank you very much.
DR. HOLLINGER: Thank you, Miriam.

Questions of Dr. Alter? Yes, Rev. Little.

REV. LITTLE: Can you just clarify for me, related to the people who use cocaine, are you saying that that is from the actual snorting of the cocaine or behaviors that follow people who have used -- behavior patterns related to using cocaine?

DR. ALTER: We have no idea why there is that association. One hypothesis is that individuals who are snorting cocaine may share straws that could be contaminated with blood and therefore, you would have mucosal transmission of the virus.

Another hypothesis is that these individuals, that cocaine use is an indication that they may also have been practicing injection drug use in the past, and the association is actually with injecting drugs, not with snorting them. We don't know.

DR. HOLMBERG: In 1992-93, there was an increase of Hepatitis C in I.V. drug users. Was there also an increase in I.V. drug use?

DR. ALTER: I am not familiar with the increase in Hepatitis C in '92 and '93 among drug users, but as far as I know, there has not been an increase in drug use. There hasn't been a decrease in drug use either. Actually, what
we have seen is a decrease in the number of cases in drug
users for both Hepatitis B and Hepatitis C, although there
has been no decrease in drug use.

However, of the susceptibles who are left, they
continue to acquire particularly Hepatitis C at a very high
rate.

MR. DUBIN: More than a question, just a
compliment. Dealing with people as we do, and my
organization does, on the ground, in the field, I have never
quite seen it put together like this. It is (a) really
helpful, something we can really get with people and work
with, so I wanted to congratulate you because we don't
usually get charts or data that we can just turn right
around and work with people with that are so effective and
so enlightening. So thank you.

DR. ALTER: Thank you.

DR. HOLLINGER: Dr. Khabbaz.

DR. KHABBAZ: Miriam, your last table showing 1
percent prevalence of Hepatitis C, HCV, in transfusion
recipients, this is a component, or where does that come
from?

DR. ALTER: That was Murphy's study. This was
published in JAMA, and it looked at donors. It asked a more
extensive history of all donors who came to donate during
'92 and '93 regardless of what their serology might have shown, and 5 or 6 percent of them had a history of ever having been transfused. If either Michael or Susan, who are nodding their head, can elaborate on that, great. I don't know anything else than that.

Then when they tested them, 1 percent of them had anti-HVC positive, which I actually thought was extraordinarily low, and perhaps someone in the audience could elaborate on that.

DR. BUSCH: Actually, that wasn't from the survey. The history of transfusion question is a routine required donor question, and it is keyed in, in all the REDS donation centers, so we are able to look at all donors relative to prevalence by history of transfusion, and that is correct, about 7 percent of all blood donors have been previously transfused.

Obviously, they are excluded for the year prior to transfusion, although, in fact, in the survey study by Williams, we found that a surprising number of previously transfused people within the past year did donate, and not admit that at the time of donation.

But, anyway, the prevalence you see among the previously transfused donors was 1 percent. It was significantly elevated relative to non-transfused donors, so
there was a significant association with C in prior 
transfusion, but it was somewhat lower than one might 
suspect.

   DR. ALTER: When I went back over that data to try 
and put this together, I was surprised. You weren't 
surprised by that?

   DR. BUSCH: Well, it's a little bit lower than one 
might predict, although you might suspect -- one issue is, 
of course, multiple-time donors were included, and those 
people had been culled with respect to anticore and also 
first-time HCV. That analysis restricted to post-first 
generation C. So, first generation C screening would have 
culled out your previously transfused positives.

   DR. HOLLINGER: Charles.

   DR. AUGUST: In the red, white and blue slide that 
you showed correlating the incidence of I think B and C and 
a number of events, it looked as if the incidence -- and I 
think it was C or I guess it was B -- started declining 
prior to anything that was identifiable, and that, for 
example, the event initiating immunization for Hepatitis B 
seemed not to change the slope of the curve, and I was just 
wondering what you attributed the initial decline in 
incident to in the first place. It sort of looks like the 
top of a mountain, but there isn't any event that you could
point your finger at in saying this is why this happened.

    DR. ALTER: No event in terms of vaccination
recommendations. Prior to 1985, homosexual men accounted
for one of the largest risk groups for Hepatitis B, and they
initiated educational efforts that were so successful, and
there was such a dramatic decline in the number of cases in
that group, that I believe that was responsible for the
initial decline in the overall incidence of Hepatitis B.

    DR. AUGUST: That wasn't mentioned on the slide, I
guess.

    DR. ALTER: Actually, no. What it is, it is
underneath the slide.

    DR. AUGUST: There it is.

    [Slide.]

    DR. ALTER: These represent immunization
recommendations or other types of screening above the line,
and below the line, which is in green, and you probably
can't see it because of the light, are declines amongst
specific risk groups.

    This shows there was this huge decline among
homosexual men and a substantial decline, as well, among
health care workers, but because health care workers
represent such a small percentage of all the infections, it
had no impact on overall incidence.
It is here that you can see that gay men represented one of the highest numbers of cases during those earlier years, and then that you have this 75 percent or more decline in cases.

DR. AUGUST: Maybe you should put on that slide the tenure of office of Dr. Koop as the Surgeon General.

DR. ALTER: I could try that.

DR. HOLLINGER: We are going to take a break now. We are going to come back for the illustrative case at the time, so we will break until 11 o'clock, but we will still start at 11 o'clock.

[Recess.]

Illustrative Case Studies

Alice Godziemski

MS. GODZIEMSKI: My name is Alice Godziemski. I work in the Office of Compliance in the Center for Biologics. I am going to go over some case studies, actual case studies that we have dealt with within the Center.

[Slide.]

The first case study. The situation is that a firm requests permission to distribute one lot of immune globulin human. The plasma pool for this lot included units of recovered plasma which tested nonreactive for all required viral markers, but were collected from donors who,
after donating, reported to the collecting facility the following postdonation information.

[Slide.]

One donor reported that he subsequently was using I.V. drugs. Another donor reported he was in high risk for HIV. A third party subsequently notified the collecting facility that the donor was high risk for HIV. A fourth donor subsequently tested positive for HBsAg. There was a total of 10 units of recovered plasma with this pool. These were only 4 out of the 10. The other postdonation information was history of cancer, tattoo, and use of antimalarial drugs.

[Slide.]

The evaluation that was done by the Center of Biologics was that all required viral marker testing for all the involved donors was reviewed for compliance with all applicable regulations, and the outcome was that the distribution of the final derivative products was granted to the firm.

[Slide.]

Case Study No. 2 is that a firm requests permission to release specific lots of plasma derivatives prepared from plasma pools which contained units of source plasma which tested nonreactive for HBsAg, but were
collected from donors who previously tested repeat reactive for HBsAG. This case had seven units of source plasma that were affected.

The plasma derivatives prepared from these pools of source plasma include anti-hemophilic factor alpha-I-proteinase inhibitor, plasma protein fraction albumin and immunoglobulin.

[Slide.]

The evaluation that was done was that there was an absence of repeat reactive testing for HBsAg, which is strong evidence against Hepatitis B infection at the time of donation. The extensive heating process used in the manufacture of albumin, plasma protein fraction, and alpha-I-proteinase inhibitor was viewed as acceptable for viral inactivation.

[Slide.]

A validated viral inactivation process used in the manufacture of anti-hemophilic factor was used. This was a solvent-detergent treatment. The fact to date that U.S. immune globulin have not been implicated in the case of Hepatitis transmission, so the outcome of this case was that the continued use of the plasma derivatives was granted.

[Slide.]

The third case involves a firm that requests
permission to release specific lots of albumin prepared from
plasma pools which contain units of recovered plasma which
tested nonreactive for anti-HIV by EIA that were collected
from donors who previously tested repeat reactive for anti-
HIV-1 by EIA and had the following confirmatory test
results.

[Slide.]

Fifty-three units and/or donors had confirmatory
test results of a negative Western blot either licensed or
unlicensed. In determining Western blot's unlicensed, there
was two units or donors that were involved in this. No
Western blot testing performed was 26, and there was one
case where there were no records of any confirmatory testing
being done.

[Slide.]

The evaluation done by CBER was that the required
biomarker testing for all involved donors was reviewed for
compliance with all applicable regulations, and the
manufacturing methods for final products were reviewed and
are acceptable for viral inactivation.

So, the outcome was that the continued use of the
plasma products was granted. In this case, also, three of
those donors that had the confirmatory testing results,
three of them had subsequent testing for reentry purposes.
They all tested nonreactive for HIV-1 by EIA with Western blot indeterminates. Of the three, one had bands at P51 and P55, another one at P51, and the third one at P17.

Those are the cases. Any questions?

DR. NESS: I would find it more interesting to know of cases which were reviewed, where products were not released. Can you give us any examples of those types of cases?

MS. GODZIEMSKI: Well, we gave examples of those last time for the units, but I don't recollect off the top of my head actually whether the donors were previously tested repeat reactive, that we did not allow the release of products. Does anybody else remember anything from FDA?

DR. HOLLINGER: Is there an answer to any product that was not released?

[No response.]

DR. HOLLINGER: Okay

DR. MARTONE: Do you do followup on these products after they are released?

MS. GODZIEMSKI: What kind of followup do you mean?

DR. MARTONE: Looking at the people who received it.

MS. GODZIEMSKI: I really don't know. I mean not
DR. HOLLINGER: Following on Bill's important question, I guess the issue is what data do we have that the product has not been responsible for any disease. I mean it goes back many years ago when people said there is no Hepatitis C transmitted by blood, nobody gets Hepatitis C by blood until you started looking at the donors and find a lot of them had the disease, so that the issue is do we have any surveillance data on this.

MS. GODZIEMSKI: I don't have any surveillance data, no.

DR. HOLLINGER: Yes, Jane.

DR. PILIAVIN: Could you come up with a hypothetical case, then, in which you believe you wouldn't allow release? What kinds of findings about donors after the fact would lead you to not allow the product to be used, because it sounds like every time they ask you about these things, you say it is okay.

DR. GOLDING: I think there is one example or at least one example that I recollect where the lots were not released, and I thought we were actually still in the process of discussing it. The situation was a donor donated the product, denied any risk factors. His unit was part of a pool. Later, on a subsequent donation, several months
later, the donor was found to be -- came back for another
donation -- was found to be positive.

They went back, there was a lookback, and what was
found was that this donor, although he was negative by
testing at that time, the unit that was transfused to the
recipient -- I think it was platelets or something -- the
recipient actually became HIV positive.

A recall of the products was instituted and those
products are now on hold, and have not been distributed, and
we have been discussing it within the agency as to what we
are going to do with these products.

Part of the process of deciding what to do involve
going out on inspection and looking at the validation data,
and testing pools. The pool involved in the actual
products, the final container products by PCR that was done
in Indira Hewlett's lab, and everything was negative, and
the viral validation showed many logs greater than 20 logs
removal of HIV by the process which had been validated.

So, that is an example of a situation, I think,
that was asked about where the final product was not
released because of a donor situation.

DR. MARTONE: I am presuming that these are actual
cases that have happened, and not hypothetical ones.

MS. GODZIEMSKI: Yes.
DR. MARTONE: In how many of these instances do you actually go back to the individuals and retest them or do an analysis or investigation of that individual, because, you know, it seems to me that part of this is that you are concerned about a window period, at least we have heard a lot about that this morning, and there seems to be some variable time interval between the donation and then when you are notified, do you go back to any of these donors and retest them when you hear of these things?

MS. GODZIEMSKI: Sometimes the actual blood establishment will do followup testing for those donors, which then they would share that information with the Agency.

DR. MARTONE: Is that a uniform thing or is that just something that may or may not happen?

DR. HOLLINGER: I think Bill is right. If you take all these cases you just presented -- I think, what, there may be about seven donors or eight donors in this whole thing maybe that had some problem -- how many of those? I mean do we have the data for the number of the donors that were retested?

MS. GODZIEMSKI: No, we don't.

DR. HOLLINGER: You would like that, Bill, is that right?
DR. MARTONE: I was just wondering if that was a standard operating procedure or not, or you just look at the facts as we have them here and then make a determination.

DR. HOLLINGER: Dr. Khabbaz.

DR. KHABBAZ: I was going to go back two questions and respond to Dr. Martone in terms of surveillance systems of recipients. You know, CDC has a surveillance system of hemophilia patients that has been expanded this past year to include all patients treated at hemophilia treatment centers, and doing testing, so looking for incident infection, so there is a mechanism to look for any infections related to products of this sort.

DR. FINLAYSON: In answer to the other question that Dr. Martone asked, is there a standard operating procedure, there is a standard operating procedure for review in the Office of Compliance, but as far as what happens in the actual collection centers, almost any scenario that you can name has happened.

For example, in one of the instances that you referred to is that a donor came in, donated, and it turned out that the person had a previous record of having been positive -- I should say reactive for HBsAg. Now, obviously, that donor should never have been allowed to donate in the first place, but he had slipped through
possibly because of having donated at another place.

There have been many instances, for example --
well, many -- over the course of a couple of decades, there
have been a substantial number of instances in which a
person came back and not only donated once, but donated
several times, and in effect what you have there is an
illegal reentry. The person should never have been allowed
to donate, but was, on each of those appearances, negative
by the test at that time.

There have been other instances in which having
become aware of this, when a donor came back and donated
once, and then was negative, but previously, the record
showed had been reactive, that donor is deliberately called
back in, but there is not a standard procedure, but all of
these things that you refer to have been seen not just once,
but on considerable occasions.

DR. MARTONE: I think that sort of makes my point
about investigation of the donor, because in the example you
use, it is conceivable that someone acquired a case of acute
Hepatitis B and donated, was positive at that time, and then
previously had been negative, but at the time of the
donation was positive and then on retesting, you might find
that they have become a chronic carrier or that they had
resolved the infection, and at the time of the subsequent
donation, were HBsAg negative and antibody positive, which
would have allayed any concerns about that particular
donation going into that product pool.

DR. EPSTEIN: I think part of the confusion over
the examples not having cases where we did withdrawal or
quarantine versus where we did not reflects the current
status of thinking wherein we have not been routinely
conducting withdrawals or recalls based on the donor risk
histories for Hepatitis B, Hepatitis C, and HIV.

As you know, that is not because of a reluctance
to do withdrawals or recalls, for instance, in the area of
CJD, where we have had even remote risk histories we have
done withdrawals.

The reason we brought this question to the BPAC is
that this paradigm is itself the thing under question, and
we are really asking you whether you think we are doing the
right thing as we are currently doing it. So, we have
presented the issue without bias, but the fact is that our
past behavior with respect to Hepatitis B, Hepatitis C, and
HIV for products where we have validated viral inactivation
procedures has not been to recall.

Now, there have been several recent situations in
which the policies have come into question, and I think that
Dr. Golding mentioned one, which was a case in which a donor
who had failed to admit risk factors subsequently
seroconverted, had previously donated, and his other
products, namely, his transfusable component, did transmit
HIV, so we had a known contaminated collection, in fact, a
known window period collection with proven infectivity, and
we simply have not reached closure what to do with the
products that have been quarantined.

They were not already in distribution, so it wasn't a question of recall, but we haven't decided what to
do with them, and that is one of the issues that we will act
on when we finally have recommendations.

Another situation which is pertinent to the issue as we brought it to the last BPAC concerned positive marker,
where a foreign government tested pools for fractionation
and found antibody positivity for HIV on the pool. Now,
there were no known donors who had been pooled with a
positive antibody, and presumably there was some error
somewhere, however, the question then became, well, what do
you do with the products.

In that case, we did have a temporary quarantine
hold on certain products, particularly clotting factor IX,
during the time when we reviewed inactivation data,
manufacturer's validation, and did additional testing
specifically by PCR to see whether that pool presented any
unusual threat.

In the end, we decided that it did not, but I think the problem that you face is that there are not very many, if any, examples to date where we have failed -- I am sorry -- where we have acted to withdraw a product because of a risk history for Hepatitis B or C or HIV, simply because it has been our policy not to do so, but it is based on these analyses which we are now describing to you.

So, that is why there aren't examples, but the key point is -- and it is the question you will be asked in the end -- is do you or don't you endorse these analyses as a basis of that decisionmaking.

So, I don't think you can try to judge it by past performance of the Agency. You have to look at the criteria that we are applying and give us your recommendation when the question comes in front of you. I hope that helps, a little long-winded.

MS. PIERCE: Actually, Jay, in terms of that, what scenario do you see in terms of all this that you would actually look at a unit, considering the inactivation techniques and all the issues we have talked about, and not release it?

DR. EPSTEIN: Well, currently, we are not releasing products if there is a known infectious unit as
opposed to risk history. I would contend that there is an inconsistency in the current assessment.

We, I think have no reason to believe that there is any greater risk with the known positive unit than a unit presumptively contaminated or indirectly learned to be contaminated, whereas, we have in recent years viewed the situation differently with a known contamination or provable contamination as opposed to a risk history.

Now, at the last BPAC, you advised us that we could indeed apply risk assessment based on levels of contamination and knowledge of clearance in inactivation to decide what to do with such potentially contaminated products, but we have in the past made a distinction between actual positive units, known positive, and risk histories, and there are instances in which we have either failed to permit distribution or done a recall based on a positive unit. That was the subject of the last BPAC.

What we are really saying is that the principles of risk assessment should be applicable either way, but that is the question we are asking you.

DR. HOLLINGER: Corey.

MR. DUBIN: I keep being struck by the sense that we don't want to operate in a vacuum. I am concerned, at least my own feeling is that to some degree we do that. I
think we have a total picture of a system that is dependent
on checks and balances at varying degrees and varying
places.

If we have a problem at the front end of
collection, it is obviously our hope that the sequence of
viral inactivation steps at the back end will catch that
problem. We know in a vacuum that when it is applied
correctly, for lipid envelope viruses, viral inactivation
works. We have seen that, we have seen the studies, we know
that.

But I feel like we keep honing in on a tree at the
expense of the forest, and not try to be too cliche-ish, and
I think what I mean is we are not always looking at the big
picture. Now we are talking about what Dr. Epstein said at
the last meeting, we allowed risk assessment into the
equation and agreed, and I think that is important to do,
but I think, at the same time as doing that, from my
perspective, we have got to be reasonably assured that the
checks and balances at the back end are in good shape.

In the last year, I think we have seen a number of
things that have questioned that substantially from the
problem with the saline backwash and collection, and the
impact that will start to have on viral testing and then the
problems at the other end with some of the manufacturers
that were found.

So, I feel we still have some questions looking at the total checks and balances in the system that we don't always address, and we are asked to answer questions to be very focused in. I understand that, but at the same time, I think there needs to be a real assessment and a bigger level at how the whole pieces fit together and are they working, are GMPs being enforced to a degree that we know at the back end or are reasonably assured that the technology we know is going to work is being applied correctly, to the best of people's ability.

We, in the last year, are not so sure about it.

DR. HOLLINGER: Reverend Little.

REV. LITTLE: I appreciate what Corey just said about the wider picture and the checks and balances. It helps to clarify something that I have been struggling with here, and I guess it's the inconsistency in how -- we know how important the risk history is, but then it seems to be not so important at a certain level, and so I guess I have been wrestling with that tension.

I would not want the message to get communicated on any level that, well, okay, you know, if you weren't aware of this or if you are not telling the truth, or whatever, that's okay because in the end, something is going
to be inactivated. So, I am wrestling with that tension right now, but thank you, Corey, because that helped.

DR. HOLLINGER: Because we have some more time to talk about this, I think we need to discuss it, but there is a section here on the open public hearing. We don't have anyone who has specifically, formally, said they wanted to speak, but there is a time period here for anyone in the audience to have an opportunity to discuss these issues as they may relate to them.

I am opening it up for anybody, then, from outside. Just be sure to give your name and the organization or association you are with, please.

DR. BUSCH: If you recognize the incidence rate of these various infections in the blood donor population -- and I am sure equal or perhaps slightly higher in the plasma donor population -- 1 per 10,000 person use, et cetera, and you recognize also the data from the followup questionnaires that were sent from REDS to 35,000 donors that indicated 1 percent-plus of individuals who donated and gotten through the whole blood screening program on a repeat questionnaire acknowledge in a private setting some remote risk.

On the other side of the coin, you recognize the size of these pools, 10,000-member pools. I can't believe there is ever a pool that does not, on subsequent followup
of the donors, evidence seroconversion for one multiple
viruses or have donors with risk, so I think the important
balance here needs to be the recognition that we are dealing
with enormous size pools -- and from prior discussion
probably potentially necessarily large-size pools -- and
that in the instance these viruses are so high, that
subsequent seroconversion, subsequent acknowledgment of
risk, if you really rigorously followed the donors who
contribute to any pool, I can't believe you wouldn't find
hundreds of donors who would, on subsequent followup,
donation, or interview, have risks.

I think that is kind of an extreme statement, but
these cases, most of them that you are finding are just the
incidences where the donors come back and seroconvert, the
donors come back and acknowledge something, and that leads
to some suggestion that the pool is risky, but they are all
like this, I think.

DR. HOLLINGER: Thank you, Mike.

Anyone else in the audience? Yes, Jay.

DR. EPSTEIN: I just want to add one more point
about Dr. Martone's question about surveillance. I think
that if we thought that a product could not be distributed
without also doing surveillance, we wouldn't distribute that
product.
Now, it's a different question when a product has already been in distribution and we learn of some incident. At that point, we will make extensive efforts to find out what can be learned from surveillance, and will often hold in abeyance a decision on further distribution, but in prospect, I think that question doesn't arise, because if we are asking it, we are not distributing.

Thank you.

Open Committee Discussion

DR. HOLLINGER: I think then this will finish the open public hearing, and we will initiate the open committee discussion, which we have already started, at this time, but to start that, Dr. Tabor is going to present the questions for the committee discussion and recommendations.

For the committee, they are on this pink No. I, Inadvertent Contamination, No. I. The questions are toward the end of that, page 3 and 4.

Presentation of Questions

[Slide.]

DR. TABOR: The first question. Do you agree that, when notified of inadvertent contamination of a pool consisting of units negative for markers of HIV, HBV, and HCV, but containing one or more units from a donor with a subsequently discovered risk factor, FDA should determine
regulatory action based on an assessment of product risk?

[Slide.]

The second question. Does the Committee agree that an assessment of product risk should take into account an estimate of the maximum level of contamination that could be associated with the risk factor and the capability for virus removal and inactivation?

[Slide.]

Three. If within 48 hours, or whatever period of time the Committee deems appropriate, of an incident of inadvertent contamination it can be determined that it raises no new scientific issue and the manufacturer has an excellent recent record of GMP compliance, can a quarantine of already distributed product be dispensed with?

[Slide.]

Four. Does the Committee agree that a negative nucleic acid test or other additional assay on the donor or the pool can be used to obviate the need to destroy a pooled product? Examples of this are PCR testing on the donor or the pool, subsequent test-negative donations by the donor, or follow-up testing of the donor.

Committee Discussion and Recommendations

DR. HOLLINGER: Let's go back to that first question, if you could. We will just deal with these
issues. This is the first question. I would like to have
comments from the Committee on this particular question.
Are there any specific comments? Yes.

MR. DUBIN: At the risk of some redundancy, and
maybe I will believe somewhat of a naive picture, I at the
face don't have a problem with this, but to circle back
again to back it up, Dr. Finlayson was saying, you know,
well, you have got all these different standards at all
these different blow establishments, in response to Dr.
Martone, and you are going to find anything, anywhere.

Well, if on one side of the equation we are moving
in this direction and we are looking at assessment and we
want to make intelligent regulatory decisions because we
have a lot involved in this, then, at the other end, why is
the situation like that ongoing, why can't we balance out
the equation, do this, and set some standards nationally
that everybody has got to meet, that FDA basically says here
is the standard, gang, anybody consistently doesn't meet
this standard, we use our ultimate power, we pull your
license. It's very simple.

And then the situation that Dr. Finlayson was
talking about evolved slowly away from it, and then we know
we have got two sides of an equation starting to build
towards a place where we are protected on all sides.
DR. HOLLINGER: Would you want to respond to that, because I thought what you said was that you all have standards, there are standards that you deal with, things that you work on, but that the manufacturers don't necessarily have specific standards of what they might do in terms of looking for the donor, doing followup, and all this other stuff. Am I correct in that?

DR. FINLAYSON: I find this particularly ironic, my talking about blood banking plasma centers, which I can attest falls in that area of the lowest 0.1 percent of my knowledge, so please bear that in mind.

I think what Mr. Dubin was asking is why do people make mistakes, and gosh, as one who taught biochemistry for 35 years, I sure wish I knew the answer, but the situation, as I would describe, is this. The FDA does put down standards. It says, you know, you will interview donors and you will have a screening program and you will have an interview program which elicits these risk factors, furthermore, you will test for this, and you will test for this, and although we are aware of both "requirements," which are in the CFR, and recommendations which are put out by memorandum, these are standard practice of the blood banking and plasmapheresis industry.

So, those exist, and that is why we have a review
program, and that is why we have an inspection program to
see that these are enforced. What we are talking about here
is that small but definitely measurable portion of the
situations in which, for reasons that are extremely varied,
there is an exception. When somebody clearly, either
deliberately or inadvertently, makes a mistake, either the
donor deliberately failed to give a truthful answer and then
subsequently has a paroxysmal diurnal burst of conscience or
when somebody just simply didn't remember that he had
Hepatitis, let's say, when he was 13 years old.

The heterogeneity, if I can use that word, that I
was trying to imply by my previous answer, is how the
individual blood establishments come on to this information,
and the fact that when they follow up, there may be
different procedures followed.

I think the procedure that the FDA uses in looking
into this and evaluating the data that come to us is
reasonably standardized.

Did that help?

MS. PIERCE: That actually feeds into my concerns
because with acute PP standards and the triple safety net,
which is donor screening, donor -- well, donor questions,
donor screening, and then the inactivation techniques, in
this scenario here for Question 1, we are already talking
about when your first two steps of your safety net have failed, and you are down to your third one.

This is where I have got concerns about this question and what additional information would be looked at to make that decision, would it just be a review of information that has already been obtained or would it be additional information would be searched out in order to make the decision.

DR. KHABBAZ: Let me make a comment with regard to this question here. As I think about it, I think there are two things that come to mind. One is a point that Dr. Busch made and I think it is clearly from what we know, large pools must have high risk donors whether we know about them or not, they are there, they exist. That is the first point.

The second is -- and I don't think that was emphasized today as much as last meeting in June -- the fact that we have not had transmission of HIV, HBV, or HCV from these inactivated products since these processes were in place, so that is reassuring.

Now, putting these two together, one is then faced with what do you do when you do find out, and although there are a number of instances where you don't, but when you do find out that you have a donor, you have a situation where
one or more level of safety -- and do you just sit and say
while we have the other level of safety that's working, or
do you go back and make sure that that level of safety is
working and assess the situation. That is how I look at
this question.

I think it is important to be consistent. Dr.
Epstein pointed out what we are doing with CJD, for
instance, where we are moving on a theoretical risk, and
naturally, you know, acting in a very different mode.

I think it is important to be consistent, but we
need to keep it in perspective and realize that we have a
very safe situation with regard to these viruses with a
level of safety that we have in place, and it's what we are
seeking is consistency and, you know, acting in a way that
is consistent.

DR. MARTONE: I would agree with Rima, and in
putting all this discussion into perspective, especially the
discussion about who we don't know about who is donating
these components, I guess all the four questions really are
going to boil down to how confident are we that if there is
something in there, the inactivation process is going to get
rid of it, for one, and that any testing that might be done
on the final products is a good test that would determine
whether there is any viable agent in that final product.
So, it seems to me that all these questions really boil down to that final question, how good was the manufacturer in ensuring that the GMPs were followed, and that is going to be the FDA's responsibility to determine that, and on subsequent testing of the product, is that product safe, because it sounds like it is almost irrelevant whether the person had a risk factor or was positive or negative when they made that donation.

DR. HOLLINGER: I think I will bring this to a vote, at least the first question here. The question you have up there is straightforward, you all can read it. How many of the Committee members, by a show of their hands, are in favor of voting yes on Question No. 1? Let me see a show of hands, please.

[Show of hands.]

DR. HOLLINGER: Those opposed?

[Show of hands.]

DR. HOLLINGER: Abstaining?

[Show of hands.]

DR. HOLLINGER: Our representatives. Paul?

DR. NESS: I vote in favor.

DR. HOLLINGER: Reverend Little?

REV. LITTLE: I abstain.

DR. HOLLINGER: Could we have the vote on that,
please, Linda.

DR. SMALLWOOD: The results of voting, 10 yes votes, 1 no vote, 1 abstention. The industry rep agreed with the yes vote, and the consumer abstained from comment.

DR. HOLLINGER: Let's see the second question then. The first question is more I think broadly based, and the next several questions are really to try to provide some guidance about how much we feel should be done when looking at assessment of product risk.

Any comments about the second question? Does the Committee agree that an assessment of product risk should take into account an estimate of the maximum level of contamination that could be associated with the risk factor and the capability for virus removal and inactivation?

Yes, Joel.

DR. VERTER: I guess it is partially why I abstained on the first one. It is the lack of clarity of what we are trying to do. I mean I understand we are trying to get the best product into the system as possible, but it is unclear to me that the tools are available to actually do the kind of risk assessment and this maximum level of contamination that they would need.

So, I find it hard to vote against any of this, but I am not sure what we are doing when we are voting for
it other than saying it's like apple pie, but are the
techniques available that would then give assurance that
once it's released, that the technology is there to actually
say we know what the maximum level is.

REV. LITTLE: I have to agree with you, Joel. I
abstained for something along those same lines, but also I
just want to add, I think it really does make a difference
what we know and what we don't know, even though, you know,
the reality is there are probably a number of people who
have risk factors. I think it is that one piece about now
that we have this information, what do we do with it. I
think that makes a big difference.

DR. HOLLINGER: Part of that would be
surveillance, I take it, is one of the issues, although it
is comforting I think to know that at least from a
clinically based disease, and you would expect at least some
cases to be clinically relevant, that there has not been any
-- I think the comforting was that at least for transfusion-
associated disease, no clinically relevant HCV has been
detected since '94, and for HIV, I think it has been since
maybe '87 or something like that except for manufacturers or
other problems, and we will deal with that in a minute.

REV. LITTLE: I absolutely agree with you. In
reality, I think the product is probably safe, but then as a
consumer, I get this picture, you know, of my son needing a particular lot of blood product, and if faced with the choice of one of the two, which one would I choose, would it in my mind make a difference, and I have to say yes, it probably would. But I agree with you, I think scientifically it probably is safe.

DR. HOLLINGER: I will say that we are participating just for information about surveillance, we have just initiated in collaboration with the CDC, a national surveillance of the hemophilia population at 150 hemophilia treatment centers that actually will start again. It has started already, but it will really start in October, looking for any evidence of infection occurring on an annual or biannual basis of patients where Hepatitis or HIV, and perhaps that may shed some light on some of these issues that we have here now.

Let's vote on this question then. Yes, please.

DR. MARTONE: The question I have about this question is what difference does it make -- and I ask this to the FDA -- on your estimate of the maximum level of the contamination whether it is $10^5$ in that donor or $10^8$, is there a cutoff that you are going to have, that you are going to use, and if you are not going to use it, why should that even be relevant?
DR. HOLLINGER: Let me come back and ask you. I mean you have looked at this, too, and looked at some of the issues. Do you have a feeling or does anybody on the Committee have a feeling of what you would advise them?

DR. MARTONE: Well, you know, the inactivation processes aren't all or none sterilization processes, as I understand it. They are log reductions. So, the question I have, is there a maximum cutoff level that people have in their minds where they would say we don't feel comfortable with this inactivation process?

Granted, the product gets diluted 10,000-fold or more.

DR. HOLLINGER: I think there was some data that was shown -- you probably recall -- earlier about $10^{10}$ -- supposedly, reportedly $10^{10}$ and $10^{17}$ log reductions over a variety of things, at least that is what has been reported. It is sort of an open-ended question obviously, asking the Committee, you know, an assessment of product risk should take into account an estimate of the maximum level of contamination could be associated with the risk factor.

DR. EPSTEIN: I think what we are trying to get at is a rational way to come to closure based on things we could measure. I think that, for HIV, we have a simpler
situation because we have good assays for measuring virus
contamination by PCR, and we have a lot of data including
virus detection, but also transmission experiments,
culturability, animal studies, that have measured the
clearance.

For HCV and HBV, it is harder because the assays
are less well developed and because we are more dependent on
marker virus data, and the epidemiological surveillance to
tell us what is true about safety of the product.

I think that the situation that we would like to
work toward is that, faced with an incident of potential
contamination, can we get to the point where we can do a
test, such as the PCR, and if it's negative, say we are
done, not because that rules out the possible contamination
of the pool -- coming back to Dr. August's earlier point --
but because it sets an upper limit on the contamination,
which can then be viewed in the context of whatever it is we
know about clearance.

So, for instance, if one could reach the point
where one could say that negative PCR means that there are
no more than, for argument's sake, 100 copies of viral
genome per milliliter, and if we know that inactivation is
in excess of, for argument's sake, 5 logs, could we then use
these principles to decide we have a safe product.
So, we are not really saying that we know all the answers at this point in time. What we are really asking is whether you endorse that kind of logic, and then, of course, we will endeavor to do our best in each case.

Now, I think it has been suggested that we have some knowledge of the upper limit of contamination that could be associated with a risk history, and the earlier speakers suggested what we know about HIV, HBV, and HCV.

At the June meeting, we gave a fairly extensive description about what we knew about inactivation and clearance, and although it can be simply stated for HIV, the problem is that we could not simply restate it for Hepatitis B and C. We would have to go back through, you know, a 20-minute presentation about marker viruses and transmission experiments.

But we do know that there is highly effective elimination of enveloped viruses, and we believe that we can combine that information with knowledge of possible titer to reach a risk assessment.

DR. MARTONE: Maybe my question is simpler than it sounded. Granted, we know what the maximum levels of contamination could be based on the data we have here. Does any of that make any difference for this particular question?
In other words, let's assume that every instance of notification could be a potential highest level of contamination possible. Would that make you automatically disqualify that product?

DR. EPSTEIN: No, but the assessment of risk could vary on a product-specific basis given different manufacturing schemes. So, I don't think that there is any particular level that would automatically disqualify all products from distribution. However, if we had potential high level contamination, such as Hepatitis C in the window period, we might make a different decision for different products based on their actual manufacturing scheme.

DR. MARTONE: Could you expand on that? I don't know specific examples you had in mind.

DR. EPSTEIN: Well, we have a range of products that are inactivated and purified in a variety of ways, and for any particular product, we have certain specific knowledge about viral elimination during the purification process and about viral inactivation or removal related to steps added for those purposes, such as a filtration step, a heating step, a solvent-detergent step, but those set of procedures are not the same from product to product.

One product may be heated in a lyophilized state. Another product may be exposed to a solvent-detergent
mixture. Another product may have a lower temperature heating combined with nanofiltration. So, what we are saying is that we would do a risk assessment, but it would be on a product-specific basis.

I mean Dr. Weinstein could elaborate more on that particular product.

DR. MARTONE: So, in fact, you will use the information as to what the maximum level could be?

DR. EPSTEIN: Oh, yes.

DR. MARTONE: Based on the product and its mechanism of inactivation?

DR. EPSTEIN: That is what I would envision.

DR. MARTONE: Have you ever done that to date?

DR. EPSTEIN: I think that to date, we have looked at the available knowledge on viral inactivation and the known epidemiology related to, in these cases since '87, absence of transmission, and we have not really factored in what we knew about residual titer.

I think that it is a step forward to try to add to the analysis, an estimate of potential contaminating titer or a direct measurement, such as through PCR, and we see that as a step forward that would kind of level the playing field. In other words, we would be qualifying pools whether we knew they were contaminated or we didn't know they were
contaminated, based on direct knowledge of an upper limit of
contamination in relation to viral inactivation. At that
point, we would have a consistent logic whether there was
inadvertent pooling of a positive unit, a high risk unit, or
no known unit, and we would be able to make the same levels
of assurance of safety.

So, that is really what we are trying to work
toward, and the way you do it is by looking at possible
contamination level, sometimes based on theory. For
instance, what is the level in a window period, but
sometimes based on measurement, such as what is the highest
possible infectivity titer if there is a negative PCR.

But we are not there yet for any and all things,
but what we are asking is whether you endorse this logic.

DR. HOLLINGER: Probably when we get to 4, we can
maybe make some specific recommendations on that, too, Bill,
which I think is important to do.

REV. LITTLE: I think one of the key phrases in
the question is take into account -- I think you should
probably take into account anything that you know and all
knowledge that you have, but according to that question --
and if I am understanding you correctly -- you are not
solely basing your decision on that. Is that correct?

DR. MARTONE: That is correct.
DR. HOLLINGER: Yes, I think that is what he said.
Let's go ahead and vote on that. All members of
the Committee who are in favor of this question, raise your
hand, please.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Abstaining?

[Show of hands.]

DR. HOLLINGER: Joel, do you want to comment --
and I don't want to put you on the spot --

DR. VERTER: I felt I had to be consistent with
the first one.

DR. HOLLINGER: Okay.

Beatrice, anything?

MS. PIERCE: I agree. It is somewhat consistency,
but again it just goes back to my concerns about a lot of
issues that I voiced before.

DR. HOLLINGER: Corey, anything specific?

MR. DUBIN: I think, Blaine, it is coming down to
for me we have to pick and choose where we raise certain
issues, and there is a certain frustration that I know I am
voicing that I feel sometimes there is a bit of a
compartmentalization of things here, and I see that here
given some of the stuff we know about the last year and what
has happened with GMPs and some of the factors, and so I
have concerns. On some level, I need to follow those.

I was a little more comfortable with the first
one, although I had some of this, this is more focused on
the capacity for virus removal and inactivation, and what I
am seeing over the last 10 months, I am unhappy about, and
this is one way to voice it.

I do think we need, as a committee, to have this
discussion. I feel like we keep having it in parts, and I
would like to see us have it in a whole, because I think
what you are hearing from our side of the table is a real
concern that GMPs are not being managed in the way we would
like to see them, and that while we accept that the
technology does exist, and is effective in this area, some
other things have to happen.

DR. HOLLINGER: Rev. Little, how would you vote?
REV. LITTLE: I would have to consistently
abstain.

DR. HOLLINGER: And Paul?
DR. NESS: In favor.

DR. HOLLINGER: Favor, okay.

Could you read the response?

DR. SMALLWOOD: The results of the voting are 8
yes votes, 1 no vote, 2 abstentions. The consumer representative abstained, and the industry representative agrees with the yes votes. I must also note that Dr. McCurdy, the temporary voting member, was not in the room at the time that the voting took place.

DR. HOLLINGER: Let's go on. Now, we are sort of perhaps getting a little bit more into the specifics. Let's go on with the third question, please. And Paul McCurdy is now in the room.

DR. McCURDY: I would have voted yes.

DR. HOLLINGER: On -- do you know what the question was?

[Laughter.]

DR. McCURDY: Yes.

DR. HOLLINGER: Okay. The third one has to do with the timing and also about whether or not one might not quarantine, whether it could be dispensed with based on if the manufacturer has had an excellent recent record of GMP compliance.

So, I would like to open this question up. I think it is going to perhaps lead a little bit more to some discussion.

Dr. Linden?

DR. LINDEN: I don't understand the question, and
I would like to request that someone from FDA explain what is meant by a "new scientific issue." Are you saying that it raises no compliance issues, that the risk factor is not something that would need a deferral, or does it mean something other than that, because that is really going to affect the answer.

DR. HOLLINGER: We are not going to let you rephrase it, Jane.

DR. PILIAVIN: I don't understand it either.

DR. HOLLINGER: Could somebody from the FDA try to respond to Dr. Linden?

DR. EPSTEIN: Well, I think what we are talking about with a "new scientific issue" is something we can't currently envision, but the kind of thing that you might be talking about is, for instance, a strain that would fail detection on PCR or if it were discovered, for instance, that there is a subset of virus that is particularly resistant to inactivation or any other factor that could otherwise lead you to believe that your assessments of viral clearance or inactivation would be incorrect in this instance, so that is what I mean.

DR. LINDEN: So, you truly mean a new scientific issue, so they are at risk and likely to be infected with Hepatitis B, Hepatitis C, or HIV, that would not be a new
scientific issue?

DR. EPSTEIN: That would not unless there were new
issues that arose for Hepatitis B, C, or HIV. In other
words, what we are saying, you know, we don’t know, but
certainly there could be new issues.

But the other point I think is directly
responsive, in fact, to you, Corey, what you have been
saying is that there has been compartmentalized thinking in
risk assessment because we haven’t been talking about a GMP
assessment.

I think that the reason for that is that FDA has
been separating the issue and that what we have been talking
about is in the face of adequate GMP compliance, can we do
X, Y, Z. What you have been saying is, well, the record
shows that there isn’t always adequate GMP compliance.

Well, when there isn’t adequate GMP compliance, we recall
products, and, you know, that is the record that you are
talking about.

I mean you are looking at the record of recalls
and withdrawals and saying, well, look, here are instances
of failure of compliance, so, you know, how can we apply
risk assessment when there is failed compliance, but in
those instances, we do not release product in process, and
we do recall distributed product.
The thrust of this question is in June, the Committee advised us always to quarantine first, and the Agency has reacted to that advice and said, well, wait a minute, you know, sometimes we have reason to believe that compliance is not at issue, and in addition, there is no novelty to this situation scientifically, what is the benefit of a quarantine.

So, we are, in fact, trying to take into account your concern that a scientific risk assessment is meaningless in the absence of GMP compliance. We understand that, okay, and in this question, we are trying to put the two things together.

DR. HOLLINGER: But, Jay, on the same question, you know, along with this -- and I have just a little concerns about what this means about "recent record of GMP compliance." I personally believe that if there is a transmission or something that is going to take place somewhere down the line, it is going to be because of a breakdown in the technology somewhere or, as we talked before, inadvertent errors, or things like this, human errors or something.

So, the question is does this mean that if a manufacturer has shown good compliance with everything, that someone is not going to go back and look specifically at
this lot, let's say you found out that there was a product
from someone, a donor, for example, or even if it was a
positive sample that is now in a pool or now been made into
a product, that someone is not going to go back and make
sure that in the manufacture of that specific product, that
there wasn't some breakdown along the way or some potential
breakdown?

DR. EPSTEIN: Well, I think you have put your
finger on it, and part of the problem with a review of GMP
is that it can be very time-consuming, and the question is
what is the threshold.

For instance, faced with an incident of a donor
with a risk history who contributed to a pool, at one level
it might be sufficient to say, well, the company had a
nonviolative inspection in the last six months, and the
batch record for this product indicates that inactivation
took place.

Now, that is a lesser level of stringency than
wanting to examine the actual record of the inactivation,
and that, too, is a lesser level of stringency than wanting
to re-review the validation data for that inactivation.

So, for instance, if it was a heating process, and
the heating step is, you know, monitored with thermocouples,
and the thermocouples are located in 40 locations in a vat,
and there is surveillance monitoring of thermocouples, you
know, you could argue that, well, we aren't really sure,
unless we have gone back and determined that the company
monitored all its thermocouples and that indeed there was no
problem with that surveillance in that run or the preceding
or subsequent run.

So, you know, the problem that you face is really
this. If a process is out of control for lack of
compliance, none of the products being made are safe,
whether there is a known incident or there isn't a known
incident.

On the other hand, if a company is operating under
control and in compliance, then, there is really no reason
to think that an incident has raised additional concern
provided that it's within the known scientific dimensions,
in other words, things we know the process handles.

The dilemma is to what extent should you
revalidate processing in the face of each and every
incident. Now, I would agree that if you are in an
environment with a particular manufacturer, where there is
an historic record of problems with compliance, why, then
you ought to be ever more vigilant in the fact of any
specific instance.

On the other hand, if you are in an environment
where there is a record of good compliance, and where
recordkeeping suggests that there are no deviations, then,
perhaps the kind of 48-hour look at available records is
sufficient.

So, we are not saying we wouldn't assure that
there were intact records documenting absence of deviations,
but it is a simpler thing to ask if there were any
deviations than to exhaustively re-review validation data.

The quandary that we were put in by the
recommendation at the June meeting is that there was no
latitude given. We were essentially being directed to
always quarantine, which is tantamount to doing withdrawals
or recalls in the instance of distributed product.

So, there is a balancing act to be done, and I
think in fact what we are trying to do is accommodate your
very point, Corey, which is that we not have tunnel vision,
that we not just look at virologic data, but that we take
into account GMP performance, but the question is how to do
that rationally.

I mean should we always withdraw or recall the
product, and then do a several-week to seven-month
investigation when there is an incident? I would contend
that that is not just impractical, which could be argued,
but also not needed.
DR. HOLLINGER: Yes.

MR. DUBIN: Two things, Jay. One obviously, given what I have said over two years sitting at the table, I would agree with what you just said. I don't want to be, I don't want my own comments compartmentalized either.

In the incidents where, for instance, with CJD, clearly, you know, we have made it vocal and to the point that we think there are improvements happening in staff's response, in the way things are looked at.

I don't want to be painted with the stroke of the brush in the same way that staff doesn't want to be, and that the FDA shouldn't be, because it is a much more colorful kind of picture than that, and I want to be really clear about that, and I am not sitting here saying, you know, in all instances, this exhaustive review. On some of those, I don't have a problem with what is up there, I think it is absolutely reasonable, but I don't think you can deny that there have been a couple, at least a couple of incidents in very recent times that have shook us up, and have not indicated the kind of on top of it, some of the other actions we can look at have, and they have been in areas that have been fairly disturbing.

The situation with the collection devices and the backwash of saline that impacted the viral testing, and the
most explosive of all, which will come up later, is the pool
size discussion where for 20 years, we sit, you know, in
belief that certain things are going on, and FDA seems to be
of that belief, and lo and behold, a congressional committee
steps in and holds a series of hearings, and these numbers
surfaces that are just shocking, and they are not only
shocking to hemophilia, all the other communities have been
calling on our 800 number to discuss this.

So, I want to be clear that I don't want to be
painted with a stroke of the brush either, that we are
absolutely strong when we say in these certain areas -- and
I have said it to Mark, I have talked with Mark a number of
times on the phone where I said you guys are doing a good
job on this issue, we see it, but I think there is specific
areas where we have concerns that we will continue to raise
them. I don't hear us sweeping the brush with you all.
Certainly, that is not our goal, but I think there are a
couple of incidents that have really troubled us this year,
that are separate from the incidents where we think you have
reacted well and quick, and nobody wants -- you know, every
time something comes up, a seventh month or a three month,
we would have so much product on hold then, nobody's
interest would be served. We are very clear about that.

So, I think we need to be real clear on both sides
DR. HOLLINGER: Corey, I think your comments sound appropriate. Give us from your example what you would do with this question. Is it a matter of timing? What things would you suggest that perhaps would be beneficial here? I guess that is the real question here.

MR. DUBIN: I mean I think, as I said, on its fact, Blaine, I don't have a lot of problem with the question as it is structured. I think it is important for us to ensure, as Bea just said a minute ago, that all three components in the safety net are functioning and functioning well.

I absolutely agree with Jay, you don't want to rip open a five-month investigation every time something happens when a manufacturer has got a good record, and I don't want to suggest for a minute anything else but certain things that have happened that are troubling that we want answers about.

On its face, this is a very rational policy if the system is functioning in a way that the safety net is in place, and the peak, the different parts of it are complementary, so if we have a break at the front, we have got that net at the end.

DR. MARTONE: Let me voice the opposite opinion.
I am very uncomfortable with this recommendation. I am uncomfortable because you are dealing -- in the first instance, you are making the assumption, when you don't get notification, that all the systems are in place, the company has good GMPs, and you are issuing safe and good products.

On the other hand, you have had a breakdown in one of the phases. I think that in addition to determining whether there is a scientific issue involved, which may or may not take 48 hours -- I don't know where the 48 hours comes in -- that there needs to be an investigation of those lots that were made.

Now, I don't know how long that takes. It could take a day, it could take 10 weeks, but whatever it takes, I think there needs to be some type of investigation. Now, maybe it means just going in and reviewing some records. I don't know that it requires a full-blown GMP investigation or something in between, because I am not familiar with the types of things that you do.

But to put an arbitrary time limit on it and to give the impression that you have been a good company so far and everything is fine, I feel very uncomfortable with it.

DR. HOLLINGER: Thank you. Jerry.

DR. HOLMBERG: Is there any magical about the 48 hours? Is that just so that we don't proceed to a five- or
seven-month investigation?

    DR. EPSTEIN: The proposal is quite the other way around. We don't know how long an investigation might take, but we are saying that if within 48 hours we can determine that there is adequate GMP compliance, can we avert a quarantine, because the recommendation of June said immediately and uniformly quarantine pending an investigation. That means that there is no opportunity to avert quarantine. It means that any incident triggers recall and withdrawal, because again, as was carefully pointed out this morning by Mr. Fogle, from the legal point of view, we don't have a quarantine, that there is a recall or a withdrawal.

    So, what we are saying is, well, is there some middle ground, I mean is there some reasonable short period during which a determination could avert an automatic recall or withdrawal.

    Now, if in that period we cannot determine that there was adequate GMP compliance, investigations would be ongoing for however long they take. So, I think the logic is, you know, maybe we are communicating it backwards. We are not saying we are going to render judgments in all cases in 48 hours. We are saying can we get some reasonable latitude during which if we can make a judgment, we can
avert quarantine. Otherwise, in all incidents -- I mean the advice we got from this committee in June, all incidents would trigger recalls and withdrawals. We think that is an untenable position.

DR. HOLLINGER: But, Jay, on the same deal, how often is GMP compliance evaluated? I mean is this something that is done for a manufacturer once a year, and therefore, there could have been a year go by before -- I mean if they have had a record over the years, but it may be once a year, is this once a month, once a week? I mean help me, give me a little feeling for it.

DR. EPSTEIN: Well, for a licensed biological manufacturers, there is a requirement for an inspection once every two years. Now, inspections in fact occur far more frequently than that. The FDA has been stepping up the frequency and intensity of GMP inspecting of fractionators in particular, precisely because of recent incidents to which Corey Dubin alluded.

Additionally, manufacturers may be more frequently inspected because they are manufacturers of multiple products. Additionally, they may be inspected for cause based on reports which we may receive of errors and accidents or based on reports of adverse events.

So, it is not possible to give you one uniform
answer. I mean the answer may be that a particular manufacturer was recently and extensively inspected, and it may be that another was not so recently inspected, but they would all have been inspected. In fact, we have inspected all fractionators distributing U.S. products since January of '97, so that they have all had an inspection in that time frame, 100 percent.

However, prospectively, as companies come into compliance, it may be possible for us to relax frequency, but again, if there are incidents, adverse event reports, or other causes, they would be reinspected.

DR. HOLMBERG: I appreciate that clarification. I guess to get back to Dr. Martone's comment about the GMPs, I think that I would feel much more comfortable if the statement was no new scientific or GMP issues, and throw the GMP in there, because that needs to be reviewed.

I appreciate the increase in inspections, however, if the biologicals are only inspected routinely every two years, I think that we need to have that thrown in there with no new scientific or GMP issues.

DR. HOLLINGER: Yes, Dr. Linden.

DR. LINDEN: It seems that if we vote yes on this, what we are saying is that if properly performed, the viral inactivation processes will completely eliminate the well-
studied lipid-enveloped viruses, and it seems that we are
saying it is therefore okay to dispense with the evaluation
that we just talked about in the risk assessment in
Questions 1 and 2.

If this question related to if the risk assessment
can be done quickly in, you know, whatever number of days,
could you then avoid the quarantine, I would say yes, but
the way it is written now, we are saying no, you don't need
to do a risk assessment, and I couldn't support that.

Part of the confusion also may relate to this
issue about quarantine and hold, and the question I asked
this morning, I am not sure that there is a really good
understanding of what happens when the quarantine is put in
place.

I think at the last meeting, when we answered some
of those questions, I think there was an understanding of
the Committee that there is some way to just sort of put
things in hold while you do some further analysis and study,
and then a decision is made, and that's what happens. I
don't think that there was an intent that you immediately
would initiate a recall when there is any report of any sort
of problem without studying it first.

DR. EPSTEIN: Again, the recommendation in June
was to make no distinction between in-house and distributed
product, so, you know, we don't have the luxury based on that recommendation to consider holding distribution, and not recalling distributed product.

So, this is why it is important to ask whether a reasonably brief period of assessment can go on concurrent with product in distribution. I mean we are really putting to you the question of did you really mean immediate quarantine. I mean the recommendation was immediate and universal quarantine pending risk assessment, and we are just trying to bring to light the implications of that recommendation.

DR. HOLLINGER: What would be the alternative?

DR. EPSTEIN: The alternative is to set some limit to the period of investigation during which a product remains on the market.

DR. HOLLINGER: There would still be immediate quarantine, would it not? I mean are you going to investigate and then quarantine afterward --

DR. EPSTEIN: We routinely quarantine the in-house product, in other words, what has not been distributed is always held, but the issue is whether to treat the distributed product in essence differently, because to deal with the distributed product, you have to pursue a withdrawal or recall.
DR. HOLLINGER: Paul.

DR. McCURDY: I think there are a couple of things that trouble me in this a little bit, and I think may trouble some of the other members of the group. If we could put a definition or get some sort of either a definite defining of what recent is, is recent one week, one month, six months, and so forth, and the other question that I would have is, is 48 hours really 48 hours, which means that for practical purposes, no report that comes in Friday afternoon can be handled in this fashion.

I think it would be easier if we could put some definition to a couple of these terms.

DR. HOLLINGER: That is a good point. Go ahead, Bill.

DR. MARTONE: I think there is about two or three issues being mixed up here. One is we keep going back to what we did in June, but that was a different issue, that was a different problem. That was known contamination. This is something different. This is a risk factor analysis type of thing. So, whether that comes under what we said before, I have no idea.

The other thing is that the way it is worded gives the implication that there isn't going to be any investigation of the company that makes this product, and
that is the part I have the biggest problem with.

Now, it is up to the FDA to decide how long and to what extent it needs to investigate that potential contamination problem, if that is going to, in their opinion, take a month, that's the FDA's business, but I don't think we can let things get off the hook by just saying, oh, the company has a good record, so we are not going to have to do anything in the company, and that is the major problem I have with this.

DR. HOLLINGER: So, if you had something that basically said in the question, just if following an incident of the inadvertent without a time period on it, it can be determined that it raises no new scientific and, as Jerry said, no new scientific or GMP issues, any new scientific or GMP issues and the manufacturer has an excellent recent record, again, the recent as Paul just mentioned, of GMP compliance, can a quarantine be dispensed with. That is the kind of thing you are --

DR. MARTONE: Yes, I think there are two different issues, (a) when an incident occurs, an assessment of scientific issues needs to be made and the company needs to be investigated, issue 1. Issue 2, during that investigation, what should happen? That is a different discussion.
DR. HOLLINGER: Joel.

DR. VERTER: I just briefly agree with what is being said. I think the thing that I am concerned about is that everything I have heard today tells me the system, when it is working, gives the nation a great blood supply, and I think the key thing here is exactly what Blaine just said. A company could have been investigated three months ago and have been given a clean bill of health, but the thing we are trying to avoid is that something in the system, human or mechanical error, happened when this new batch was put together, and it gets out there.

So, the fact that they have an excellent bill of health three months ago could be totally irrelevant. I think that is what we are trying to focus on. That is my biggest problem with it. I think that is what I heard Blaine say and others.

DR. HOLLINGER: It is probably tied in a little bit also with the fourth question, which we will get to, too. I mean theoretically, if you could get to the donor right away and test the donor by a very sensitive test, like PCR and serology, and/or you could test the product by the same technology, then, I think one would feel a little bit more secure about what to do about this particular issue because these are donors who have come in, have been marker-
negative donors who have had some risk factors. I mean that would be the other issue.

Then, for me, if I saw that kind of thing and looked at both the donor and the pool and found them to be negative, I would not have a problem with the others.

DR. VERTER: In some sense, it is kind of like a random act against the company that had the unfortunate happenstance of some donor saying, oh, by the way, I have donated, but now I remember this.

What I have heard today is that probably everything out there has some contamination, but the system, when it works, takes care of that. So, this group is being singled out only because some person shouldn't have contributed, did contribute, and then through guilt or whatever decides to own up to it.

DR. HOLLINGER: Dr. Khabbaz.

DR. Khabbaz: Is the inadvertent contamination, this question, limited to risk, or this encompasses what we dealt with in June, which was positive units? I mean standing alone, I am not sure it just means risk. Can somebody clarify that?

DR. EPSTEIN: I would prefer that the question apply both to risk history and positive unit. If the Committee is uncomfortable lumping them for whatever reason,
then, certainly today's discussion was focused on risk history, but I think that we are really dealing with similar risk assessments in both kinds of incident.

DR. LINDEN: I am troubled that the question implies that we said that a quarantine is necessary if there is a risk factor problem, and we haven't said that. That is not what we said in June.

DR. HOLLINGER: Say that again, Jeanne.

DR. LINDEN: I think that the question implies that default there is a quarantine if there is a risk factor problem that has come up.

DR. KHABBAZ: It says "be dispensed with."

DR. LINDEN: Right, because it says "be dispensed with," that it is there, and we are talking about can you do away with it, but I am not sure why there is the implication that it is there when the Committee hasn't said that, and I am not sure why else there is an assumption that there will be a quarantine if there is a risk factor that comes to light.

DR. KHABBAZ: In June, we did not address risk factor, but we discussed inadvertent contamination, i.e., a reactive unit or pool.

DR. LINDEN: We are talking about positive --

DR. KHABBAZ: This encompasses both.
DR. EPSTEIN: Again, it is my opinion that if we take this question broadly to apply to both positive units and risk factors, that we will make progress more readily. We are asking you in essence to revisit a question you were asked in June, but I mean I think what you are hearing is that the Agency is uncomfortable, that the concept of an immediate and universal quarantine is going to be difficult advice to follow.

Now, it may be the view of the Committee that that was the right advice for positive unit and that we should simply reopen debate on risk factor histories, but I would contend that, at a practical level, there is not a big difference because the issue is degree of contamination and we have shown you that it can go either way, that sometimes contamination levels are higher with marker positives, and other times they are lower with marker positives.

So, to my own way of thinking, that is not the distinguishing feature.

DR. HOLLINGER: Yes.

MS. PIERCE: In terms of that, I guess one of my concerns is that we are talking about risk factor here, but in 48 hours, you are not going to be able to really determine whether that risk factor actually equates a positive unit or not, of it is just a risk factor, because
of window periods and things like that, and you are not
going to be able to get that additional information in 48
hours.

DR. HOLLINGER: Dr. Verter.

DR. VERTER: I think you just confused me, Dr. Epstein. For a positive unit, I can see going the full
limit, because we know it is positive, but here I thought
the issue was we don't know that there is anything positive
in there, if it was just some random act which said someone
who contributed to the making of the unit is now saying he
has a risk factor, he or she has a risk factor, and the
question is what should be done with the totality of that
unit, admitting from what I have heard that this is
happening all the time, it is just random that this one
happened to come up. Is that not accurate?

DR. EPSTEIN: That is correct.

DR. KHABBAZ: But you should keep in mind that
with the risk factor, you may as well have positive. You
know, we have window periods. So, you have not tested to
find out whether you have positive.

DR. VERTER: Let's take it to an extreme, be
absurd. I will be absurd. If every one who contributed to
everything that is out there was swearing on a stack of
Bibles and anything that he held sacred, it would seem to me
everything out there would be recalled or quarantined from what I have heard today.

DR. HOLLINGER: Any other comments? You can hear, Jay, that there are some issues here that are of concern. I think the issues primarily are not so much when did they walk as it is a concern about whether there has been any breakdown and what assurances the company -- at least I am uncomfortable, I will speak for myself, with the fact that the assurances, be sure that there hasn't been a breakdown in the product in terms of manufacturing, and so on, is the only thing, whether it is positive or not. I mean that is the real issue, and now the question is how long that takes without going through a full-fledged evaluation is another story. But I would be uncomfortable if a manufacturer had been just evaluated two years ago or a year ago, and we are now looking at an issue right now about what is there.

Yes, please.

DR. Khabbaz: Can I propose rephrasing the question?

DR. HOLLINGER: How would you rephrase it?

DR. EPSTEIN: Jerry already proposed some rephrasing.

DR. HOLLINGER: Yes.

DR. Khabbaz: Rather than recent record, the
manufacturer has an excellent recent record -- what was the wording that you used?

Drop the "recent" and put "no new scientific or GMP issues"? How about the 48 hours are people comfortable with that?

DR. MARTONE: I am sorry, I think that is vague.

DR. HOLLINGER: Which is vague?

DR. MARTONE: "No new scientific or GMP issues."

I mean somebody sitting in an office could look at a report and say, okay, there is no new scientific or GMP issues here, let's get on with it.

DR. HOLLINGER: Do you have a suggestion, Bill? It's a tough issue. This is not easy.

DR. MARTONE: "When an instance of inadvertent contamination occurs, there will be a determination of new scientific issues in an investigation of the company's compliance with GMP."

DR. HOLLINGER: Dr. Linden.

DR. LINDEN: I still have the same problem that unless the question is going to be rephrased to include the risk assessment, I think to say yes to this is completely inconsistent with having voted yes on Question No. 1, which is that we said that there has to be an investigation to assess product risk in order to determine regulatory action,
and here we are saying we are going to determine regulatory
action without doing that risk assessment.

DR. HOLLINGER: Would you like to see the FDA come
up and rephrase their question for us, give us a better
definition? I mean you have heard a lot of the issues here.
I mean that would be one issue.

Yes, Bill.

DR. MARTONE: Could I ask one thing? If I say an
investigation of a company's GMP, does that legally bind you
to do some nine-month horrendous thing, or could it be at
your discretion what you do, could you go in and look at
some batch records as a spotcheck?

DR. EPSTEIN: Yes.

DR. MARTONE: And interview some of the employees
and get this done within a few days?

DR. EPSTEIN: Yes. But again I think the notion
of things we could learn in 48 hours suggests a certain
depth of investigation. In other words, you could verify
that there was a complete batch record with no history of a
deviation. You could not, on the other hand, verify all
details of manufacturing or review the validation history of
equipment. You know, if you are limiting yourself --

DR. MARTONE: But you would get a feel for that
while you were there, you would go there and you would look
DR. EPSTEIN: Or maybe just from the lot release record. I mean not everything requires going to the plant.

DR. MARTONE: Do you disagree that you would need to do something?

DR. EPSTEIN: No. I would be comfortable adding the phrase "If within 48 hours of an incident of inadvertent contamination it can be determined by suitable investigations and risk assessment that it raises no new scientific or GMP issue and the manufacturer has an excellent record of GMP compliance, can a quarantine be dispensed with?"

That puts the focus on doing an investigation and an assessment, which is where I am hearing the concern.

DR. MARTONE: Will it be done over the weekend?

DR. EPSTEIN: Yes. I mean we do these things over the weekend. I mean the presumption that we don't is a little startling, but we do.

DR. MARTONE: You may do it, but the company may not be open.

DR. EPSTEIN: They will work through the night, over the weekend. If the FDA calls, they will be open.

MR. DUBIN: Jay, I can substantiate that you have called us late Friday night and worked through the weekend
and had conversations and the company has called.

DR. FINLAYSON: I must again confess that I have not sat down and in cold blood -- bad pun -- read 21 CFR 211, however, according to GMPs, these same GMPs that tell you that you have to keep records, and you have to have sufficient illumination, and so forth, it also says thou shalt have a quality controlled unit, and that quality controlled unit shall do certain things, and among the things that that quality controlled unit -- and we extend that to quality control/quality assurance you shall do -- is review the back records of every single lot before it is ever turned loose.

In fact, that can mean if we are doing release at the FDA, before it is ever even sent to the FDA for testing.

Now, when an incident like this, that we are talking about today, the company gets word of a donor who didn't behave appropriately comes in, we would certainly expect that company to go back and have their quality controlled unit again re-review the records.

So, it isn't that nothing is happening in the company, and as Jay says, it doesn't matter whether it is Friday afternoon, in fact, it seems that it is Friday afternoon, that the risk assessment would begin at that time on our part, as well.
But I sort of perceived that this role of the company's quality control/quality assessment function was not appropriately appreciated.

DR. MARTONE: What you are saying and what is written here are two different things.

DR. FINLAYSON: That's correct. What I am saying is part of the background that would be assumed before No. 3 up there.

DR. HOLLINGER: Good part of the background. Thanks for sharing that.

Yes, Paul.

DR. NESS: I would like to echo what Dr. Finlayson just said, because I think the Committee, in the discussion, is underestimating what the FDA inspection process does in the manufacturing world, and that they come in at a point in time, and obviously, we find a problem at a point in time, but when they come in, they look prospectively and retrospectively at all of the systems to make sure that there hasn't been a failure at that time.

The inspection is also totally random, so any prudent manufacturer is going to be doing these things continuously anyway. So, it seems to me that, you know, within 48 hours, with a known inspection program, which occurs at some frequency, that one could verify that, in
fact, this company is operating under control.

DR. HOLLINGER: Good point.

Jay, do you have that?

DR. EPSTEIN: I am almost there.

DR. HOLLINGER: Okay.

MS. PIERCE: I guess I have a follow-up question to that. In terms of all of this that goes on, on a routine basis, what additional information do you think would be obtained from going back in and looking at those batch records again, and all that, if they have already been looked at as part of the basic process?

DR. NESS: In general, very little.

DR. HOLLINGER: Thank you.

[Overhead.]

DR. HOLLINGER: I am going to call for the question here on this basis here. Everybody take a look at that, and then we will vote.

MS. PIERCE: Blaine, I have a question. I heard a number of us ask that the excellent recent record of GMP compliance be removed, and I additionally would like to see the excellent recent record of GMP compliance removed.

DR. PILIAVIN: Why?

MS. PIERCE: Why? Because I think that the issue comes up that some of this is random and that going on the
fact that they have a recent good record does not exclude the fact that something can go wrong in the manufacturing process.

DR. VERTER: But this is in addition to --

DR. HOLLINGER: Yes, this is in addition to.

Linda just told me I need to read this here, so let me read it for the record.

If within 48 hours of the incident of inadvertent contamination it can be determined by suitable investigations and a risk assessment that it raises no new scientific or BMP issues, and the manufacturer has an excellent recent record of GMP compliance, can a quarantine be dispensed with?

DR. AUGUST: A point of clarification. The quarantine has been initiated and now we are talking at 48 hours or however long it takes to get the message out, it is going to be terminated. Is that really what we are saying?

DR. HOLLINGER: I think it is saying that that is why they are putting the 48 hours, that they are going to let that go, and then the quarantine would be placed on it.

DR. AUGUST: So, they are not going to quarantine it or hold anything, they are going to make a decision about quarantining in that 48-hour period.

DR. EPSTEIN: I think there was loose use of words
here. We would quarantine product under the control of the manufacturer. The issue really is whether to act against distributed product.

   DR. HOLLINGER: So, it would be actually can further quarantine be dispensed with. Is that right?

   DR. EPSTEIN: Perhaps we should say a quarantine has previously distributed product.

   DR. HOLLINGER: Yes, previously distributed products be dispensed with. Can we write that in just for the record?

   DR. AUGUST: I think you are putting yourself in the position of possibly getting into a situation where at the end of 48 hours, if your investigation in fact turns up new scientific issues, you have been in a situation where you have quarantined, you have known about it and you have quarantined the stuff under the manufacturer's control, but you haven't stopped stuff that has already been distributed, when you knew that you might want to do that, and I think that puts one in or puts the FDA in an interesting and unfortunate position of having some information, and not acting upon it, and the people who would be most affected by it would be potentially our citizens, the patients, and health care institutions.

   So, my feeling is that if you are going to
quarantine it at one level, to be consistent and I think
most ethical, you have got to quarantine it across the
board.

DR. HOLLINGER: Without recall?

DR. AUGUST: Without recall, but just --

DR. HOLLINGER: Just hold, quarantine hold.

DR. AUGUST: -- from further distribution, yes,
put a hold. I would like not to think that, for example, a
company that is manufacturing my immunoglobulin G has got a
hold on the product, and yet I am continuing to use it in
patients when it might be deleterious to their my patients'
health. I am uncomfortable with this.

DR. HOLLINGER: Yes, Bill.

DR. MARTONE: I am probably not going to vote for
this mainly because I think it is extremely complicated and
I don't fully understand it, but for those of you who will
vote for it, I would recommend that you put the word
"manufacturing" after "suitable."

DR. HOLLINGER: "Determined by suitable" --

DR. MARTONE: -- manufacturer investigations and
risk assessment.

DR. EPSTEIN: It could be epidemiologic also.

DR. MARTONE: Then, manufacturer and epidemiologic
just because you haven't explicitly stated yet in this
question the concept of investigating the manufacturer.

    DR. HOLLINGER: And I don't know how we would put
in the other one. I take it, Jerry, that they usually do
not ask the product to be held at the distribution sites. I
mean it would be very difficult to do that, I guess, if you
are talking about only 48 hours.

    DR. EPSTEIN: We often will request that all
product under the control of the manufacturer be held, and
that can include distribution sites. It is just that
sometimes the full knowledge of where the product is, is not
available to the manufacturer anymore, but other times they
have a central distribution point and they can hold it
there, too, but basically, it's a hold on everything under
their control.

    But, again, this all harks back to the
recommendation that we make no distinction, which was the
point of view of the Committee with respect to inadvertent
contamination by positive unit, we have no distinction
between the product under the manufacturer's control and the
distributed product, and really, I think it was Dr. August,
who just commented that that distinction would continue to
bother him.

    So, I mean you get to vote in favor or against,
but sort of that is the point.
DR. HOLLINGER: Let's call for the question then.

All those in favor of the question as currently written, raise you hand, please, all those in favor.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: All those abstaining?

[Show of hands.]

DR. HOLLINGER: Paul?

DR. NESS: I would vote in favor.

DR. HOLLINGER: And Rev. Little?

REV. LITTLE: I would be opposed.

DR. SMALLWOOD: The results of voting for Question No. 3. Four yes votes. Six no votes. Two abstentions.

The industry representative agrees with the yes vote. The consumer representative agrees with the no vote.

DR. HOLLINGER: Let's go on to the fourth question, please. It has to do more with what one should do when a question comes up of whether to destroy a pooled product, and it has listed -- I want to open this up for discussion.

[No response.]

DR. HOLLINGER: No discussion on this. I have a problem with it. It just says, "on the donor or the pool."
It says, "Does the Committee agree that a negative nucleic acid test or other additional assay on the donor or the pool can be used to obviate the need to destroy a pooled product?"

I would must prefer to see the donor tested than the pool, if we are talking about the donor here now with a product released not because it was positive -- I mean inadvertent contamination not because it was positive, but because of this question.

Bill?

DR. MARTONE: I would only also point out a potential inconsistency because when we get to the IPPIA proposal, one of the responses that the FDA had to one of the suggestions was that detection limits of greater than or equal to 100 copies per milliliter were not adequate, and I think that is probably what we are talking about with current technologies today, and if it not adequate for the IPPIA proposal, I fail to see how it could be adequate in detecting copies in a donor pool.

DR. HOLLINGER: You would prefer to use some other lower level for donor pool.

DR. MARTONE: I don't know. I am just pointing out the inconsistency.

DR. EPSTEIN: If I could comment, Blaine?
DR. HOLLINGER: Yes.

DR. EPSTEIN: Certainly, detection limits of 100 genomes per milliliter is not adequate to rule out infectivity to pool, but it may be adequate to ensure adequacy of downstream inactivation in the face of such a viral load. I think that is the way you have to look at those numbers.

DR. HOLLINGER: Yes, looking at log reductions, and so on.

DR. EPSTEIN: Right. In other words, if you have a 5 log reduction, and you have no more than a 2 log load of particles, let alone infectivity, which we think is less, then, the adequacy of the process may have been assured even though absence of infectivity was not demonstrated.

DR. HOLLINGER: Paul.

DR. NESS: I would interpret the intent of this question to be asking the Committee to say that does the Committee agree that nucleic acid testing or other kinds of testing is additional useful information to make a decision as to whether a product ought to be destroyed.

The way the question is sort of phrased implies that it is only yes/no, which I don't think is your intent, and so I think if we broadly interpret it, then, I certainly would favor that these kinds of tests on the donor or the
pool should be used and may be useful additional information in terms of making the appropriate medical and regulatory decision.

DR. HOLLINGER: Let's bring this to a vote also. All those in favor of this question, so signify by raising your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[No response.]

DR. HOLLINGER: Dr. Ness?

DR. NESS: In favor.

DR. HOLLINGER: Rev. Little?

REV. LITTLE: Favor.

DR. HOLLINGER: Could you read the responses?

DR. SMALLWOOD: The result of voting for Question No. 4 was a unanimous yes. There was also unanimous agreement by the industry rep and the consumer rep.

DR. HOLLINGER: We are going to break until 1:45, and we will start again at 1:45.

[Whereupon, at 1:00 p.m., the proceedings were recessed, to be resumed at 1:45 p.m.]
[1:55 p.m.]

DR. SMALLWOOD: We are going to start the afternoon session.

I have received numerous handouts to distribute to the Committee and I will be continuing to do so while we are proceeding with this afternoon session. Although we greatly appreciate everyone providing their handouts, I must let you know that when the Committee only receives the handouts at the time of the meeting, it doesn't afford them a lot of time to read it before your presentation, but I would encourage you, please, to send in and submit copies of your handouts prior to the meeting, as soon as you can, and we would like to always have copies for the record.

Thank you for your cooperation.

Discussion of IPPIA Proposal

DR. HOLLINGER: We are going to open up the discussion today on the International Plasma Products Industry Association proposal.

First, we are going to have the introduction and background by Dr. Weinstein.

Introduction and Background

DR. WEINSTEIN: In this section of the meeting we will have discussion of voluntary standards made by the
International Plasma Products Industry Association or IPPIA in conjunction with American Blood Resources Association or ABRA to improve the blood collection and manufacturing of plasma products.

[Slide.]

This is an outline of the list of speakers here. After my introduction, an IPPIA representative will describe the proposals in detail. We will then have an FDA commentary on the proposals by Dr. Aebersold of Hewlett and Lynch, and then a presentation of the questions.

An outline of these standards has been presented at a number of public forums over the past year including at the Blood Products Advisory Committee in June. I will briefly summarize these proposals as presented to the FDA earlier this month.

[Slide.]

First is an applicant donor standard, plasma from one-time donors, the group most likely to be at risk will not be used to make plasma-based therapies. Only donations from those individuals who test negative on two separate and sequential occasions, and on each and every subsequent occasion, will be used.

[Slide.]

The next standard that I have listed -- these
might not be quite in the order that IPPIA has, and we will get to that later on -- is an inventory hold.

All donations will be held in inventory for a period of at least 60 days. During this time, if a donor seroconverts and subsequently tests positive or is otherwise disqualified, the earlier donation can be retrieved from inventory and destroyed.

[Slide.]

There is a viral marker rate standard which will manage the quality recruitment and retention of the donor population at the centers. The voluntary standards establish a maximum allowable viral marker rate incidence of disease in the plasma donor population. Each donor center will be required to maintain a viral marker rate for anti-HCV, anti-HIV, and HBsAG.

There is a voluntary standard for PCR testing. All plasma used in the manufacturing process must test negative through genome amplification testing for HIV and Hepatitis C. There is a donor exposure limit which will create a 60,000 donor limit for all major products including Factor VIII, Factor IX, albumin and IGIV.

It is important to remember that these voluntary standards are above the minimum required by current regulations and thus do, in fact, represent an advancement.
At the same time, they are not as complete as they might be, and after the IPPIA presentation, the FDA will present its commentary on these standards.

I offer the following preview about some of the comments that we will have regarding these standards to keep these in mind as we have a review of the many positive elements of the standards.

[Slide.]

We have outlined a consideration regarding the applicant donor standard. We have concerns about the time between the first and second donation when talking about the inventory hold. We have a question about the material held outside of the window period for significant viruses, in other words, is the hold sufficiently long.

We wonder whether there is a method in place here to track the donor to the donation. Regarding the viral marker rate standard, how will it be assessed. With regard to PCR testing, it would be good to have details and methodology standards and algorithms, and with regard to pool size, the question, is IPPIA's proposed limit a reasonable alternative to that proposed by FDA in December of 1996, will manufacturers using pools that are now less than the ceiling limit be allowed to raise the limit.

These are just some of our concerns, but at the
same time, we urge you to keep in mind the positive aspects of these proposals.

With that, I will turn over the presentation to the IPPIA representative.

Presentation of Proposal: IPPIA Representatives

Douglas Bell

MR. BELL: Good afternoon. My name is Douglas Bell. I am Director of Public Affairs for the International Plasma Products Industry Association or IPPIA.

I will serve as moderator for our presentation regarding the ABRA Quality Plasma Program and IPPIA's Voluntary Initiatives. Immediately following me will be James Reilly, President of the American Blood Resources Association, who will discuss the background and history of QPP. Following him will be Dr. Tom Waytes for IPPIA who will outline the IPPIA Voluntary Initiatives and the scientific reasoning and data supporting their implementation. Finally, I will return to summarize.

Also, I want to point out and clarify that our Voluntary Initiatives are not proposals, but are existing initiatives that are either in place or being implemented. It is one important clarification on your agenda that these are either existing or being implemented.

Before the technical presentations begin, I would
like to briefly outline for you the role of IPPIA and its relationship with ABRA. It is also worth noting that the IPPIA is affiliated with the European Association of the Plasma Products Industry which represents the vast majority of the commercial fractionation industry in Europe.

IPPIA is the international trade association representing the commercial producers of plasma-based therapies. IPPIA members produce approximately 80 percent of the U.S. market for plasma-based therapies. IPPIA members include the four largest commercial fractionators: Alpha Therapeutic, Baxter Health Care, Bayer Corporation, and Centeon.

ABRA is the trade association representing the U.S. source plasma collection industry. Because many fractionators have plasma collection operations, there is overlap in the IPPIA/ABRA membership. Distinct from IPPIA, ABRA members also include both large and small independent source plasma collectors and other European/U.S. plasma industry-related affiliates.

With IPPIA representing the fractionation industry's interests and ABRA representing the source plasma collection industry's interests, we represent virtually the entire commercial plasma industry.

Because of the unique way source plasma is
collected and our membership being exclusive to the "commercial" sector, our Voluntary Initiatives that exceed FDA regulatory requirements do not apply to those that exclusively collect or fractionate plasma recovered from whole blood collection.

Before I yield the floor to my colleague, Jim Reilly, who will discuss the QPP program, I would like to provide you with a little background on the evolution of the IPPIA Voluntary Initiatives.

About two years ago the industry of its own volition began formal discussions regarding innovative ways on an industry-wide bases we could improve upon the margin of safety in plasma-based therapies. These discussions required a significant amount of time, personal commitment, compromise, and financial investment.

As a result, industry drafted four Voluntary Initiatives that focus on minimizing the risk of "window units." We determined that there were three primary opportunities for window units to enter the manufacturing process: units of plasma from previously untested, one-time donors; previously collected negative units of plasma from repeat donors who subsequently seroconvert; and units of plasma collected from repeat donors who have tested negative but do not return after their last donation.
We have developed an industry initiative to address each of these theoretical threats from window units and also developed a standard to institute new, more sensitive testing technology to further close the window period.

More broadly, we believe that these initiatives address three fundamental risks: that of the known pathogens; that of the unknown or emerging pathogens; and that of the limited access to plasma-based therapies. Dr. Tom Waytes will talk in more depth about each of these four voluntary initiatives.

During 1997, we have been implementing these standards one by one as technology and regulatory approval will allow. We have started the collection of data to measure the progress and effectiveness of the program. Our objective is to continue to collect more data to validate the program and subsequently report publicly on the progress that we have made.

These efforts will be a component part of an additional comprehensive initiative that we are in the process of developing.

Now Jim Reilly will discuss the QPP program. I would ask that you hold any questions until the end of our presentation and that each of our speakers will remain in
the front to answer any of your questions.

Thank you.

James Reilly

MR. REILLY: Thank you, Doug. Good afternoon.

[Slide.]

Before we move on to the current initiatives that Dr. Waytes will present, I just want to take a few moments and give you a brief overview of the Quality Plasma Program. The QPP is a series of voluntary standards that if adopted at an FDA-licensed facility would make them eligible for our QPP program certification.

The QPP requires, as a baseline, FDA licensure. From that point, as an industry we have developed consensus standards which take advantage of unique opportunities in our collection and testing procedures, and donor population to ensure a high quality plasma. One of the most critical steps is the aggressive and targeted recruitment of a community-based donor population.

[Slide.]

Before I go into the standards themselves and some of the changes we have made to the program over the years, it would be useful to review a few basic facts about the industry and QPP.

First, the program was established in 1991. We
actually began discussions I think as much as two years in
advance of that for some portions of it. QPP has 380 of the
413 eligible centers -- the typo there should be 413, and
not 410. To place this in a more meaningful context,
roughly 1.5 million donors donate plasma 13 million times a
year. Of those, about 12 million of them are at certified
centers. It results in total in about 11 million liters of
plasma.

The program is supported by the National
Hemophilia Foundation by a letter that went to each of the
manufacturers encouraging them to incorporate this into
their purchasing practices and also by Board Resolution
endorsing the program.

To put the worldwide market into perspective, the
11 million liters produced here in the U.S. is roughly 60
percent of the entire world supply, and it has been widely
recognizable.

[Slide.]

I am going to work backwards a little bit and
quickly review the changes to the QPP since 1991 and then
discuss the current standards in total.

The employee training standards that we have were
upgraded once and the minimum educational requirements were
added to them when we did that.
The National Donor Deferral Registry -- which I will explain in some more detail later -- has received several relatively minor to major, depending on your point of view, software upgrades since 1992, when it was entered in as a pilot program. It has also more recently, on March the 20th, 1997, received FDA 510(k) determination of substantial equivalence, which would allow us to market it as a device if the association so chose to.

We have added additional positive test results as a cause for listing a person on the deferral registry, specifically p24 and PCR when it is fully implemented, and viral marker rate standards have been upgraded in two ways, one by adding HCV when we began HVC testing, and the standards were lowered for HBV and HIV, and I will come back and discuss them in a little more detail.

With that summary of the changes behind us, I will describe in a little more detail each of the QPP standards. I would ask, as Doug said earlier, if you have specific questions, to hold them until the conclusion. We will try to address them as a group.

First, facilities must have a formal training program. The QPP provides guidance by dictating the
components of the program, such as initial, annual and
interim training; documentation; retraining; and that all
functions in the center are covered in the training
requirements.

Some of the ways we create a community-based donor
population are through requirements for donor identification
and local address as an example. These criteria actually
serve a dual purpose in that they provide us on the rare
occasions the ability to contact the donor to bring them
back in for appropriate counseling and referral for medical
evaluation and treatment.

We have very rigid criteria intended to ensure
that each location maintain their facility as a professional
medical operation. These include criteria related to
signage, cleaning, storage facilities, donor flow, lavatory
facilities, et cetera.

Donor screening criteria include a variety of
additional standards. Each is designed to focus on the
retention of qualified donors and the exclusion or deferral
of donors at increased risk of known or possibly unknown
viral transmission.

As you know, the unknown is very difficult, if not
impossible, for us to quantify until it becomes a known, but
we believe these do help us in that endeavor.
The additional screening criteria we require include increased emphasis on donor education of high risk activities, exclusion for incarceration, and drug testing.

We are particularly proud of the next requirement. It is participation in the National Donor Deferral Registry. We have successfully developed a national computer system capable of capturing the name and donor identification number for any person who has tested positive -- any plasma donor I should say -- who has tested positive for any viral marker test that we perform, the laboratories listed on a private computer network.

Each collection facility can instantaneously check donors against the Registry using an 800 number and a series of location specific passwords and codes to check any donor. All QPP centers and associated laboratories are required to participate in the NDDR.

One of the more creative standards at the time was the application of a viral marker standard at all locations. I am going to describe this one in a little more detail in just a second.

[Slide.]

Finally, each facility is required to submit specific documents and data for review related to the standards, and they are subject to both a biennial as well
as random inspections by third party.

[Slide.]

Now, I would like to describe the viral marker rate standard that we have in effect in a little more detail because we are developing a significant change to this standard this year.

In 1991, we established a standard for HIV and HBV. At that time, and until very recently, plasma products were manufactured from plasma obtained from both applicant donors and qualified donors, new and repeat.

With this in mind, we set the standard based on the mean industry average of all positive tests per center plus two standard deviations.

In 1993, we added a standard for HCV and lowered the acceptable standard for HIV and HBV by 19 and 32 percent respectively. The rates for HIV and HBV were lowered because we were seeing a steady improvement in the industry mean as a result of the overall QPP program.

In 1997, we are making an even more substantial change based on the imposition of an applicant donor exclusion standard which Dr. Waytes will describe in just a moment.

[Slide.]

Finally, before I turn the microphone over to my
colleague, Dr. Waytes, you should also be aware that we don't view the QPP, the current voluntary standards, or any of the industry's programs as stagnant. This slide is simply a list of the initiatives we currently have in various stages of discussion and implementation.

These initiatives are the development of basic and train the trainer level workshops, expanding QPP standards in the areas of the National Donor Deferral Registry, viral marker rates, donor screening, and cGMP and QA criteria. We intend to expand our patient and regulatory liaisons and communication efforts, and development of a plasma center location guide.

[Slide.]

Next, Dr. Waytes will describe several new industry voluntary standards, which I think Mark was kind enough to already lay out in summary. Two of these, which are related to the plasma collection portion of the product manufacturing process, will or have become QPP standards. They are the use of plasma from non-returning applicant donors from further manufacture, which became effective actually in July of this year as a QPP standard, and the new viral marker rate standard which will be based specifically on confirmed positive viral marker tests from Qualified Donors.
With that background of QPP and the building, if you will, of our comprehensive initiatives, I will now turn the microphone over to Dr. Waytes who will describe the current initiatives.

**Dr. Thomas Waytes**

DR. WAYTES: Good afternoon. My name is Tom Waytes and today I am representing the IPPIA.

[Slide.]

The member plasma fractionators of the IPPIA have continuously sought to improve the quality of their therapies by increasing the theoretical "margin of safety," which is the difference between the maximum potential viral load of the manufacturing plasma pools and the sum of the virus removal and inactivation steps incorporated in the manufacturing process.

My presentation today will focus on industry initiatives to increase the safety of the plasma starting material.

To address further the issue of reducing the potential maximal viral load in manufacturing pools, the IPPIA took the historic step of implementing what are now known as the four "Voluntary Initiatives."

[Slide.]

These initiatives include the Applicant Donor
standard, the viral marker rate standard, an inventory hold period, and PCR testing. ABRA has subsequently endorsed these initiatives and has committed to incorporating those standards applicable to plasma collection into its QPP. Over the next few minutes, I will discuss the Voluntary Initiatives in detail.

[Slide.]

A recent investigation has shown that, although only a small percentage of source plasma units are collected from first time donors, or "donor applicants," these units account for approximately 95 percent of all positive viral marker test results.

The first of the Voluntary Initiatives, implemented in July of 1997, as an element of QPP, requires that no units of plasma be accepted for further processing unless the donor has successfully passed at least two health history interviews and two panels of all required screening tests.

This standard takes advantage of the repeat donor population unique to the source plasma industry, to further reduce the risk of undetected infectious units of plasma being manufactured.

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By definition, Applicant Donors are described as
all individuals presenting themselves who have not been previously qualified as a donor in the past six months.

On the other hand, Qualified Donors are all individuals who have been qualified for continued donations by successfully passing two donor screening and viral testing panels.

More specifically, individuals will be considered Applicant Donors until such time as they have successfully passed the following two-stage minimum donor screening process:

In Stage 1, persons presenting themselves for donation initially will be screened according to all applicable government and QPP screening and testing criteria. This applies whether a complete plasma unit or sample only is collected. At this stage the person will be considered an Applicant Donor.

In Stage 2, reclassification of a person from Applicant Donor to Qualified Donor is achieved by passage of a physical examination as required by government regulations and either: (a) subsequent donation of a complete unit and acceptable donor screening and testing based on all applicable government and QPP requirements; or (b) subsequent donation of a sample only for the purposes of viral marker testing and successful passage of the complete
medical history screening questionnaire.

The subsequent screening of Applicant Donors must occur no less than the minimum time interval allowed by applicable government requirements and no greater than six months.

Testing and donor screening to classify a person as a Qualified Donor must be administered by collection centers operated by the same company.

No units of plasma from an Applicant Donor will be acceptable for the manufacture of therapeutic plasma products until the person has become a Qualified Donor.

What this accomplishes is that no plasma will be used for manufacturer that has come from a donor who has not shown a commitment to repeat participation at the plasma centers. This markedly reduces the probability of using plasma from unacceptable populations such as persons who appear primarily for free viral testing or those in immediate monetary need.

This standard also ensures that at least two acceptable virus screening panels are performed on each prospective donor, which reduces the probability of testing error, and, to a lesser or greater degree, depending on the interval between samples, reduces the window period for each virus.
In summary, the use of plasma from one-time donors is completely eliminated through this initiative. Through this standard, industry is also able to retrospectively assess the acceptability of initial donations with subsequent interviews and test results.

The second initiative is the viral marker rate standard. This will redefine the existing standards and reestablish the maximum allowable viral marker rate for incidence of anti-HCV, anti-HIV, and Hepatitis B surface antigen in qualified donor populations.

It was agreed by the member of the IPPIA and ABRA that the quality of plasma from a given center is best determined by measuring the confirmed reactive rates of all plasma units obtained from the Qualified Donors of each center.

Because the donor population and testing requirements are precisely defined, this standard will provide an ability and opportunity to monitor and assess the overall quality of the repeat donor population at each center.

All participating centers are committed to have begun to perform confirmatory testing of anti-HCV, anti-HIV, Hepatitis B surface antigen as of July of this year. From this date, the confirmed reactive rates of Qualified Donor
units obtained at each center will be collected for each of the three viral markers.

The data collected over the first six months will be analyzed statistically, so that a meaningful maximum cut-off level can be established. Each donor center will be required to maintain a viral marker rate below this limit as part of its QPP certification. Facilities exceeding the limit will be identified for corrective action or exclusion from the program. This standard will be implemented in January of 1998.

[Slide.]

In order to obtain an estimate of the expected viral marker reactive rates to be obtained in the above plan, ABRA has undertaken a viral marker data collection effort concerning confirmed positive rates of units from Qualified Donors at participating centers.

Retrospective data as collected prior to July of this year from varying time periods ranging from 6 weeks to 6 months from all industry laboratories. This data represents a total of 3.175 million donations collected from nearly all industry plasma centers and is shown as follows:

[Slide.]

The Hepatitis B surface antigen of 0.005 percent; confirmed anti-HIV, 0.0019 percent; and confirmed anti-HCV,
0.0112 percent.

This retrospective data was collected to obtain an immediate glimpse of where our prospectively determined rates are likely to be. ABFA will publish data collected during the July 1 to December 31 period, as well as that collected on an annual basis. Viral reactive data collected from all participating centers will be evaluated on a routine basis, so that meaningful cut-off limits can be maintained.

[Slide.]

The inventory hold. The third Voluntary Initiative is the institution of an inventory hold for units of plasma prior to pooling for further processing. A minimum 60-day hold will be implemented on all units collected by January of 1998.

The inventory hold program takes full advantage of the frequent and repeated participation of source plasma donors. As can be seen in this example, if a donor becomes infected with a given virus, such as HIV or HCV, a window period exists during which time he or she is potentially infectious, but is not detected as such by current screening tests which measure antibody response to the viruses.

By holding all seronegative units in an inventory hold, this standard provides manufacturers with the
opportunity to retrieve units from previously qualified donors who seroconvert on a subsequent donation, or are otherwise disqualified. Thus, window period units, as those shown in this illustration, can often be prevented from entering the manufacturing pools.

Data have been collected over a five-month period from an IPPIA member company incorporating an inventory hold program. During that time, over 300,000 units of plasma were entered into the inventory hold. It is important to note that approximately 97 percent of these units were followed by a subsequent donation by the same donor.

A total of 2,555 units were removed from the inventory hold as the result of 331 donors being identified by subsequent seroconversions, other surrogate testing, or post-donation information. As a result, these units were prevented from entering the manufacturing pools.

The voluntary inventory hold identifies units obtained from seroconverters for HIV, HCV, and HBV. It also has the capacity of removing units that may contain any known or unknown virus of which transmission may be associated with the potential high-risk behavior identified by the current testing methods or post-donation information.

PCR testing. The fourth Voluntary Initiative is the implementation of Genome Amplification Technology,
commonly known as Polymerase Chain Reaction or PCR. This technology can further reduce the window period by identifying potentially infectious units which fall below the detection threshold of existing donor screening and testing technologies. Each of the manufacturers is working closely with the FDA and other affected parties to obtain the required agency approvals necessary to implement PCR technology as rapidly as possible.

Not only can PCR testing limit the maximum potential viral load to the detection limit of this sensitive assay, it can also serve to validate the effectiveness of the previously described standards.

In summary, the four Voluntary Initiatives, described above, represent a tremendous cooperative effort between plasma collectors and fractionators, and are expected to have a significant impact on increasing the margin of safety of all products derived from human plasma.

It should be emphasized, however, that these standards represent not a final solution, but a dynamic process which will be continuously evaluated and improved. These Voluntary Initiatives discussed above are part of a comprehensive package of initiatives put forth by industry to take advantage of new information systems and technology used to continually improve the margin of safety in plasma-
based therapies.

It is hoped that the significance of these efforts will be recognized by the appropriate regulatory agencies, as well as the consumers of our life-saving products.

I will turn the mike over to you.

Douglas Bell

MR. BELL: Thanks, Tom.

[Slide.]

Our commitment to safety is clearly illustrated by the QPP and the Voluntary Initiatives. More importantly, what can be seen is that we have responded to the challenge and pursuit of making plasma-based therapies ever safer, not with rhetoric, but with action.

You have heard a detailed discussion of the ABRA Quality Plasma Program and the IPPIA Voluntary Initiatives. As you see, these initiatives are dynamic and continually evolving in our search for safer therapies. Some of these initiatives have been in place for years, other are being implemented and we are proud to announce yet another addition to our safety initiatives.

In our testimony this summer before Congressman Shays, Human Resources Subcommittee, we outlined seven layers of safety in the manufacture of plasma-based therapies. The uniqueness of fractionation allows for these
additional layers of safety. We believe that these layers of safety are fundamental to achieving the level of safety our patients expect and need.

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These layers of safety are donor screening, donor deferral, donor testing, inventory hold, quality assurance and good manufacturing, viral inactivation and removal, and recall notification. In fact, earlier, I think there was a triple safety net remarked on earlier and some discussion at BPAC. We believe that there is much more than that, at least seven layers of safety we believe to have achieved.

As you have just heard, the industry has for years actively and methodically undertaken a series of voluntary initiative to address these opportunities for defense. These industry initiatives serve to complement the individual efforts made by each manufacturer to safeguard against impurities. Together, these efforts form a protective safety barrier that is far stronger than each of the component parts. Yet, all of these parts must be strong in order to provide the best assurance of safety.

What we are pursuing -- and what we committed to at Chairman Shays oversight hearing -- is a comprehensive plan that builds upon the seven layers of safety. A comprehensive plan that will review the existing initiatives
to measure their progress, assess the need for new
initiatives, and communicate to key individuals our
objectives and the progress that we have made.

In a staged process, we are assessing our existing
voluntary initiatives, our commitment to reduce pool size,
and the need for new programs. In the context of this
examination, we will determine accurate forms of measurement
to quantify our progress.

As IPPIA Executive Director Robert Reilly stated
to Congress, "That is our goal, our challenge, and our
commitment -- and we will verify the success of our efforts
through accurate measurements."

[Slide.]

If you examine the QPP certification standards and
the four voluntary initiatives at the macro-level, each is
an important piece of the safety puzzle. Each has its
critical role in maximizing safety. Each has its critical
time in the process. Finally, each has its critical place
in the system.

What is evolving -- and what industry has
committed to develop -- is a keystone to these programs that
will be the glue bringing all of the pieces of the puzzle
together.

[Slide.]
IPPIA over the next several months will be examining the key elements of this plan. We will share those key elements with Congress, the FDA, and consumer groups for feedback and comment. After receiving comment from interested parties, the industry will then finalize the details.

The seven layers of safety are the foundation upon which we are building in our ongoing commitment to making plasma-based therapies safer still. The basis of our strategic plan should then be no surprise.

The industry has a long history of multifaceted voluntary initiatives that address the seven layers of safety. We are looking toward expanding those voluntary initiatives to include a keystone or comprehensive plan that will help interlock the existing voluntary initiatives together with the seven layers of safety into one unified program.

As providers of plasma-based therapies we are, and must continue to be, leaders in the commitment to safety. It is a responsibility that we take very seriously. The message we are sending through these voluntary initiatives and our commitment to this comprehensive plan should be clear: Industry is dedicated to continuous improvement, so that the people who depend on plasma-based therapies for
their health and their very lives will know that those therapies are safe, available, and effective.

In sum, what you have heard in our presentation is that industry has a number of robust voluntary programs underway. The QPP, which began in 1991, and the four voluntary initiatives that began in 1996, and are being implemented this year, these industrywide programs serve to complement additional measures that each individual company employs.

What we have said is that we will reexamine all of four existing initiatives, add a comprehensive initiative to our existing plan, and report publicly on the progress we have made.

We are very excited and proud of these programs. We hope that you can embrace and support us in these endeavors.

Thank you very much, and we will be happy to answer your questions.

DR. HOLLINGER: Thank you.

I think what we will do, if the Committee doesn't mind, I think I will go on and have the FDA commentary on the proposal first, and perhaps even go into the comments from the group before making we can respond. Is that all right with the Committee?
What don't we have the FDA's commentary and then we will move forward.

**FDA Commentary on Proposal**

**Paul Aebersold, Ph.D.**

DR. AEBERSOLD: My name is Paul Aebersold. I am in the Division of Blood Applications. I will start the commentary. There will be three speakers, as Dr. Weinstein indicated.

[Slide.]

First, to comment on the inventory hold, I would actually comment on all of the proposals. They are definitely very positive steps to reduce the frequency of window period donations from getting into the manufacturing stream.

That is the underlying comment about the proposals, but let me say about the inventory hold, that in an ideal world, I think we all know what the inventory hold would be. It would be a period of time that was longer than the window periods for these three viruses, and any unit would be released only when a donor subsequently returned after the longest window period, 89 or 90 days, or something like that, than the previously released unit older than that age would be released.

This would mean essentially that only units would
be used for whom a subsequent test existed past the longest window period. That is the idea situation. There is a lot of impracticalities about it, not the least of which would be that anytime a donor dropped out of the donor pool, since they wouldn't be coming back, you would lose a number of units.

In terms of a commentary on this, as probably the ideal perhaps not being practical, the question would be is the 60 days long enough to encompass the window periods. Of course, again, there is no guarantee that a donor would be returning before the product was released. As it stands, the product would be released at 60 days whether or not there was a subsequent test for qualified donors.

[Slide.]

We will look at the next slide. The applicant standard. These are also, of course, under the 60-day hold, inventory hold. Again, eliminating plasma for which the donor never returns, not using that is a positive step based on the numbers that were given that 95 percent of the positive tests come from a small percentage of donors who are the first-time donors, this would be expected to reduce the number of window period donations entering the manufacturing stream.

The business of qualifying the donor by two tests,
as Dr. Weinstein gave you a preview, that raises the question of what time frame should be considered between these two tests for a person to be considered a qualified donor. I gathered -- I should say I am substituting for someone who is on jury duty, and I am not in the plasma collection business myself -- but my understanding is that the time between donations could be two donations in a week or something like that, and then the question that comes up is, is this a suitable period, have you really learned that much more about a donor to qualify that person because they came back twice in a week, or are they twice as desperate for money on the other side of things, would one want to see a longer period between donations to consider someone a qualified donor.

One could conceive perhaps that an absolute quarantine or hold for the long window period time, although maybe not practical for every donor, might be something that could be considered for first-time donors to enter them into the qualified pool, so that you would actually get a second test past the window period donations before you would consider them a qualified donor.

This would have a down side, of course. There may be more plasma units that couldn't be used.

[Slide.]
The last part of the QPP program that I will say anything about is the viral marker rate standard, and I guess this is like apple pie, of course, one is in favor of it. I guess the questions that the FDA would most likely have to ask would be how is it handled if one of the collection centers falls outside these bounds, how do they take corrective action to ensure a better marker rate standard or compliance in the future, how would they change their donor recruitment, for example, if they fell out of bounds, and, of course, in the memo that was in the BPAC package, the question was asked what about first-time centers, since they are going to have first-time donors, you would expect their rates to be higher. So, we don't have probably all of the information about how this program would work for first-time centers or for centers what fall out of compliance, and yet obviously, it is a very desirable thing to hold the rate of positive donors down as much as possible.

Dr. Hewlett will talk about the PCR testing.

Indira Hewlett, Ph.D.

DR. HEWLETT: Good afternoon.

[Slide.] I am going to present a critique and an FDA response on the aspect of the proposal that talks about
implementation of gene amplification technology.

[Slide.] The IPPIA proposal does talk about implementation of gene amplification technology, specifically, PCR testing with an eye towards early detection of the infectious agent and reduction of the window period.

They also are currently working with FDA to implement testing. However, the proposal does not provide any details on assay methodology, on the standards that will be placed for PCR testing, and algorithms for testing, as well as how donor notification of positive results will occur.

[Slide.] FDA's current perspective and thinking is that nucleic acid testing is perhaps the most sensitive method currently available for early viral detection. Nucleic acid testing would result in reduced viral burden in blood and plasma, and this is a good thing.

The plasma industry has proposed, however, testing plasma pools rather than single donations for the presence of viral nucleic acid. Part of the reason for this is that pool testing may be the most practical at this time given the state of the technology and the rapid evolution of this technology.
FDA believes and recognizes that plasma pool testing implementation is in the best interests of public health. We also believe that it is an interim step toward single donation testing, which we hope will be the future in terms of donor testing.

The test is considered to be a donor screen because donors are being tested in the process of generating plasma pools, and as a result and consistent with our approach in the past with regulation of donor screening assays, these tests will be evaluated under the IND/PLA mechanism for licensure.

The purpose of the review under this mechanism is to establish manufacturing consistency of the test, as well as to establish the performance characteristics of the assay.

An integral part of pool testing would be donor notification, and the issues here have to do with the public health benefit that is derived from donor notification including treatment and prevention of subsequent viral transmission. Therefore, we believe that plasma pool testing while being implemented should occur in concurrence with procedures for donor notification and deferral, as well
as product retrieval.

[Slide.]

I am going to very briefly outline some of the regulatory concerns in regard to the test methodologies, and I have actually spoken in greater detail about this at a previous meeting of this committee.

So, to summarize the issues, the key issues have to do establishing a rationale for the pool size, taking into account its impact on test sensitivity. Although FDA has not yet defined a specific lower limit of detection, the current thinking is that the lower limit should ideally be below 100 copies per ml.

The test should also be evaluated for clinical sensitivity and specificity in addition to analytic sensitivity, and test sensitivity should be established for viral variance, and this, of course, will be determined by the design of primers and probes used in the assay.

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Other regulatory concerns include establishment and evaluation of sample and reagent stability, the reproducibility of the assay, the effect of interfering substances in generating either false positive or false negative results, which is of particular concern in a pooled matrix.
In addition, the issue of controls is important with pool testing, of course, and PCR testing, one has to be concerned about controls for contamination, as well as internal controls that would ensure that the assay has, in fact, been performed as expected and described.

Other issues have to do with the establishment of quality control methods that would monitor manufacturing consistency.

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Finally, validation of the pooling matrix is, of course, very critical. We have seen in our discussions with industry a variety of pooling matrices and pool sizes, and that this of course has to be validated including validation of mechanisms that would allow tracing of positive results back to the original donation and to the donor.

This type of setup, of course, would necessarily involve software and instrument use, and validation of both software and instrumentation should be provided by the industry.

In addition, since this product or this type of testing will fall under the IND mechanism for review, the test methodology of course will fall into the category of tests that would be under lot release requirements using CBER panels.
In the next couple of slides, I would like to outline some proposed regulatory options that are under consideration by the FDA, and this of course is an effort that FDA has taken on to facilitate implementation of PCR testing.

The first option is one where the blood product manufacturer would take on full responsibility for the testing. The manufacturer would submit the IND and the PLA, and assume responsibility for the quality of the test. Other manufacturers wishing to use the test would then file PLA supplements for each product, and the test method would be subject to lot release testing to monitor test performance.

In the second option, the blood product manufacturer may choose to send plasma or pools to a testing laboratory. The testing laboratory would submit then the IND and the PLA toward licensure, and licensure would then permit labs to test for multiple customers. The blood product manufacturer would then submit individual PLA supplements for each product, and the test lab would then come under lot release surveillance.
In a third option -- I do want to emphasize that all of these options are proposed and are under discussion, and comments will be solicited from the industry -- the third option is one where the blood product manufacturer develops an in-house test as a manufacturing control.

In this instance, any reactive specimens that are identified would be tested by an independent laboratory, and this would be set up in the framework of shared manufacturing between the testing laboratory and the blood product manufacturer.

The main concern and the important point here is that the in-house test should be no less sensitive analytically than the outside test lab method. The blood product manufacturer and the testing lab then submit INDs and PLAs, and the combined test method is then licensed as a donor screen.

[Slide.]

In the last option, the blood product manufacturer would use a test kit developed independently for pool testing. The test kit manufacturer and the blood product manufacturer would submit separate INDs and PLAs, and the test is then licensed for the specific intended use, which in this instance is pool testing, and for the use for which adequate clinical data is provided. Again, the test kit in
this instance would be subject to lot release testing.

[Slide.]

In summary, FDA's view is that implementation of nucleic acid testing in the form of plasma pool testing is in the best interest of public health, although we see that this is an interim step towards single donation testing in the future.

As a validation, should be evaluated under the IND/PLA mechanism, consistent with other donor screening tests, since we have established at this point that this in fact is a donor screening mode.

Finally, testing or implementation of plasma pool testing is expected to occur in conjunction with donor notification of positive test results.

I would like to conclude by saying that the options that were presented, the last four options that were presented are in fact part of a Federal Register notice that is being drafted at the FDA and will be circulated for comment, so what you are seeing here is in fact the current thinking of the FDA in terms of plasma pool testing, and the mechanisms that we have explored under the regulatory purview that this set of products would fall under to facilitate the implementation of PCR testing and gene amplification testing for the testing of plasma pools.
Thank you.

I think the next speaker is Tom Lynch.

Thomas Lynch, Ph.D.

DR. LYNCH: Good afternoon.

[Slide.]

This subject, pool size limitations in manufacturing plasma derivatives, is a subject that we have brought before the Committee before, the most recently in December 1996.

It may be useful to review that initiative now before we go on to review the current IPPIA proposal. In brief, FDA came forward with a system that has several key features. Number one, in addition to suggesting that limits should be proposed, we suggested that those limits be phased in over a period of time.

Second, we proposed recognizing a difference between products made from source plasma and those made from recovered plasma, and set different limits for those two categories.

Third, we suggested that the pool size be measured in terms of donors rather than donations or volume.

Fourth, in doing this bookkeeping, we suggested that donors contributing to the albumin that may be added as a stabilizer excipient were even added to an in-process
material during manufacture, not be included in the final
total.

Fifth, recognizing that some products are
different from other products, we proposed a mechanism by
which exemptions might be granted for particular products
where the limits were either impractical or would adversely
affect the quality of a product.

This was debated rather energetically in December,
both the effectiveness of these measures and their impact on
product availability and cost were called into question.
The FDA undertook an information gathering process in an
try to assess actual manufacturing practices among the
nine largest plasma fractionators who hold U.S. licenses.

That process is ongoing, however, we have received
some preliminary data from the firms in question.

[Slide.]

Over the past month of six weeks, FDA has also
received a proposal from IPPIA to institute a voluntary
limit of 60,000 donors. Notably, this limit would apply
across the board to both recovered and source plasma. It
would include in the sum, donors who contribute to the
manufacturer of the active ingredient of a product, as well
as any stabilizing protein that may be added to it.

Finally, the proposal that FDA has received
specified that this limit would apply to the major products.

As I see it, this proposal does have two main virtues. Clarity is one. It is a very simple because it does not propose a complex multi-tiered program. The limit is easily understood. Therefore, compliance with it, should this limit be adopted, would be simplified.

Secondly, we may assume that this limit is practically achievable since it comes from a major segment of the industry itself. However, I would ask you to bear in mind that not all U.S.-licensed plasma fractionators are members of IPPIA, although those members do account for the bulk of the market for plasma fractionated products.

[Slide.]

Just a brief side-by-side comparison points out certain differences that are already fairly apparent. Both FDA and IPPIA agrees that donors are an appropriate measure of pool size for a variety of reasons, however, the number, the gross numbers do differ in some respects.

However, those differences are not easy to resolve because of, first of all, the FDA proposal initially encompassed only the active component in any given product whereas the current industry proposal includes the active component and any excipient protein added.

The differentiation between sources and recovered
plasma that was part of the FDA program has been eliminated in favor of a single limit, and while the FDA proposal explicitly encompassed all plasma derivatives and the industry proposal suggest perhaps only major products are included, in fact, this may be a difference without a real distinction, since most of the "minor" plasma-derived products are manufactured from smaller pools. There is a point of clarification there.

Finally, the time frame for implementation, we initially suggested a three-month and 12-month period of implementation. Of course, those limits have largely been mooted by intervening events. Nonetheless, the time frame for the current proposal is not clear, at least to me.

In terms of evaluating the numeric limits, one must consider separately products that are made with and without albumin or other stabilizing protein in the process. I will turn first to the ones that include albumin. That would be intravenous immunoglobulin and anti-hemophilic factor. These products are currently formulated with albumin and of course would add, under certain circumstances, to the effective pool size, the donors that are represented in any given final container of product.

In this context, the 60,000 proposed limit is at
or near what I would term a hypothetical industry limit or
industry average as it exists today. By "hypothetical," I
mean that number of donors in a manufacturing pool that one
would arrive at by considering the average size of a plasma
pool from which the active ingredient was derived and the
average size of a plasma pool from which the excipient is
derived.

That is not always the case. In some cases, the
addition of stabilizer may increase the effective pool size
by a larger proportion, and in some cases, by lesser
proportion. It depends on the precise number of donors that
contributed to the particular lot of albumin used as a
stabilizer.

That notwithstanding, the 60,000 donor limit would
in fact reduce pool size by eliminating the occasional
exceptionally large plasma pool that a given lot of product
may be manufactured, and by eliminating the above average
pools, the fairly routine manufacture, that may occur above
the 60,000 donor limit.

[Slide.]

Turning to those products that are not formulated
with any stabilizer, the 60,000 donor limit appears to be
substantially above the average pool size as it currently
exists for most manufacturers, for most products.
Now, I hasten to point out that that is not necessarily true for plasma derivatives manufactured from recovered plasma, but with that caveat in mind, we are looking at numbers substantially larger than current industry practice on average.

Nonetheless, the occasional exceptionally large pool does exist for these products, and the 60,000 donor limit would eliminate those. It is a concern of ours that a 60,000 donor limit, however, would permit increases in scale from what is currently practiced, and would ask whether or not a cap at current levels would not be appropriate.

If it was decided that capping current industry practice at its current level is an appropriate thing to do, the issue of how to define that cap comes up, and this is not an issue that we have resolved yet.

[Slide.]

Other unresolved issues regarding this proposal is the time frame for implementation. We are not sure exactly how soon this limit can be adopted, whether it is appropriate to allow this restriction to be entirely voluntary or whether it should be folded into some sort of formal regulatory mechanism, such as a change to a product license.

The exact scope of the proposal is also not clear,
whether it is intended to be restricted only to the "major
products," or whether all plasma derivatives should be
included, and finally, because this proposal derives from a
trade association that does not encompass all U.S.
licensees, it is not clear whether the non-members, the non-
IPPIA members, do in fact endorse this limit.

[Slide.]

Finally, we would ask whether or not a distinction
between source and recovered plasma is appropriate. We are
given to understand that it may in fact be possible to
maintain the use of recovered plasma at the 60,000 donor
limit. Eliminating the distinction that was proposed in
December of '96 would of course eliminate the issue of
whether such a distinction can be scientifically justified.

Finally, the question of whether or not FDA should
continue to evaluate this manufacturing issue and
contemplate additional measures in the future should those
become appropriate.

Thank you very much.

Open Public Hearing

DR. HOLLINGER: There are four additional speakers
in the open public hearing that want to speak on this issue
also, so I think we will have those four go ahead and give
their talks, but I would have you limit this to no more than
eight minutes a person. We have 30 minutes designated here, and the first one will be by Kathy Miles Crews from the Immune Deficiency Foundation.

MS. CREWS: Good afternoon. I am Kathy Miles Crews. I am a member of the Immune Deficiency Foundation National Board of Trustees, and I am President of the Texas Gulf Coast Chapter. I am also the parent of an immune deficient adolescent, and I have two brothers who have primary immuno deficiencies. So, this is something that I have lived with for a long time.

Growing up I watched my younger brother suffer from chronic illness. Their physicians suspected that the immune deficiencies that ran in our family were possibly genetically linked. Concerned with this possibility, I hesitated to have children. With the advent, though, of IVIG, my brothers' quality of life changed for the better, and I found myself rethinking the possibility of starting my own family.

I married and with great anticipation my first son Cody was born healthy. Four years later my son Clayton was born, and within six months my worst fears came true. As a carrier, I had passed a genetic disorder on to and had given it to my second son. But at the age of eight months, he began the IVIG therapy. This therapy has enabled Clayton to
grow into a very normal healthy adolescent.

IVIG has been instrumental in helping our family live a very normal life, free of the fears of constant recurring and life-threatening illnesses. However, in 1994, we learned that the medication that kept him healthy had developed some serious problems. Hepatitis C had been transmitted through the use of IVIG. We were not able to adequately obtain the lot numbers from the manufacturer associated with the Hepatitis C virus. To this day, my family is not sure of the lots that were affected by Hepatitis C.

At that juncture, our family, along with thousands of others, became very proactive in issues related to blood safety. Issues related to recalls, withdrawals, and notification became a paramount concern. This leads me to the point I would like to make today.

Patients and physicians need to be notified directly in the event of a recall or a withdrawal.

The Immune Deficiency Foundation’s National Patient Survey has revealed to us that over 20,000 patients receive regular infusions of IVIG. Although we do not have formal studies, as President of the Texas Gulf Coast Chapter, I am in regular contact with 200 to 250 patients in my area. I can therefore present what I believe to be a
The typical scenario for immune deficient patients. The typical patient does not record lot numbers, and some are not even aware of the brand of IVIG they are on. Patients who want to record their numbers and use an infusion log sometimes are not able to do so because the person who is giving the infusion does not know the lot number.

In the event of a recall or withdrawal, the product often stays in the pipeline and because the majority of patients are not being notified directly, infusions of withdrawn products occur frequently. The result is and will continue to be that the patients, even the vigilant patients, are likely to be infused with withdrawn products.

The Immune Deficiency Foundation is anxious to join with other patient groups, the FDA, and industry in a joint effort to provide prompt and direct notification of product recalls and withdrawals to patients and physicians.

The IDF is currently working with the Alpha 1 Foundation, the National Hemophilia Foundation, and other parties in an effort to develop a patient notification program directed towards regular users of plasma products.

In essence, the system would encourage patients and physicians who regularly use or prescribe plasma derivatives to enroll in a voluntary registry or database.
It would be managed by a third party, as a means to permit
the plasma industry to directly notify patients and
physicians of all recall and withdrawals.

Without going into great detail on the specifics
of the program, let me just state five basic criteria which
must be met in any patient notification system.

1. Patient confidentiality. It must be
guaranteed. Patients will not enroll if they believe that
their confidentiality is going to be breached.

2. Any notification system must be industry wide.
Many immune deficient patients are having to switch from
brand to brand particularly in this time of shortages.
Patients should not have to be burdened with a multi-system
and also we should be provided with a single point of
access.

3. Direct and active notification of individual
patients and their prescribing physicians a must. Patients
must not be required to seek out this information on their
own initiative.

4. Patient and physician education must accompany
a more effective recall system to ensure compliance. We
must be ever mindful of the patient's fears in the face of
this information.

5. The FDA has the responsibility and should
oversee the implementation of such a system. At the
November 1996 workshop on patient notification, FDA
officials indicated that the preamble to the 1978 guideline
on recall does require industry to conduct effective recalls
to reach end users. IDF believes that the FDA has the
responsibility to enforce this implementation.

I would like to make the Committee aware that IDF,
the Alpha 1 Foundation, and the National Hemophilia
Foundation are currently working cooperatively to design a
program that meets these criteria.

Permit me to close with just two personal
observations.

My brother, Stephen, is now a practicing allergist
and immunologist. In his practice, he treats patients with
primary immunodeficiencies and he prescribes IVIG. To date,
he has never received a recall or withdrawal notification
from any manufacturer of IVIG. As a patient and as a
physician, and as a member of numerous medical societies, it
is shocking to me that he has never received direct
notification.

As a mother of a 13-year-old child, Clayton will
be infused with this product 17 times this year alone. The
present system makes me certain that one of his infusions he
will receive will have been a withdrawn and recalled product
without our knowledge or we are going to be notified too late. In fact, this is a fact that I personally just cannot accept. I urge the Committee to oversee the implementation of a patient notification system to reach all users, all end users.

Because of this morning's discussion, I am compelled to point out that there are no formal CDC or FDA sponsored health surveillances or lookback studies in the primary immune deficient community, and I would encourage CDC or FDA to contact the Foundation.

I would like to thank you for letting me voice my concerns today. Thank you very much.

DR. HOLLINGER: Thank you.

We have two speakers for the National Hemophilia Foundation. We can either have one that speak for eight minutes or two that can speak for five minutes each, because we only had one actually that asked to speak here.

One is Bruce Ewenstein -- I am sorry, Patrick Collins, and the other Val Bias.

MR. COLLINS: Good afternoon. I am going to read a prepared statement from Dr. Bruce Ewenstein, as well as the rest of the members of the National Hemophilia Foundation's Blood Safety Working Group of which Dr. Ewenstein is a co-chair.
A rapid and effective notification system for consumers of blood products that have been the subject of market withdrawal or recall has been a long sought goal of the National Hemophilia Foundation and remains one of the agency's highest priorities.

The availability of timely and accurate information is an absolute requirement for informed decisions on the part of consumers and treating physicians as they balance the risks and benefits associated with the contemplated use of such products.

We believe that a primary notification system must reach all concerned parties, should not require that consumers seek out information, and must respect the patient's right to privacy.

It remains our position that the posting of updates pertaining to market withdrawals, recalls, and ongoing investigations by toll-free telephone lines and Internet web sites provides a valuable adjunct to, but not a substitute for, an adequate primary notification system.

We agree with FDA's previously stated position that the creation of such a system is the responsibility of the manufacturers of these products. We also believe that the FDA has the regulatory responsibility to monitor industry performance and to enforce compliance with
established standards.

We propose the creation of a system comprised of two complementary components that together would assure that participating consumers and prescribing physicians receive rapid notification of product withdrawals and recalls while also providing written documentation of the manufacturer's actions to all end users of these products.

We envision that the first of these components involve the use of a single independent agency that would issue telephonic and/or overnight mail notices to consumers and prescribing physicians who voluntarily submit their names. Medical necessity as well as recurrent shortages in the marketplace require that many consumers receive products from more than one manufacturer.

Often, these substitutions are made on short notice. Thus, the NHF strongly encourages all of the United States plasma product manufacturers to contract with a single notification system, providing a single point of access for all concerned parties.

The NHF is fully committed to working with the manufacturers, other organizations representing regular consumers of plasma products, such as the Immune Deficiency Foundation and the Alpha 1 Foundation, and the FDA in the selection of an appropriate agency. NHF is also committed
to promoting the voluntary use of this segment of the primary notification system among our membership.

The second component of the primary notification system would be designed to reach every consumer of a product that has been the subject of a market withdrawal or recall and to provide written documentation of these events pertaining to these actions.

This notification should follow the path of the product from manufacturer to end user and prescribing physician. It may, be necessity, involve multiple segments of the plasma product distribution network and a considerable period of time may therefore be expected to elapse between the withdrawal or recall decision and the receipt by the manufacturer that all consumers of the affected product have received written notification.

Nonetheless, it would provide that every consumer of plasma products receive appropriate notices of potential health hazards without requiring that these patients submit potentially sensitive medical information to an agency not directly involved in providing their medical care.

In closing, a primary notification system must be implemented immediately in order for the end user to be secure in the knowledge that he or she has been notified of a withdrawal or recall. The status quo is totally
unacceptable as there is no certainty that the end user becomes aware of the product withdrawal or recall. NHF believes that it is the obligation of industry to rectify this problem in an expeditious manner.

I thank you and I thank the Chair.

DR. HOLLINGER: Mr. Val Bias.

MR. BIAS: Good afternoon. My name is Val Bias, and I am a person with severe hemophilia, Factor IX deficiency. I have served as a past volunteer and currently as a consultant to the National Hemophilia Foundation.

I would like to present NHF's response to the IPPIA initiatives. NHF supports, in principle, the voluntary initiatives proposed by IPPIA and ABRA to enhance the safety of source plasma used in the production of pooled plasma derivatives.

Many of the proposals have been discussed over the past two years by industry, FDA, NHF, and others, as measures to prevent inadvertent transmission of known agents, and as importantly, to minimize the potential impact of unknown emerging agents on chronic users of plasma products. In fact, Immuno initiated many of these initiatives for their plasma products two years ago.

The initiatives we received prior to today did not include all of the scientific data to fully comment on their
merits. There is no doubt that these initiatives will improve the safety of pooled plasma products. We look forward to reviewing the more detailed plans when the NHF's Medical and Scientific Advisory Council (MASAC) convenes at the end of October. In the meantime, we would like to offer some specific comments on each industry proposal:

Applicant donor standard. This calls for preventing first-time donors from contributing to plasma pools. This is a significant improvement in the safety of plasma pools.

Viral marker rate standards. This measure will provide for upper limits on antibodies for HIV, HCV, and HBV in donor populations at each donor center. We need to know what the limits will be, how they will be determined, and what will occur if they are exceeded before we can comment further.

Inventory hold. A 60-day hold will be implemented for all plasma prior to processing. This measure, coupled with not using plasma for first time donors, could provide an enhanced removal window for period donations. However, the window periods for HCV and HBV are frequently greater an 60 days, thus, some of the donors could contribute to the pooled plasma. A hold of at least 90 days would make more sense. Alternatively, the use of genome amplification
technology, PCR, would shorten the window periods considerably, and would allow for a shorter hold period.

PCR testing. The detection of viral nucleic acids would significantly decrease the window period for all infectious agents transmitted via plasma. The preliminary proposal did not specify which agents would be screened. We would strongly urge HIV1 and 2, HAV, HBV, HCV, and parvovirus B19 as the initials agents to be subjected to PCR testing.

Furthermore, we support FDA requirements for donor notification of positive tests. The methods for PCR testing must have significant sensitivities and limits for infectious materials in each pool needed to be established. We know from Immuno's experience that PCR testing can detect and eliminate HCV and HBV from pooled plasma, however, we need additional information on the proposal before we can comment further.

Donor exposure limitation. Industry proposes a 60,000 donor cap for plasma pools which make major products including Factor VIII and Factor IX, albumin, and IVIG. We use the term pool size to mean the number of donors contributing to each lot of product, thus, all the excipients and stabilizers need to be included in the total figure if they come from pooled plasma. This proposal is
very disturbing to the health care providers who prescribe
and the consumers who use coagulation products for the
following reasons:

We were surprised, as seemed to be the FDA, at the
blood safety hearing convened on July 31, 1997, by
Congressman Christopher Shays, that up to 400,000 donors are
used in a single plasma pool. That is 27 times more than
the 15,000 donors which we were led to believe by industry
were the upper limits, and considerably greater than
industry acknowledged last spring when we queried each
manufacturer.

Industry offered at the Shays hearing to reduce
pool sizes by 40 percent. We support all initiatives that
will reduce plasma pool size and we continue to support FDA
goals that will eventually lead to donor pools of 15,000 in
the future.

In summary, the bleeding disorder community
welcomes these initiatives and once supporting data has been
reviewed by MASAC, we will support these initiatives if they
contribute significantly to safety.

As a person dependent on these products, I think
this is a step in the right direction that industry is
taking. I thank them and I thank BPAC for considering them.

Thank you.
DR. HOLLINGER: Thank you.

The next speaker is Christopher Lamb from the American Red Cross.

MR. LAMB: Thank you very much, Mr. Chairman, and members of the Blood Products Advisory Committee, for allowing me the opportunity to speak with you about the important issue of plasma derivatives safety. I am Christopher Lamb, Vice President, Plasma Operations, of the American Red Cross Biomedical Services under which our plasma program operates.

The American Red Cross is the largest not-for-profit provider of blood services in the United States, collecting almost 6 million units of whole blood from volunteer donors annually, or about 45 percent of the nation's blood supply. Blood collected for transfusion is made into specific components such as red blood cells, platelets and plasma, which Red Cross distributes to over 3,000 hospitals in the United States.

In addition to these components, approximately 1 million liters of plasma recovered from our volunteer blood donor units are annually processed, or fractionated, into plasma derivatives. Approximately 800,000 liters are fractionated at Baxter Healthcare's Hyland Division under that company's FDA license, and approximately 200,000 liters
are fractionated by the Swiss Red Cross under its FDA license. These plasma derivative products are distributed under the Red Cross label to hospitals, hemophilia treatment centers, and other intermediaries. The Red Cross itself does not fractionate plasma.

Plasma derivatives manufactured for Red Cross include Factor VIII Concentrate used by persons with hemophilia, albumin used to restore plasma volume in treatment of shock and burns, and immune globulins used to treat immune disorders. Red Cross plasma derivatives account for approximately 15 to 20 percent of the nation's supply and are produced solely from voluntary, non-remunerated donations.

1. Red Cross Initiatives to Improve Safety.

Before discussing specific initiatives to improve safety, it is necessary to distinguish between recovered and source plasma. Red Cross plasma derivatives are made from voluntary whole blood donations. Plasma obtained when whole blood is divided into components is called recovered plasma. In contrast, plasma derivatives made by commercial companies are manufactured principally from plasma obtained by a procedure called plasmapheresis. Plasma obtained by plasmapheresis is called source plasma, almost all of which is collected from paid donors.
The amount of recovered plasma from a unit of whole blood averages 250 ml. The amount of source plasma obtained by plasmapheresis averages 700 ml. Therefore, an initial pool of recovered plasma contains plasma from more than two to three times the number of donations as the same size pool made exclusively from source plasma.

The Red Cross has taken several steps to reduce the number of donations in pools of recovered plasma. In early 1996, we directed Baxter to initiate processes to ensure that American Red Cross labeled AHF-M and IVIG were derived from pools containing approximately 16,000 liters or between 54,000 and 60,000 donations.

Since mid-1996, the majority of Red Cross AHF-M and IVIG lots have been derived from pools containing fewer than 60,000 donations. Importantly, this process ensures that albumin used to stabilize these products is also derived from the same pool, in other words, material from different pools is not mixed together. Efforts will continue with our contract manufacturers, Baxter and the Swiss Red Cross, over the next year to reduce negotiated validate pool size to similar levels for the production of all products and batches intended for transfusion.

In addition, we are incrementally increasing the volume of recovered plasma donations through improved
collection and separation techniques. Through these efforts the average volume of recovered plasma per unit of whole blood has increased from an average of less than 250 ml to 283 ml and we expect further improvements to follow. We also intend to increase the amount of volunteer plasma obtained by plasmapheresis to further decrease the number of donors in Red Cross plasma pools.

2. Other Red Cross Efforts to Address Plasma Derivative Safety. Pool size is only one of the elements to consider in improving the safety of plasma derivatives. The Red Cross is actively exploring new methods to inactivate or remove potentially transmissible agent from blood and plasma, such as gamma irradiation, iodine treatment, and the use of high efficiency filters. These techniques can be effective against both known and newly emerging threats to blood safety. Dr. William Drohan of the Red Cross Holland Laboratory recently reviewed these and other technologies at a meeting of the FDA Blood Products Advisory Committee.

In addition, within the next year, the Red Cross will also implement a highly sensitive testing technology called polymerase chain reaction or PCR, to detect early evidence of infectious virus in plasma to be processed into derivatives.

Preliminary studies, which were presented to this
committee in March of this year, suggest that PCR testing may prevent the transfusion of several hundred blood components each year that may be infectious for Hepatitis C.

3. Efforts to Reduce Window Period Donations.

Please note that because whole blood donors can donate blood at most once every 56 days and most repeat donors donate twice a year, the likelihood of multiple window period donations from a volunteer donor of recovered plasma going into a pool are remote.

The American Red Cross is committed to providing the safest blood from volunteer donors. We participate in epidemiology studies, such as REDS, which was referenced here earlier today, and ARCNET, an American Red Cross program that track viral marker rates and assess the risk of transfusion associated with transmission of viruses.

The results of our studies are published in peer-reviewed articles and journals, such as the New England Journal of Medicine. A review of data related to the reduction of HCV and HIV risk shows substantial improvements since 1985. With regard to HCV, risk has been reduced from 1 in 200 in 1985, to a risk of 1 in 103,000.

With PCR we anticipate reducing the window period currently estimated at 59 days, by between 20 to 40 days. With regard to HIV, the risk has been reduced dramatically
from 1 in 3- to 4,000 prior to 1985, to 1 in 225,000 in 1990, and 1 in 675,000 after introduction of HIV p24 in 1996.

PCR testing might provide incremental improvement. However, the experience with HIV p24 testing perhaps offers some additional insight in assessing the potential for improvement. Since introduction of that test, there have been 2 antibody negative/antigen positive cases out of approximately 18 million tests in the volunteer sector. This is much lower than expected and suggests that there are in fact far fewer window-period donors than previously thought in the volunteer donor population.

4. Regulatory Issues. The Red Cross blood and plasma programs are regulated by the Food and Drug Administration. We are inspected by FDA Office of Regulatory Affairs and by several other governmental and professional organizations. Since 1993, the Red Cross has been operating under a consent decree agreed to by the Red Cross and FDA that is designed to improve our operations in several key areas.

We have essentially completed all requirements of the consent decree. For example, we have consolidated our 50 testing laboratories into nine new standardized state-of-the-art facilities that test all blood donated to the Red
We have also developed a powerful quality assurance program that is the model for the industry. The FDA has been very tough but fair throughout this process. The Red Cross is now a stronger, better managed, more efficient organization because of these efforts.

5. Creutzfeldt-Jakob Disease. The American Red Cross takes all potential threats to blood and plasma safety very seriously, and we have moved aggressively to expand the body of scientific information related to CJD.

We have several research studies underway at our Holland Laboratory and in collaboration with Dr. Paul Brown at NIH and Dr. Robert Rohwer at the Veterans Administration. The Red Cross has committed over a million dollars in research studying possible links between CJD and transfusion, probably more than any other private organization.

The Red Cross is also conducting a CJD "lookback" study under the direction of Marion Sullivan at the Red Cross Holland Laboratory in collaboration with CDC. We have studies 179 recipients of blood transfusions from donors subsequently diagnosed with CJD. These recipients have been followed for up to 25 years following transfusion. None of the recipients has died of CJD or shown any signs of
illness.

These data are encouraging, however, until there is further convincing evidence of non-transmissibility, the Red Cross will continue to quickly withdraw plasma derivatives following receipt of post-donation information from a donor or a donor's family about a risk of CJD.

Conclusion. The American Red Cross is committed to providing an adequate supply of blood components and plasma derivatives that meet the highest standards of safety. Red Cross plasma derivatives have proven to be safe and effective. We are proud of our volunteer donor tradition and believe this also contributes to a high quality starting material as suggested by the recently published Government Accounting Office report.

We have taken steps to insure this safety by reducing the number of volunteer recovered plasma donations in pools for fractionation. These steps are part of a larger program of initiatives -- unique to volunteer recovered plasma -- to improve safety by an aggressive quality assurance program, focused research programs, and improved donor screening and testing.

Thank you, Mr. Chairman.

DR. HOLLINGER: The last speaker that has asked to speak is Wayne Swindlehurst from the Committee of 10,000.
MR. SWINDLEHURST: Mr. Chairman, members of the BPAC, I am Wayne Swindlehurst. I am a person with hemophilia, severe Factor VIII deficient. I am also the Vice President of the Committee of 10,000.

I come here today on behalf of our Board of Directors. We have reviewed and considered the IPPIA. While we are pleased to see voluntary initiatives on the part of industry, we question these proposals and are not sure whether certain aspects of these proposals will impact the safety equation in a substantial fashion.

First of all, we are somewhat surprised at the pool size proposal given what we have learned over the last two months. If industry is proposing to increase baseline pool size, yet we remember that over the last 20 years, we have been led to believe that we were infusing products produced from plasma of up to 20,000 donors.

This was the accepted standard that we, the consumers, Congress, the FDA, and others were led to believe was operative. To our shock, we recently learned that we had been fed a line for over 20 years. Given this, it is not hard to understand our dismay at first understanding this 20-year cover-up and then being presented with this new limit, which we know represents a smaller size than many of the previous pools.
Our board is unanimous in its opposition to this standard and again state that its only justification is industrial economies of scale. We are also unsure as to the real efficacy of the inventory hold given what FDA has raised about window period.

We want a serious attempt to address the dangers of the window period transmission, not just a window dressing. We support PCR testing, but need much greater detail regarding standards and parameters if we are to seriously consider this part of the proposal.

In closing, we again call for a new approach on the part of the manufacturers. We look toward a time when our relationship evolves into one of trust and cooperation. It is clear given the recent revelations regarding pool size that industry is yet to be ready for this new era of cooperation. We continue to look forward to a future where we can all -- industry, consumers, Congress, FDA -- can all work together in a climate of mutual trust and respect.

Thank you.

DR. HOLLINGER: Thank you.

Is there anyone else during this open public hearing that wants to speak?

[No response.]

DR. HOLLINGER: Not having seen anybody, we will
take a break now until 4 o'clock. It is 3:36. We will be back here at 4 o'clock to continue the discussion of the Committee.

[Recess.]

Open Committee Discussion

DR. HOLLINGER: The meeting will come to order.

Dr. Weinstein will present the two questions that are up here. I would like to comment that recipient notification, although it is really critical and we need to discuss it, that is not one of the topics for discussion today. Donor notification is part of this, but recipient notification is not, and that is an issue that we will probably have to deal with in the future. So, keep that in mind as we discuss these things today.

Presentation of Questions

DR. WEINSTEIN: For each separate voluntary standard, should the FDA recommend this voluntary standard as an interim measure? If the standard is not recommended, what further action should be taken?

Committee Discussion and Recommendations

DR. HOLLINGER: Thank you, Mark.

Basically, obviously, if the answer to the first question is yes, then, we are not going to deal with the second question. If it is no, then, we deal with the second
question.

I think I want to just feel out the Committee for just a minute because I think I know where we are going to go initially with this, so I would like to see a show of hands on the first question about should the FDA recommend the voluntary standard as presented completely by the IPPIA without any changes, would they recommend this voluntary standard as an interim measure.

How many would be in favor of that from the Committee? Raise your hands. The whole package as it is.

[No response.]

DR. HOLLINGER: How many would be opposed to it?

[Show of hands.]

DR. HOLLINGER: So we can move to the second question, which is if the standard is not recommended -- I think what they are asking here, if the standard is not recommended, what further action should be taken.

So, I think we need to discuss this. Yes, please, Jane.

DR. PILIAVIN: It says for each separate voluntary standard. I think we can do it more easily. We could say yes, yes, no, no, or whatever it comes out, and then all we have to do is work on the parts we don't like.

DR. HOLLINGER: Thank you for picking that up.
That is a very important point. Let's then look at each of the voluntary standards.

DR. PILIAVIN: The first one is not using the plasma from first time donors for which I would like to give a rousing yes.

MR. DUBIN: It's inventory.

DR. PILIAVIN: Inventory? What happened to that other first one?

DR. HOLLINGER: No, the first one is absent donor standard, plasma for one time donors, on page 1, the group that is widely acknowledged as the most likely to be at risk will not be used to make plasma-based therapies. Only donations from those individuals who test negative and complete the full donor interview process on two separate and sequential occasions, and on each and every subsequent occasion, will be used.

Now, tied into that has to do with the question which they discussed, has to do with the timing for those subsequent donations or the separate and sequential occasions, I believe, which is a critical one and which they wanted to deal with.

Any questions or comments, please, about that first standard? Yes.

DR. AUGUST: I think we have to deal with the
issue of the timing of the two separate and sequential occasions. It was pointed out to us that if those happen to be just a few days apart, they could then hold the material for 60 days and you wouldn't really have learned very much or assured much in the way of safety.

DR. PILIAVIN: But you would have depending on how fast they can do the testing, you would have at least learned whether they are safe on the basis of testing.

MS. PIERCE: I think that if the first donation does not exclude the person, being that it is negative, but the fact that it might be in the window period, the donation then actually will qualify that one that is negative, but a potential window period really should be taken 60 to 90 days after, when you would be pretty much out of the window period.

DR. PILIAVIN: No, they don't do that with other people.

MS. PIERCE: No, but what I am saying that is what I say as the fallacy here, because you have a second donation that is going to qualify your first donation, but it can be -- what was it -- three days after your first negative donation you can have a second negative donation, which would still be in the window period, it is something that may have a window period of 60 to 90 days, and it would
qualify both donations as being acceptable.

        DR. PILIAVIN:  No, that is not true.

        MS. PIERCE:  Yes, it is.

        DR. PILIAVIN:  They still will not use, they will not use the first one. The person comes back. By then, the testing has been done.

        DR. HOLLINGER:  Let's find out. Why don't you go ahead from the group.

        DR. PILIAVIN:  Then, that second one goes into a hold for 60 days, just like everybody else's donation.

        MS. PIERCE:  Right, but then there is nothing at the end of the 60 days, there is not another test at the end of the 60 days.

        DR. HOLLINGER:  Why don't you go ahead and see if you can elaborate on that a little bit.

        DR. LYNCH:  The purpose of the applicant program is to only accept donations from donors who have committed to repeat participation. The purpose of this was not to close the window period, but to select a totally different population of donors who we call qualified donors, who have taken it upon themselves to come to the center on two separate occasions and have shown that commitment.

        Obviously, all collectors of blood and plasma would like to ideally get all of their product from
committed donors who are healthy, who we know, who come on a
regular basis.

As one measure of that commitment, we would like
two visits to the center. Now, what this does is it
eliminates any donor who wants to come in once to validate
high-risk behavior, for example, by getting some free viral
testing, and this is a problem throughout the industry and
the volunteer blood industry.

To discuss the specifics, any qualified donor who
returns, even that first unit and the second unit, and every
other unit, will be held in the inventory hold for a period
of not less than 60 days.

DR. HOLLINGER: On the two separate occasions,
what is the least time interval that you will accept that
person? If I come in today and then come back and see you
tomorrow, that is perfectly okay with you?

DR. LYNCH: No, because that is shorter than the
time allowed by federal regulations.

DR. HOLLINGER: And what is that time?

DR. LYNCH: A two-day period is the absolute
shortest period of time.

DR. HOLLINGER: So, if I come in today and come
back on Saturday, that is perfectly okay?

DR. LYNCH: Absolutely. If you come today to
donate, you come back again on Saturday to donate, we see a
commitment that we feel much more comfortable with than if
you only came in today, and we never saw you again. We find
that as being a critically important determination for risk.

DR. HOLLINGER: Joel.

DR. VERTER: I guess I have some confusion and a
suggestion. I think it is clear that we all support that if
it is a single time donor, that person shouldn't be
accepted, and I think the confusion is that they are trying
to do too much in this one suggestion.

If we could separate that out and say that we
support that part, I haven't seen enough data today to tell
me whether the 60 days is enough for all the viruses that we
are talking about. The idea of someone coming back three or
four days later and then how that would do is not clear to
me from this, so that is the issue.

I think there is two important things here, one
which the Committee can probably agree to, and one in which
there is confusion.

DR. HOLLINGER: Paul.

DR. McCURDY: I am assuming from this that
somebody could come back twice in a week for four times in
two weeks, and then disappear and seroconvert or whatever,
and 60 days later, those units would then be usable. I mean
assuming they make a four-donation commitment in two weeks.

DR. LYNCH: Remember we are looking at a series of initiatives, and no single initiative is going to eliminate all risk. In the series of initiatives, we have the applicant donor standard, then, we have the inventory hold, and you are correct, that if somebody comes four times in two weeks, two weeks later seroconverts to HCV, then, how would we identify those units?

We do the PCR testing of the manufacturing pools or however each company wants to arrange their PCR testing, so there is a followup with the PCR testing. The PCR test itself closes that window period to some degree.

DR. McCURDY: Could I ask one question? Do you really mean PCR testing in every instance or do you mean genomic amplification which the most common is PCR? There are other techniques that have perhaps similar sensitivity.

DR. LYNCH: Let's call it genomic amplification although I believe most companies will be going with PCR.

DR. HOLLINGER: And the companies right now would have the option of doing donor testing on individual units versus doing pools?

DR. LYNCH: The reason I was as vague and the IPPIA standards at this time are as vague as they appear to be is that every individual company is currently discussing
their specific programs under an IND/PLA situation with the regulatory authorities.

It was determined that we would involve this PCR or genomic amplification testing. Each individual company will do it in cooperation and as approved by the FDA in their own FDA-approved way.

DR. HOLLINGER: Rev. Little.

REV. LITTLE: Two questions for clarification. Am I understanding correctly that the idea of the applicant donor is not so much addressing the issue of window period as it has to do with motivation or with the consistency in their donating? That's the first part.

The second part is, are the donors aware of this or do they come back for a second time on their own, or do you say this is part of what it takes to be a donor here?

DR. LYNCH: Here again, that is a center-by-center and company-by-company matter. You are absolutely correct in that the donor applicant program, we believe guarantees that we will not manufacture any products from units accepted from one-time donors. We consider a one-time donor who comes to the center and who we never see again to be an extremely high risk donor, and the main thrust of the donor applicant program is to not accept plasma from one-time donors.
DR. HOLLINGER: Corey.

MR. DUBIN: A basic statement, just to kind of maybe keep the focus. If it's a duck and it quacks, it's a duck. These are still paid donors, and I understand the concept behind a one-time paid donor who is in the door and out, but I think Dr. McCurdy made a really important point. You know, it is hard for me sitting here as an end user knowing the difference, and the studies in Europe and elsewhere that have been done on paid versus unpaid donors, to listen to this almost as if we are talking about some kind of altruistic commitment from a donor who has got the check, and I just want to remind people that we are still talking about paid donors.

Now, that doesn't mean I am totally opposed to where you are going as maybe an improvement over where you have been, but I would like to keep the terms pretty clear because we are still not talking about your average altruistic donor that walks into the local Red Cross in Santa Barbara at tri-counties and gives blood.

You know, I have got friends that go in every month and give blood. They don't get a check, they don't get anything, period. So, I kind of want to keep that -- remind people of that.

DR. LYNCH: And I do want to --
MR. DUBIN: Let me finish, I am not done, and I want to go back to what you were saying that we don't want to make more out of this, this isn't a window period thing, and we don't want to try and make this a window, the hold is a window period thing, and we will come to that.

So, I agree we ought to keep them focused on what it is.

DR. HOLLINGER: Go ahead.

DR. LYNCH: I just want to say that I really believe that the altruistic element is a major component of the donors that we have in the center, that we can keep coming back on a regular basis. Every company compensates for time and travel, a certain amount on each visit, and I think that certain helps for that kind of commitment. I think I would expect it, too, but I really believe that our donors do keep coming back with a sense of altruism. I think we would not be able to have the quality of the donors that we do have if it wasn't for that.

DR. HOLLINGER: Can I ask a question just because I am not sure -- what is compensation like? Give me an idea of how much they are compensated for donating plasmapheresis or a range. Give me a range.

MR. REILLY: I will try to address that and some of things that Corey said.
The rate is let's say roughly somewhere between $10 and $20, it is company-specific and may vary for a variety of reasons.

With regard to the paid donor issue, nobody has said that they are not paid, and we are not implying that they are not. What we are talking about, though, is a program that takes advantage of the donor population that we have and looks at the uniqueness of the situation and the opportunities that we have to improve the product.

Although two days does not seem like a particularly long period of time, if you look at the data that Tom presented before, what is shows is that our experience is that those donors that come in initially are where we see the risk, both in real test results and then presumably in potential for window units.

So, what we have done is we set in place a mechanism that says until the donor comes back and makes that commitment that he is going to repeat, because our experience is that they don't just come back once, they come back repeatedly, they either come in only once or they come in repeatedly for a number of times.

So, with that experience in mind, let's find a way to take that at-risk unit and move it out of the manufacturing process, and that is effectively what we have
done.

DR. HOLLINGER: Jane.

DR. PILIAVIN: I have an empirical question for you. The example that was given is of someone's concern about the effectiveness of Item 2, which we are not going to talk about, but let's say you have someone who comes in twice a week for three weeks, and then you never see them again.

Have you ever done any studies that indicate anything about the viral markers in those folks, like on the last time they give? Is it more likely or less likely that they will have a viral marker of some sort than people who stay long enough, so that you can have the whole window period go by? I know it would be real hard to do.

MR. REILLY: That is one of the problems, is what is long enough to know. Eventually, every donor stops donating. How do you decide what's long enough that you -- we know that there is a major gap between donation one and two, beyond. From two, beyond, the gap seems to be -- our experience is that it is less or nil.

DR. PILIAVIN: But I mean you have already thrown out a lot of the people on the first go. You don't know whether they would have come back.

DR. LYNCH: I think the data you are asking for, I
think is very pertinent, and I think as all of the companies adopt the PCR testing and as the individual donor who contributed that unit is identified, the data will be available then to answer those questions that you have.

DR. MARTONE: Let me try and get something straight. The person comes in the first time. Do you draw a unit of plasma and then hold it, and then if they come in again, you will use it, or do you not draw anything on them the first time except for their baseline lab studies?

MR. REILLY: The standard would allow for you to do either. From the practical point of view, they draw the unit and they would hold it until the donor returns.

DR. MARTONE: How long would you hold that unit? Sixty days?

MR. REILLY: Well, that varies from company to company. I would presume they are going to hold it at least two days.

DR. MARTONE: Well, when are they going to throw it out?

MR. REILLY: We have not set an ultimate cutoff of how long they have to hold it, but I don't know that that is necessarily relevant to the safety question if the donor comes back in two days or 12 months or 6 months.

DR. MARTONE: Well, I think it is just relevant to
my understanding as to what is going on.

   DR. HOLLINGER: But you wouldn't use it if it's a
first time donor, is that correct, if it's marker negative?

   DR. LYNCH: That's correct.

   DR. HOLLINGER: Regardless.

   DR. LYNCH: That's correct.

   DR. HOLLINGER: You are just drawing it because it
is easier. You presented some earlier data that showed that
in your qualified donors -- I am assuming these are donors
who have been negative, that you had rates that ranged from
2 to 12 per thousand dollars, and that seems pretty high to
me. I mean you presented that very early, 0.005, 0.019,
0.012, I think it was.

   DR. LYNCH: These are percentages.

   DR. HOLLINGER: I know they are percentages. So,
0.005 is 5 per thousand, if my percentage is right -- oh,
it's 5 percent, not 0.005, sorry about that. So, it is 5
per 100,000. Okay. And the HCV would be 12 per 100,000, 1
per 10,000. Okay. So, it is pretty low at that level, but
surprisingly, there are still people within that group that
are seroconverting during followup. Is that higher than you
would expect ordinarily?

   MR. REILLY: We don't know what the norm would be.

This is what our numbers are. We don't have a comparable
data set to assess it against.

DR. HOLLINGER: Thank you.

Yes, Jay.

DR. EPSTEIN: I think that there is an underlying confusion in that the marker rate in a first time donor and the marker rate in the repeat donor do not mean the same thing. The marker rate in the first time donor represents prevalence in the population from which the donor is drawn. The marker rate in the repeat donor represent incidence in the population from which the donor is drawn.

Now, the confusion is whether having eliminated the first time donor, you have then selected for a lower incidence subpopulation, and that is by no means clear.

In other words, it may be that repeat donors still are representative samples of the same underlying population, and I think that what Jane was trying to get at is that if you were to be able to measure incidence in those rejected first-time donors, you could learn whether or not there is a difference comparing them to your repeat donors, but that is the think we will never know if we simply defer them.

I think the other point of confusion -- and this point needs to be very clear -- that the scheme that is being prevented in no way rules out a window period
collection in the donor who re-presents as a repeat donor, because there is no control over the interval of testing.

However, I think the point that is being made by the industry is that an individual who is screened once for, you know, examination and risk factors, and then comes back again and is again screened by examination and risk factors, the argument would be that that is an individual less likely to actually have risk factors, and I think that if there is any benefit at all to rejecting the first time donor, it is not the fact that you are rejecting the marker positives, and it is not merely the fact that you are rejecting a first-time donor. It is the belief that you are selecting for donors who truly don't have risk factors based on being screened twice, and I think that that is really how to frame the issue.

We are simply getting confused comparing marker rates.

MR. REILLY: Thank you, Jay. I think you probably stated it better than we have.

DR. PILIAVIN: Just for the record, I do have one set of data that I took in Poland where, at least in the time I was doing it, back in the eighties, they had a blood collection center in Warsaw where you could come in and either give blood for free or give blood for money.
It was the same personnel. It was like a controlled experiment except you don't randomly assign the people to conditions, and I was collecting questionnaire data from all of them. It is indeed the case that the paid donors answered my altruism questions in a very similar manner to the way that my unpaid donors answered the questions, and, in fact, some people said that when they could afford it, they gave for nothing, and when they needed the money, they took the money.

Now, this is a completely different system, but it is just to sort of underscore the idea that people who do accept money for giving blood products don't necessarily have no altruistic motivations at all. I mean they are probably of a different nature and not as strong, but they are there, they choose this way to make money rather than some other way.

MR. REILLY: And there have been some discussions of, for instance, marker rates as a measure, that have shown relative comparability.

MR. DUBIN: What year, Jane, were you in --

DR. PILIAVIN: This was in the eighties.

MS. PIERCE: Just to clarify, the first time a donor comes in, does not actually donate a unit, but does enough to be tested on that. The second time they come in,
and donate, if they do not come back again, that second-time
donation will be used, because of the testing done on the
first one?

MR. REILLY: Presuming that all of the testing,
all the screening criteria were in fact met.

DR. HOLLINGER: Let's vote on this question in
terms of this particular standard, the applicant donor
standard, which basically says that they won't use one-time
donors, and the issue still is open about the separate or
sequential.

I would like to see how many are in favor, though,
of the way this standard has been presented, how many of
those are in favor of the way it is so stated? Please raise
your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?
[Show of hands.]

DR. HOLLINGER: Any comments, Paul?

DR. McCURDY: I just think, taken by itself, the
applicant donor, particularly one who may donate just a
couple of times before he moves on, he or she moves on, I am
not sure that that really does much.

By itself, I can't see that, and I am not sure
that it adds anything to some of the other standards that
are there.

DR. HOLLINGER: You would feel more comfortable if the donor stayed around for at least a period of time, more than just a couple of times or three times?

DR. McCURDY: I would like to see testing done at an interval, so that you wouldn't be testing almost the same circuit of blood. I mean every two days or twice a week or a couple times in two or three weeks, that is essentially testing the same blood volume.

DR. HOLLINGER: What would you put as a number?

DR. McCURDY: I haven't given enough thought to it, but I suspect that the inventory hold issue, particularly if one of the goals is window period, I think if the 60-day hold were coupled with the repeat testing, as is done for I think some biologic products, not blood.

DR. HOLLINGER: I think Jane's comments initially are very pertinent. I would hope the industry would take this into account. It is critical, and Jay also mentioned that, too, is that it really is important. If you have people who come in for a short time, as you mentioned, three weeks, six weeks, or something like this, that that blood is evaluated in comparison with a large amount of data which you already have to see where these are truly at higher risk than your regular donors.
MR. REILLY: One of the paths, if you will, we are going down is I guess a continually expanding data set to start to make these kind of decisions from. We are in the middle of collecting the first set, and we will be able to figure out exactly what means to us and how to proceed into the future.

DR. HOLLINGER: Paul, I am sorry, I didn't mean to ignore you and Rev. Little. How would you vote from the industry?

DR. NESS: Yes.

REV. LITTLE: Yes.

DR. HOLLINGER: Yes for consumer.

MS. PIERCE: I just wanted to clarify. These four standards are a package, is that correct? These four standard are being implemented as a package, not as individual --

MR. REILLY: We have adopted them as a package.

MS. PIERCE: Right.

MR. REILLY: But they all have sort of individual implementation deadlines. This one, in fact, was adopted in July.

MS. PIERCE: I guess that is what I was considering when I saw the applicant donor, is that then you go to inventory hold, and that somewhat modifies the
MR. REILLY: They all have some interrelation, but they can be developed independently, and they have value independently, but collectively, they have a greater value.

DR. HOLLINGER: Let's move on to the one on the inventory hold.

DR. SMALLWOOD: I will read the vote.

DR. HOLLINGER: Yes, please, I am sorry.

DR. SMALLWOOD: On the IPPIA Standard No. 1, applicant donor, the vote was 10 yes votes, 1 no vote, no abstentions. The industry representative and the consumer representative both agreed with the yes votes.

DR. HOLLINGER: Thank you.

The inventory hold is the next one, which has stated that, "All donations will be held in inventory for a period of at least 60 days. During this time, if a donor seroconverts and subsequently tests positive or is otherwise disqualified, the earlier donation" -- and I presume that earlier donations should really be in there -- "can be retrieved from inventory and destroyed."

Comments, please. Yes, Dr. Linden.

DR. LINDEN: I think we have already heard some comments in regard to the concern that this is only a hold, it is not really true quarantine and retesting as is done in
some other industries, such as the tissue industry where
living donors are retested and I believe also blood donors,
when the blood is used for stimulation.

In the semen donor industry, there is six-month
quarantine and retesting, and in most cases, the donors are
given a strong incentive to return for that final test
because a portion of their payment for their donations is
withheld.

Is there a reason why that type of strategy would
not work here to induce the donors to come back after be it
60 days, 90 days? I know there is some discussion on that
point, as well.

MR. REILLY: There is probably a fairly subjective
decision, but my guess would be the amount of money involved
isn't nearly enough to stimulate somebody who has decided to
move on in their life, and not donate any longer.

DR. HOLLINGER: Jane.

DR. PILIAVIN: Another empirical question. Have
you any idea what proportion of the plasma donors do indeed
hang around for over 60 days?

DR. LYNCH: Shall I talk on our own experience?

DR. HOLLINGER: Yes.

DR. LYNCH: On our own experience -- and this is a
little bit dated plasma which we are in the process of
updating right now -- it is better than half.

DR. PILIAVIN: Actually, the only people for whom this helps are those who are around after the window period has been closed, and you can test them again. Otherwise, it doesn't help.

DR. LYNCH: Oh, not at all. Actually, anyone, even 60 days after a donation if somebody seroconverts during that time, remember, a window period isn't a set data that everybody has the same window period. There is a broad range of time, and if at anytime during that minimum of a 60-day period, either from seroconversion to one of the three major viruses, a surrogate test like elevated ALT or a number of things, we could identify this person as a high risk person, we can go back and retrieve units, and this not only has value for the three viruses that we are specifically testing for, but actually for any known or unknown virus that might be associated with high risk behavior.

DR. HOLLINGER: Charles.

DR. AUGUST: It seems to me that if you wanted to set that time period in a biologically meaningful way, you would have to do a couple of things. The first is you would have to define window periods in terms of mean and standard deviation for the three viruses that are of interest, as
well as for the assay that you were going to use, be it antibody, antigen, or a nucleic acid by PCR, and then knowing that data, you would have to decide to set your holding period in terms of a second or a third perhaps standard deviation above the mean to encompass everybody that you would like or to encompass a certain percentage of the people that you would like to eliminate.

Obviously, you would like to eliminate everybody, but you might not be able to do that, so you might have to take the second standard deviation at the 95th percent confidence limit or the third standard deviation for the 99th or even go out another one depending on whether it would involve an impractically long holding period.

But this kind of information, it seems to me, is what is required to make what you now have as a 60-day holding period, more meaningful and relevant to the issue of excluding infected units than it now seems to be.

DR. LYNCH: I would like to respond to that. Actually, when the 60-day minimum unit or inventory hold was established, it was with the belief and understanding that this is a meaningful and an achievable goal at this time. The nice thing about these voluntary initiatives is that they are not static, they are not carved in stone, they are completely, all the time being
reevaluated and can be changed.

Your point about the window period is important because this inventory hold period has to be taken into the context that we are following this up to nucleic amplification testing or PCR testing, and we will as time goes on get a lot more information based on the numbers and the types of donors that we are identifying beyond the window period with this testing.

And you are absolutely right, as this information comes across, we as an industry and as individual companies get more information from the PCR testing results, we can always go back and reanalyze how meaningful and how valid was the 60-day period, is there some value to extending it, and if there is, that would be certainly taken under consideration.

DR. VERTER: Again, I applaud the industry for coming forth with standards and also the attitude you just expressed, but I wonder if someone from FDA could clarify something for me and maybe the committee.

The question is should the FDA recommend this voluntary standard as an interim measure. What is the intent of that?

DR. WEINSTEIN: This would become part of the GMP, it would be put into a guidance document, and it would be
made enforceable under our GMP guidance once it had gone through good guidance practices, notice, and comment period, and all members of the organization would be expected to follow the given standard, and it would no longer in a sense become quite so voluntary. There would be more FDA overseeing of making certain that this was being carried out.

On the negative side of this, the recommendation standard being adopted at this time would be put in place when we can see now that there is, from your questions, insufficient data to actually demonstrate that these claims would have effectiveness on the safety of the products.

It is our impression that they would in many cases, but we would not have the data here to clearly support this, and one might imagine that industry would advertise that these things are in place, and there would be perhaps an indication that they are effective safety measures.

In a sense we can see, yes, there are positive outcomes of these voluntary standards, but at the same time, there are, as you are raising these questions about their true effectiveness in input of the safety of the product, so those are what an FDA recommendation might mean.

DR. VERTER: I kind of understood the word
"recommendation," it was the interim that I needed some clarification on.

DR. WEINSTEIN: The interim is just the acknowledgment that these are a process, that they are changing here, but what we are saying here we accept them now. We are taking them now at this point in time without asking for this additional data and validation of the processes that are being proposed.

MR. REILLY: If I could just make a brief comment. One of the things that may come out of this is probably somewhat obvious. In some cases there is good data to support precisely what and why we did things. In other cases, the data is not as precise.

What we have tried to do is to say we know instinctively that these things will make a difference, so have not let, if you will, the pursuit of perfection stand in the way of implementing anything at all. So, we have tried to take measures that we could take quickly, that made sense, that we could demonstrate at least some minimum level, of not a full level, of effectiveness.

MS. PIERCE: My concern here is that just holding for the period of 60 days without some additional test further apart from the donations doesn't really give you the information whether or not someone is in a window period.
I guess my other question is what is the rate of repeat donors who will come back maybe the fourth and fifth time, but would be out of the window period for an earlier donation. Say they come back in 30 to 60 days.

MR. REILLY: Let me take the first question. The inventory hold was not intended to absolutely close all window units out. It was a practical standard which allows us, for donors that we have identified as seroconverting, to go back and, if you will, ensure that at a minimum we can get the window units from those donors we have identified.

From those donors who have dropped out of the program for whatever reason, and we don't have a test result on, we are not suggesting that the 60-day inventory hold has done anything about those window units.

MS. PIERCE: I guess that is what I am asking. How many then would you catch the seroconversion on before the test or whatever donation?

MR. REILLY: The data that we put up before is the percent of seroconverting qualified donors. So, those are the donors who, whether it is for the second donation or the hundredth donation, they have seroconverted and for that percent that -- I think HIV was, what, 0.005 -- that is the number that we are able to retrieve from that inventory.

DR. PILIAVIN: Beatrice, when I asked him a
question earlier, I don't know if this is part of what you are asking, he said that roughly half of the plasma donors are still around that long after their first donation. It will help with like roughly half of them.

DR. HOLLINGER: But that really creates, too, I mean I look at the other way, half are not, which means it creates a two-tier system. You have a tier which says those who are going to be around, we are going to look at you, and if you seroconverted, we are going to discard all your previous donations.

Then, you have got this other half here, you are saying we aren't going to look at you, because you didn't give one in 60 days, so we will look at it in the pool maybe we aren't going to look at them individually, and the question is should they be looked individually if they are not going to be around in 60 days.

In my opinion, I think the 60 days is too short personally, I think it ought to be 90 or 100, and the issue is what do about people who are not going to be around for those periods of time, rather than pool those, should those be looked at individually for any evidence of disease by perhaps some of the more sensitive measures, and perhaps I would even permit those to be pooled if they are not large volumes, and looked at in a small concentration, if you
will, 1 out of 100, or 1 out of 50 rather than -- I mean I
would be even happy with that. That would make me even more
secure to look at them in that way in terms of cost savings.

DR. KHAMBAZ: The range, the inventory hold says
for a period of at least 60 days? Is there an upper time
that is considered? Let's say after 60 days, somebody has
not been back, but then they are back at 70 or 80 days, is
it at least intended to allow keeping the hold longer?

MR. REILLY: A company could decide to hold
longer. The minimum would be 60.

DR. HOLLINGER: That's a good point, Rima, because
then the question is do you hold indefinitely, how do you
know these are people that are not going to come back, and
that you are going to pool.

Theoretically, then, you probably couldn't pool
anybody as you would read this, because you are saying it
says at least 60 days, so then you come up a year from now,
if they are not back in a year from now, you go back and use
those first six units, at what point do you decide that you
are going to use those six units if these people are never
going to come back versus waiting until they come back for a
second time?

I think they will use them, too, I think you are
right, but the question is at what point do you say you are
not going to use that because we haven't seen this man after
90 days, let's say. It's a good point.

Could you respond?

MR. REILLY: I think one thing that we need to be
clear on is the way the standard works. It is, in effect, a
rolling 60 days from date of collection. So, if the donor
donates 60 days later, if he was a qualified donor, in other
words, it was at least his second donation, 60 days later
that unit could be pooled.

DR. HOLLINGER: Regardless of whether he is there
or not, whether he has come back in 60 days?

MR. REILLY: That is correct.

DR. HOLLINGER: Jay.

DR. EPSTEIN: It is very clear that the inventory
hold is not a quarantine and release strategy which would
capture a window period unit. Having recognized that, it
seems that the key question is what is your estimate for the
percent of window period units that would be caught, and I
have not heard an answer to that.

It would require a fairly sophisticated analysis
of the interval at which repeat donors return, and you would
have to then stratify against that the different window
periods of the different conditions for which you screen,
and I have not heard that that analysis has been done, but I
think it would be very clarifying to me, and I assume to the
committee, if such an estimate has been made and what the
result is.

    DR. LYNCH: I think the estimate that has been
made are the amount of the PCR reactivity of the small
minipools that have been done by some companies. This would
basically tell you how many donors seroconverted and you did
not remove by an inventory hold if it was your policy to do
PCR testing after the inventory hold. So, that data is
available. I am wearing an industry hat right now, and it
would be inappropriate for me I think to discuss independent
company data, but those numbers have been presented
publicly.

    DR. EPSTEIN: I mean I think that that is what we
are all looking for here is an answer to that question, and
so it would be illuminating if anyone here knows the answer
and knows the estimate, because I think that it is obvious
that the answer is non-zero. Certainly, there will be some
seroconverters who come back within 60 days, so it is non-
zero.

    On the other hand, it is also obvious that it
can't possibly be 100 percent because 60 days is -- for two
reasons -- one, that is less than certain window periods,
such as for Hepatitis C or Hepatitis B, and also because not
all donors will come back within that hold period.

So, you know, we know it is non-zero, and we know it is not 100 percent, and I think the issue is in order to have a feeling for whether it a benefit worth recommending from a regulatory point of view, we would like to know how good is it, and I have not heard any estimate.

DR. MARTONE: I agree with that. It would seem that the recommendation is almost pointless if you are not going to do something after 60 days other than hope that you might catch somebody who comes in, and those numbers I would suspect to be fairly small.

On the other hand, if you could give us an idea of how many repeat donors would be coming in and getting retested for another unit, therefore, you would know that this one got through most of the window period and could be released, you might tier your strategies and say, okay, we are going to use this one, we don't know anything about the person, they haven't come back, and those are the ones we will do PCR testing on if we are going to do PCR testing on a fraction of units rather than pools.

DR. HOLLINGER: I think that's right, you know, without knowing a number, you know, I certainly would feel better if I am going to do a PCR testing even on a pool, I would require a pool of a much lower number for those
patients who did not come back after 60 days in this rolling
type of thing than I would, say, on the final pool, if you
will, for a fraction, and so on, just for that reason, until
we have some information about this estimate that was
discussed.

DR. LYNCH: I could answer some of that, actually,
some of the data that has been published, and it's data that
is a couple of years old, based on one manufacturer's
findings.

PCR testing of minipool testing, if broken down to
a per-unit basis, would be about 1 to a million for
Hepatitis B, there was none for HIV, and it was
approximately 1 per 50,000 at that time for Hepatitis C.
This is again older data that has been published, so I feel
much comfortable releasing it.

As far as how many units are followed up by a
subsequent donation, as I said earlier in my presentation,
97 percent in one survey, 97 percent of units that were
entered into the inventory hold were followed up by at least
one subsequent donation. There is at least at a minimum of
one additional time when that donor could come in, be
requestioned, be retested, and I think that adds value to
the confidence that you have in that unit of plasma.

MR. REILLY: We are trying to take some notes
about where your concerns are with these standards. As they
go into place, allows us the capacity then to look at what
kinds of questions emanate and what data would then be
supportive of the position that we have taken.

DR. HOLLINGER: The numbers, it was like 1 in a
million for B, and obviously, the numbers must be larger
than that, because you quoted that it was something like it
was 5 out of 100,000 of your qualified donors are found to
be HBs antigen positive sometime later.

MR. REILLY: But we have removed all of them and
their previous units.

DR. HOLLINGER: You have removed them, but there
must be others that are coming at the same time. I mean
these were discovered, so they must have had a PCR-positive
unit somewhere in that period of time if they were a
qualified donor, and later you found that to be HBs antigen
positive.

MR. REILLY: But the inventory hold that was in
place allowed them to remove those previous donations which
had tested negative.

DR. HOLLINGER: Which had tested negative.

DR. LYNCH: In other words, although these are
individual initiatives, the value is synergistic with one
initiative with another, taking an inventory hold along with
the PCR testing. Couple that with the donor applicant standard. These are more than additive, they are synergistic on each other.

DR. HOLLINGER: If I can go back, you say that they were removed, but on the other hand, you told me that after 60 days, this is going to be dumped into the pool, so you really -- if a person comes back 90 days later, they may have had two or three that you didn't remove, and you may have found then now to be HBs antigen positive, but since you said it is a rolling type of thing, they would have had transfusions that would already have been dumped in that could have been positive in that time period.

MR. REILLY: Correct, if it exceed the 60 days, it could well have been added.

Yes, please, Jeanne.

DR. LINDEN: I would like to just take a slight different tack. I think everybody here agrees that the absolute ideal situation would be to have a true quarantine and retest where there would be holding for a period of probably at least 90 days, and coming back and retesting 90 days after the last donation, because, of course, this will only help you for your earlier donations, the last donations just before they stopped donating aren't going to have much of a check on them.
I would certainly encourage the industry to try to pursue some sort of incentive program to try to get people to come back for a blood test, but I think that we are not in an ideal situation. Firstly, for recovered plasma, this isn't doable at all. I mean this doesn't even apply, and think actually, the industry is to be commended for voluntarily having taken the step to even address this at all. It is not the ideal, but I think it is actually a pretty good first step. It is better than what was done before. It is a step in the right direction, and maybe one can build on that looking at the experience perhaps with this type of approach, seeing how many things are caught.

The other thing is, of course, the role of PCR. If the window period is shorter, then, a shorter hold time is going to be more successful in more cases.

MR. REILLY: To be really frank and honest with you the cost and logistics far exceeded what we thought they were.

DR. LINDEN: I actually am very concerned about shortages. We right now have a shortage, that I am aware of at least, of 5 percent albumin and I.V. gamma globulin, and in the past we have had a lot of shortages of different products that have actually caused problems for us as public health agencies.
I think if we make demands that are too unrealistic and, you know, cutting out half of the donations, then, you are going to have potentially real supply problems, and I think, you know, maybe looking at incremental steps is perhaps a realistic way to go.

DR. HOLLINGER: I think the albumin problem was one for some bacterial contamination from a major supplier. Is that correct? It may be different. It is an important issue.

I guess we could vote on this. It sounds like there is a lot of -- yes.

DR. McCURDY: It seems to me apriori, I would be more comfortable with a shorter period and a retest than I would be with a longer period and no retest. I suspect that that kind of approach, varying those is modelable, that is, I think you can probably -- there are data around that could be used to model that and see what the losses are.

I would guess that if half of your donors are around, as somebody pointed out, half of them are not, and if you lost half your one to three or four-time donations in the process, that might be much too costly in product and dollars to do. But, as I said, without seeing modeling apriori, I would be more comfortable with a whole period with a retest, a so-called true quarantine than I would with
a longer period and no retest.

MR. REILLY: The supply frankly, as well as logistics, but supply is a rather substantial part of that equation, and I don't remember the precise data, but several years ago, someone did take a look at how would you impose a full-scale quarantine, and it was a fairly rough calculation, so I can't maybe stand on it with great firmness, but the most conservative estimate they came out with, I think, if I remember right, was a roughly 90-day quarantine would result in an ongoing loss of 50 percent of collections, in other words, 50 percent of every unit you ever collect forever would be trashed.

DR. McCURDY: How about a 30-day hold?

MR. REILLY: I don't know what the 30-day would do.

DR. McCURDY: I think if you had a model that worked, then, you could plug in all sorts of different numbers and come up with something that might be useful and doable. Maybe not.

DR. LYNCH: If I could just add a little bit more information, I was reminded, talking about what percentage in an inventory hold program, what percentage of units that are removed because of the program, are removed at what period of time, and I was informed by one of the member
companies who had looked into that, is that 90 to 95 percent
of the units that are removed from inventory hold, even a
long inventory hold, are removed during the first 60 days.
So, as you go beyond 60 days, the yield of units being
removed is further and further decreased.

DR. HOLLINGER: I will call for a question here, if I can.

Rev. Little?

REV. LITTLE: I just wanted to sort it out a little bit. I am glad to see that industry is doing something like that, but I am still confused about if this is an FDA recommendation, does there need to be more data before it is a recommendation, or is it a recommendation just based upon it seems a good thing to do?

DR. HOLLINGER: I think the issue is where these standards should be as an interim measure, understanding that there will probably be -- well, will clearly be -- changes as it goes along, as more information is obtained, hopefully, they will ask for those.

Yes, Bill.

DR. MARTONE: I just think we should be given more information about this before we could endorse it. Either way, I mean it is either going to beneficially get rid of some bad units or it's going to do nothing, and I don't have
a good feel. I mean you are asking industry to do something here, and I don't see the strong positive benefit in terms of data.

I guess what I would ask for is more information on this point.

DR. HOLLINGER: I guess the question then would come up would this a better interim -- I am just asking the question now -- would it, at least as an interim measure versus doing nothing -- yes?

DR. MARTONE: Is doing nothing the same as doing this?

DR. HOLLINGER: I guess that would be the issue.

MR. REILLY: It is probably worth saying that the industry is committed to this.

DR. MARTONE: Okay, but tell me why, so I can be committed to it, too.

MR. REILLY: What we have tried to provide is what data we do have and what logic we applied or reasoning we applied to the development of the standards to date.

DR. MARTONE: Well, I can see the initial donor deferral issue, but I can't see the 60-day hold. Maybe you presented data, and I just forgot it.

MR. REILLY: Well, let me maybe contrast it against the existing situation. The existing situation is
that there is no minimum requirement, and that as fast as
you could get the plasma to the plant and pool it and
manufacture it, it is used.

What this does is it guarantees you at least 60
days at which point you could retrieve the units.

DR. MARTONE: How many of those units are you
going to retrieve?

DR. LYNCH: I presented that data in my
presentation. Out of 300,000 units over a five-month period
by one company, I believe it was 2,555 units were retrieved
as a result of 330 or 331 donors subsequently being
identified by seroconversion, by surrogate testing, or by
post-donation information.

DR. MARTONE: In that 60-day period?

DR. LYNCH: That was a 90-day inventory hold.

DR. MARTONE: That was a 90-day.

DR. LYNCH: Yes.

DR. MARTONE: I just missed that part of the
presentation.

DR. LYNCH: So what I am saying is, if I were a
consumer of a blood product, I would find a lot of comfort
that these 2,555 units from donors who were subsequently
identified as being at potentially higher risk were removed
from the plasma pool.
DR. MARTONE: That was a 90-day hold and you said something a little bit earlier that -- is it 95 percent of those would have been caught in 60 days?

DR. LYNCH: Yes.

DR. MARTONE: Okay.

DR. LINDEN: I have one other question. When this concept was introduced, was it with the intention specifically of partially closing the window period and catching some of these units, or was it also significantly an opportunity to interdict pools that you might otherwise have to destroy because of post-donation information that comes up later if the processing were to occur right away?

MR. REILLY: It provides us benefit on both sides, but I think the first was our impetus.

DR. HOLLINGER: I am going to call for a question on the inventory hold. All those who agree with the proposal as an interim measure, so signify by raising your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: All those abstaining?

[Show of hands.]

DR. HOLLINGER: Paul?
DR. NESS: Favor.

REV. LITTLE: Abstain.

DR. HOLLINGER: Abstain.

DR. SMALLWOOD: Votes on the inventory hold as an interim measure, there were five yes votes, three no votes, 1 abstention. The industry representative agreed with the yes vote. The consumer representative abstained. Those votes represent the remaining members that are here. Two members left.

On that particular question, Dr. August's response was yes at 90 days. Dr. Piliavin's response was as follows: that she believes that the viral marker standards are vague, but liked the idea. Again, as Dr. Linden suggests, it is a step in the right direction.

DR. HOLLINGER: Is there a yes, no, or abstained?

DR. SMALLWOOD: She did not indicate.

DR. HOLLINGER: I think, Jay, what you can hear from that is that there are some things -- and I think you picked up on all those obviously.

Let's go on to the next section which has to do with viral marker rate standard. It is manage the quality recruitment and retention of the donor population at the centers. The voluntary standards establish a maximum allowable viral marker rate incidence of disease in the
plasma donor population. Each donor center will be required
to maintain a viral marker rate for anti-HCV, anti-HIV, and
HBsAG below a set limit as part of its QPP certification.

Comments? Yes, Jay.

DR. EPSTEIN: It wasn't clear to me from the
presentations whether the marker rates used to set limits
would include the first time donor rates. We understand the
units are discarded, but are you using only the repeat donor
rates or are you using the combined rate, what rate are we
using?

MR. REILLY: The existing standard was based on
the combined rate. The new standard that is in the
voluntary standards is to be based uniquely on the qualified
donor rate, which would be the equivalent, if you will, of
the donor, so the units that are used in the manufacturing
process.

DR. MARTONE: Can I ask a question?

DR. HOLLINGER: Yes, you may.

DR. MARTONE: How do you respond to the important
FDA statement on the bottom of page 2 here in the handout,
that CBER has received reports of some centers using two or
more testing laboratories and only reporting the results
from the laboratory with the most favorable outcomes? I
think that is an important point that I would like
addressed.

MR. REILLY: I haven't seen that report, but as we administer the QPP program, we obviously asked them to report that data to us to evaluate their compliance. At least when we are aware of it -- which I believe is all the time -- we get the data in total, and to the best of our knowledge, we have not found a situation where they are doing that.

DR. HOLLINGER: Is there someone from CBER here that could comment on that specifically?

MR. REILLY: CBER raised that with us once before as a hypothetical that could occur. To the best of our knowledge, it has not and we are aware of some dual laboratory situations.

DR. MARTONE: They say they received reports. What would you do to a place if you found out they were doing that?

MR. REILLY: I think we would take action to decertify them from QPP.

DR. HOLLINGER: Paul.

DR. NESS: A comment and a question. In view of Dr. Epstein's comments about the difference between the prevalence of infection which might be determined by first time donors and the incidence of infection which may be
subsequent donors, it would seem that the standards would be
better if they covered both, first time, nonqualified
donors, and qualified donors. I would think that would
really be the ultimate way of looking at it.

The second question would be they said they were
going to come up with some sort of standards, and if you
don't make the standards, then, there would be a corrective
action. I wonder what kind of corrective action they would
think of doing.

DR. LYNCH: I will take the first question and
then pass the second one on to Jim.

When it was decided as to define the donor group
to base the standard on, the decision was made on finding
the most meaningful and relevant data, and it was obvious to
us that the most meaningful and relevant data to the safety
of our manufacturing pools is to look at the viral rate of
every unit collected from every donor who was qualified to
contribute to the pool.

We feel strongly that this is the most meaningful
data to collect and compare.

MR. REILLY: The other side of the question was
what kind of enforcement action. At the moment, we are
transitioning through all the standard from one to the
other. The current enforcement action is if they are not in
compliance, they are decertified.

The future standard is very refined, and there are a number of new issues that have come up from it, and there may be action levels in between the initial noncompliance and actual decertification, but ultimately, if they cannot come into compliance, they would be decertified.

DR. HOLLINGER: What does decertification entail?

MR. REILLY: What does it entail?

DR. HOLLINGER: Yes.

MR. REILLY: It seems simplistic in its nature that we simply would not allow them to advertise or take advantage of the fact that they have been certified as QPP. What that means to them, though, is that nearly ever fractionator in the world has now made QPP certification a specification in their contract, so they are effectively out of business.

DR. HOLLINGER: Thank you.

Paul.

DR. McCURDY: I am curious as to what the purpose of this is. It occurred to me initially that the purpose was to see how well you select your donors, because if you select them well, you will get them with a low marker rate, but that would be first time donors mostly, because those are the ones that you are selecting initially.
I was wondering what the purpose of this is, what do you expect to gain out of it.

MR. REILLY: I think that is what Tom was sort of alluding to. Maybe I will try and say it a different way. It is about the quality of the donor. It is about the quality of the donor that we have retained and we are going to use in the manufacturing process.

In other words, if you will consider it as an additional part of the screening, if you will. We go through all kinds of screening questions and tests before we tell somebody or before their unit is considered to be acceptable, we have simply added yet another screening barrier to the unit being acceptable.

So, that is the quality of the donors that we ultimately retain and consider acceptable.

DR. MARTONE: Based on that, I would say that you don't have too much control over who walks through your door the first time, so I don't see why that should be included in this minimum standard here, but you do have control over who you follow up and retain, and there I think are in the standard.

MR. REILLY: And that is why we set the standard where it is, because that is what we are trying to measure is who we retain.
DR. MARTONE: I thought you said you would include
the first entry.

MR. REILLY: No.

DR. MARTONE: You are not going to use that.

MR. REILLY: We are not going to use that.

DR. MARTONE: Okay.

DR. HOLLINGER: And new centers that come aboard?

MR. REILLY: Effectively, that makes no
difference. New centers are always in with a whole new
donor population, so we are only measuring what they decide
to retain.

DR. HOLLINGER: Thank you.

Let's go ahead and vote on this one. All those in
favor of this particular standard as written, so signify by
raising your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Abstaining?

[Show of hands.]

DR. HOLLINGER: Three, three, three.

Paul?

DR. NESS: Favor.

REV. LITTLE: Abstain.
DR. HOLLINGER: Okay.

DR. SMALLWOOD: Results of voting on No. 3 viral markers. Three yes votes, three no votes, three abstentions. Industry representative agrees with the yes votes. The consumer representative would abstain.

DR. HOLLINGER: Oh, yes, we have two others. Just a second. There may be tie-breaker here.

DR. SMALLWOOD: Dr. August would have voted no, too vague so far as criteria definitions are concerned. I believe I misunderstood Dr. Piliavin. She agreed with the viral marker standards, but they are vague, but she likes the idea, so yes.

MR. REILLY: If I could just make one comment. The vagueness is really a circumstance of timing. We are, if you will, right literally in the middle of collection of the data and setting of the rates and assessment of that, or we would have provided you enormously more definitions.

DR. HOLLINGER: Thank you.

Yes, Jeanne.

DR. LINDEN: Am I allowed to clarify my no vote, which is to say I really support the idea. The only reason I voted no was I thought it was too vague and would not want to see this imposed as a standard the way it is, but I would encourage further work in this area to develop something
more specific.

DR. HOLLINGER: Thank you for comment.

Anybody else want to ask for forgiveness?

[Laughter.]

DR. HOLLINGER: Let's go on with the PCR testing. All plasma used in the manufacturing process must test negative through genome amplification testing for HIV and Hepatitis C. Procedures such as PCR are more sensitive than the antigen or antibody detection methods currently employed to screen collected plasma.

Comments? I just have a question. Why just HIV and Hepatitis C, and not Hepatitis B included?

MR. REILLY: If I recall back from the debates that we had, I think it was a sense of trying to prioritize, if you will, which ones to attack first, because it wasn't practical to do them all at the same time, and B is actually, if I remember correctly, on the list, but just farther down on the priority.

DR. HOLLINGER: Do you recommend vaccination for your plasma donors that come in, so you don't even have to worry about B in the future at all?

DR. LYNCH: No, our donors are not routinely vaccinated.

MR. DUBIN: Clearly, they haven't considered it.
DR. HOLLINGER: It would certainly seem appropriate.

While we are waiting for Bill to come back, let's go and just read the other part and we will come back and do this -- oh, here is Bill.

We are here to vote on this as written. All those in favor of the standard for the PCR testing, so signify by raising your hand.

[Show of hands.]

DR. HOLLINGER: All those in favor that the plasma used in manufacture must test negative through genome amplification testing?

[Show of hands.]

DR. HOLLINGER: Let's do it again.

DR. McCURDY: Blaine, I am making the assumption that some of the objections about the completeness of information in here, exactly how they are going to do it, and validating the test are going to be taken care of.

DR. HOLLINGER: Yes.

MS. PIERCE: But the only concern is that is why we have gotten all these yes/no, because people have made those assumptions differently on the different questions.

DR. HOLLINGER: Let's ask Jay for a clarification.

MR. REILLY: Jay, I am hoping is going to say the
same thing I am. Basically, the ambiguity in this standard really is that it has to be a cooperative effort with an IND and PLA between FDA and each individual manufacturer, so literally, all those questions that Indira went through have to be answered before anybody can implement it.

DR. EPSTEIN: Yes. The point of Dr. Hewlett's presentation is that FDA will be exercising close regulatory control over such systems that may be implemented. The question really on the table is should we go further and recommend it rather than leave it to a voluntary evolution.

DR. HOLLINGER: Will you be including B or not?

DR. EPSTEIN: I think that it is clear that the earliest developments will be for HIV and HCV. I think we look forward to closing as many windows as possible and screening for as many agents as we can, especially those for which there is not viral inactivation where you could make an even stronger case for doing it than for agents where there is viral inactivation, but the scientific development has followed the path of HIV, HCV first, so that's at hand. We might want the others, but the technologies are not yet developed.

DR. HOLLINGER: Part of this will also include whether you are going to test single donors or pools and of what size.
DR. EPSTEIN: Well, I think the immediate proposal is pool testing. FDA's point of view, which represents our current thinking, is that pool testing should be regarded as an intermediate control strategy to be followed as technology permits with single unit testing.

DR. HOLLINGER: Corey.

MR. DUBIN: If they come back to you guys and say they want single unit testing done, are you prepared to do that?

MR. REILLY: I think what has been offered up and what people are working with FDA on is a variety of matrixes which allow you to, not necessarily test the unit, but test a matrix and work back to the donor when you find the positive.

The net result, Corey, is yes, the donor would be identified.

MR. DUBIN: Thank you.

DR. HOLLINGER: So, once again, all those in favor of the interim standard or the standard for interim evaluation as written, so signify by raising your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[No response.]

DR. HOLLINGER: Abstaining?
[No response.]  

DR. HOLLINGER: Paul?  

DR. NESS: Yes.  

REV. LITTLE: Yes.  

DR. HOLLINGER: All right.  

DR. SMALLWOOD: No. 4. PCR testing vote unanimous, 9 yes votes. The consumer and the industry rep both agreed with the yes vote. Those that left, Dr. August would have voted yes and Dr. Piliavin would have voted yes, as well. 

DR. HOLLINGER: Thank you. We are now down to the last one, and not necessarily the easiest one, donor exposure limitation. Plasma pool size measured by total number of donors will be limited to 60,000 for all major products, both source and recoverable of blood including Factor VIII, Factor IX, albumin and IGIV. 

This measurement takes into account the composition of starting pools, the combining of intermediates from multiple pools, and the use of plasma derivatives of additives or stabilizers in the manufacturing process. 

Comments? 

DR. LINDEN: Before we get into a lot of discussion, I actually have a question for the industry.
The Red Cross speaker mentioned the concept on the excipient albumin of using the same lot from the same pool. Is that something that the source plasma industry is committed to or are you intending to just say, well, as long as it's less than 60,000 that's okay, and it's okay to double it by adding these additional donors?

MR. BELL: Each, the answer from manufacturer to manufacturer will differ, but the important distinction that I think Dr. Lynch made there is that our 60,000 donor limit includes the excipient to the equation, so some manufacturers may be pursuing it in that manner, others may not, but the assurance is that including the excipient in the manufacture of the products, there will not be donor exposures to exceed that 60,000 donor limit.

MR. DUBIN: Two things I want to say, and the first comment is probably not directed at the two of you because you guys are in the public policy side, but I have just come off a week of hundreds of phone calls from out of my community.

I will just use myself as an example. I have a four-decade relationship with all four of the major companies. My oldest is with Baxter because I was one of their first guinea pigs for Factor VIII. My father was very close to the original president. We have a long-standing
relationship in the Dubin family. We believed for four
decades what we were told, that the exposure factor and the
risk factor was somewhere between 12- and 20,000 donors per
pool.

Those numbers were given to the United States
Congress over the years, they were given in this committee,
and understand I am the soft end of the reaction out there,
not just in hemophilia. I get calls from other user
communities who, after raking me over the coals a little
about sitting on the BPAC, and not knowing this, or did you
know it, we got down to some serious discussion.

So, this is a tough discussion for us because
everything has changed. All of a sudden, you know, 60 looks
better than 120, or 60 looks better than 200, and there is a
process going on now that we have to reassess it, and that
is why I am trying to isolate you guys out of this critical
part of the comment.

But we are pretty angry about it, and it's not too
good a way to treat your customers, first of all, and it's
not something that is really too smart to do for four
decades when we are in a period now when we are trying to
pull out of a very rough period between us and build some
kind of working relationships for the future, which we keep
talking about, and we are still talking about.
This didn't help those of us who are at the front line of trying to recreate the environment or the ground between us. That said, let me get on to the specifics. We were very pleased at FDA's December '96 recommendations, 5,000, 20,000 short term, long term. We thought those were intelligent numbers to go move towards and we still haven't seen anything that tells us these numbers are nothing more than based on economies of scale and not safety, and until we see hard evidence that that is not the basis, this is the position we will continue to take, and I think it will be unchanged, and I think you will find most of the organizations on the user side are somewhere in this end of the continuum.

MR. BELL: If I could address the comment, that is a good point that Corey brings up, and we don't take it critically. I have been involved in the discussion and debate of pool size at least for the past two years through BPAC and other forums.

In our cursory review, and as you know, it taxes your memory to go back and recollect who was saying what, when, and what was the context of the debate. When we did a cursory review of the BPAC transcripts, you can see over the course of time how the debate unfolded and changed. At the very inception of the debate, at least as industry was
responding, we were looking at the question of what are your pool sizes in the context of what is the volume of the pool.

As it continued to unfold, there seemed to be more and more questions about we were focusing on donor, donor exposure, and then another portion on the debate unfolded, something that we met a learning curve on, which is, well, not only is it the size of the pool that is important, but it is the excipient that you use when you manufacture it, but which creates additional donor exposures, if you will.

So, really, when we look back on the debate, it really has significantly changed from the very beginning of time to the point it is at now. So, I think that is an important point to recollect or as the transcripts would reflect the way the debate was unfolding. I think that is important.

I think also, the second point is that the numbers can be inflammatory when you look at them in the context of different products and different donor exposures for different products.

In the context of the four major products which our commitment over the summer to Congressman Shays was, is very different from some of those other products which require increased volume to create the small capacity of product that is actually sold. So, that is why we had to
put it in the context of only the four major products, and keep those donor exposures in check.

DR. VERTER: Originally, I was going to vote no on this, but I have decided I am going to vote yes, and this is the rationale. I was going to vote no because it seemed inconsistent with what we did in December and certain other philosophies that have been expressed.

On the other hand, what I have heard today is this may be of marked benefit and change in procedures that have been going on for 20 years, that no one knew about, even though they thought they knew about it. And it's voluntary, and the FDA, I assume would continue to interact with these groups. Furthermore, I don't recall seeing them in December, although I would have to go check my notes, and I certainly didn't see them today, as to what as the rationale for 5 or 20 or 60 or 420, and so it seems to me until we see some data, this might be the best good interim step that this committee can take. So, for that reason when the vote comes, I am going to vote yes.

MR. BELL: That's an excellent point because what we saw, even as Corey reflected, in the testimony in Congress, Dr. Zoon did an excellent job of really weighing the benefits and detriments of pool size that clearly there is no convincing argument for one or the other, but it is
something that clearly needs to be explored and considered as we move forward, and I think in recognition of that, the industry has put forward this voluntary initiative.

DR. HOLLINGER: Joel or the rest of the Committee members, would you make a distinction between recovered plasma and source plasma, as the FDA has wanted to, based upon the volume size, recovered plasma being about a quarter or a third the volume of the source plasma in there or not? I think that is the other issue here besides -- and I agree with you, I think one number that is lower is better than all the others. The issue I think also is where there should be a distinct difference between recovered and source.

MR. DUBIN: I have to ask a question. I mean if this is voluntary, all right, then, how do we know they are doing it? The BPAC can vote to recommend that we agree with this 60,000 number, but we haven't held them to anything, we haven't changed anything. They have simply come to us and said -- and I want to add something else -- this is in part damage control. Let's understand what's happening.

They took a beating up on the Hill and came back and did some damage control. Now, if that damage control has some substance, you guys might have some impact on even my thinking, but I don't see any guarantees that what we are
really about to do if we vote yes is create the conditions
where they are going to meet this standard, and this is what
the standard becomes.

    DR. MARTONE: My understanding of it is that they
will monitor this, and if they don't comply, they will be
decertified. Is that incorrect?

    MR. BELL: This standard is exclusive from the QPP
certification program, which is an ABRA program, and this is
an IPPIA voluntary initiative.

    DR. MARTONE: So, this is just like a guideline
that you don't monitor.

    MR. DUBIN: Right.

    MR. REILLY: The QPP is specific to plasma
collection, so this is really a manufacturing plant
standard.

    DR. MARTONE: So, this is a guideline that you
will not monitor.

    MR. REILLY: I think that is in part or at least
on the surface correct, but maybe Jay could weigh in on
this.

    DR. EPSTEIN: I think that if this becomes
recommended by FDA, there is, first of all, the expectation
that industry will adopt it. We would then be in an
enforcement posture, in other words, we would monitor this
and take enforcement actions. So, that is why it is material to FDA whether we ought to recommend these limits.

Now, of course, really the options are accept these limits with the various limitations, you know, such as that it is not stratified by product, it is not stratified by source plasma versus recovered plasma, but recognizing that it is a step forward and that it is an upper limit where there were no upper limits before, and that is inclusive of excipients, which we hadn't really come to terms with before, and, you know, take this and go forward.

But the implication of an advisory committee recommendation is that FDA would move forward and recommend that these become the enforceable industry limits.

DR. MARTONE: In that case, what my recommendation is, is to endorse the concept of limitation of pool sizes and leave it up to you guys to decide how large or small those sizes should be rather than take some pool size limit from this guideline, so I would change the question.

DR. HOLLINGER: You would vote no on it.

DR. MARTONE: I would vote no on this particular question, but what it really means is yes to an FDA limitation on pool size.

DR. HOLLINGER: Yes, Beatrice.

MS. PIERCE: I have two questions, but the first
one has to do with the statement that was made at the July 31st meeting with the Shays Committee, and that was that pools could be decreased by 40 percent.

Now, from the numbers that we have here, 40 percent in some cases would definitely be below 60,000, and I guess that's -- why 60,000, and not 40,000 or lower?

MR. BELL: That's a good question. The answer is this. The numbers that we were debating in the context of for all major therapies, let's not include anything but albumin, IVIG, Factor VIII, Factor IX, were pools sizes that were approximately the 100,000 range, and what we said is that we could, as an industry, without detrimentally affecting safety, efficacy, or the availability of these products, decrease it from that 100,000 level 40 percent to the 60,000.

In addition, the other point that I guess you raise is that this is a 60,000 cap, an absolute cap, so manufacturers are at, at least that level or below that level, and will continue to be below that level, and we will work forward from there.

DR. HOLLINGER: Paul.

DR. McCURDY: As I understand it, we are being asked to accept or not accept this as an interim measure, and I think as an interim measure, it's probably a
reasonable approach.

I think it is probably better than nothing. I don't know what the right number is, I have a feeling it probably is lower than this, but with the idea that it's an interim measure, I think I can support this.

DR. HOLLINGER: Let's not forget that there are many companies here who have much smaller numbers in here than 60,000, and I don't think that they are going from -- I would hope not -- from 23,000 to 60,000 because of this measure, but they could.

DR. KHABBAZ: If we vote to recommend the standard, can we also take a vote on an additional separate comment that the FDA work on setting up a lower standard?

DR. HOLLINGER: I think we could, but I think that the FDA probably hears all this. Am I right, Jay, that if one votes -- I mean it would depend on how you are hearing this -- or should there be an additional vote? I guess there could be an additional vote.

DR. EPSTEIN: Well, I mean we had your recommendation last December that we move toward even smaller limits, and we wouldn't expect to stop here, but the question is, is this a point at which we can have a policy with respect to current industry practice. That is not going to be the end of the story. An interim policy, would
you support this as an interim policy? That is the question.

MR. DUBIN: Jay, how long an interim policy?

DR. EPSTEIN: Well, I can't answer that.

MR. DUBIN: Ballpark?

DR. EPSTEIN: The trouble is that it will take time to investigate the feasibility of driving the numbers even lower, and that process has been started, but, you know, it isn't over until it's over.

DR. HOLLINGER: Corey, let me just say we have two Committee members who might be leaving here soon, so we are going to have to come to a decision because we have a quorum right now. If one person leaves, we don't have a quorum anymore.

MR. DUBIN: And what have we got, about two minutes left?

DR. HOLLINGER: We have actually no time left from when we said we were going to be finished.

MR. DUBIN: All right. Let me throw my one sentence out and I will get the heck out of the way and we can vote.

DR. HOLLINGER: Go ahead.

MR. DUBIN: The bottom line for me, if we vote for this, this cannot be the end. We are going to keep
agitating like crazy, and the last thing I want to say is
forget I have hemophilia, forget who all of us are. At what
point do people get outraged about the truth?

    At what point does it matter that for four decades
people don't tell the truth, and then we come to this
meeting and we act as business as usual, and at that point
for me, it just becomes a question of it's going on all over
our society as far as I am concerned.

    DR. HOLLINGER: Beatrice, go ahead.

    MS. PIERCE: Real quick, I would like somebody
from the FDA to comment on the fact that the FDA
recommendations for numbers do not include excipient donors,
whereas, the 60,000 does, and considering that that is
mainly from albumin, those excipient donors which has a very
safe record, can you speak to that point, the value of
having excipient in there?

    DR. EPSTEIN: FDA has certainly recognized all
along that it is donor exposures that we seek to control,
not just volume or scale of manufacturing, and there is no
question that one has to include all downstream pooling
procedures including the addition of excipients in
formulation as contributors.

    We knew that of course in December. However, at
that point in time, we had only a very sketchy knowledge of
what the downstream processes were, and the impact that they
were having on the pool sizes, so we took the point of view
of starting down that path by setting limits to the upfront
fractionation pool, but with the definite notion that we
would come back with discussion of downstream pooling and
use of excipients.

So, really, it was never an either/or situation.
It is just that you have in front of you a more limited
initial FDA proposal, and now, if you will, the paradox that
if you have a larger number, but a more inclusive system in
the current IPPIA proposal, but there is no question that
FDA's goal in this is to drive the total donor exposure as
low as possible.

DR. HOLLINGER: Thank you. Let's not always
forget in the final here, that these products are very safe
right now, and that what we are really trying to do is make
things even safer as such.

Yes, Paul.

DR. NESS: Just one quick comment. I understand
the emotionalism and the fact that people are unhappy that
they may not have thought they heard the truth, but we have
heard I think pretty convincing evidence today that there is
a major -- that the levels of contamination are relatively
small, that the systems of inactivation have many logs of
protection over those levels of contamination, seven or eight logs we heard, and we are talking, we are arguing here about small arithmetic differences which are maybe two to sixfold.

I am impressed by the medical impact of really lowering donor exposure for these agents. Therefore, I would vote no if I had a vote.

DR. HOLLINGER: We will vote on the question of the donor exposure limitation as stated.

All those in favor of the standard as set --

MR. DUBIN: Are we voting to have FDA recommend this just so I am clear?

DR. HOLLINGER: Yes, that is correct, as an upper limit.

DR. McCURDY: Interim measure.

DR. HOLLINGER: Interim measure, yes.

All those in favor of the donor exposure limitation as stated, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Abstaining?

[Show of hands.]

DR. HOLLINGER: Paul?
DR. NESS: Opposed.

DR. HOLLINGER: Opposed. Rev. Little?

REV. LITTLE: I would vote yes. Can I say why?

DR. HOLLINGER: Yes.

REV. LITTLE: I am voting yes because it's an interim measure and it's something, but I have to tell you I am sitting here and I am really feeling outraged because I feel that, you know, for so long the truth hasn't been told, and in a sense now it's almost being -- I don't want to say rewarded -- but held up as, well, look, this is being done, so I do hope that this is clearly seen as an interim measure. I don't think that number is acceptable, but as an interim measure I am voting yes.

DR. HOLLINGER: Thank you.

DR. MARTONE: I voted no because I am unconvinced that that is the optimal upper limit for the number.

DR. HOLLINGER: You think it should be higher or lower, in your opinion, or you just don't know?

DR. MARTONE: I think we have been hearing from the FDA it should be much lower, and I think this committee voted for a higher limit based on -- nothing.

MS. PIERCE: Let me qualify why I said yes, and it is with a lot of mixed emotions, but it is yes to get the process going, to get it moving toward 60,000 with the
intention that this is not the end, and it should be rapidly
moved even lower.

DR. HOLLINGER: I think Jay is hearing that.

Yes, Corey.

MR. DUBIN: And I have to say the same reason. If
I think a majority of our guys our getting product out of
pools over the 100,000 range, 60 obviously is a slight
improvement. I didn't want to vote yes. It is pretty clear
I did because I do think Jay is listening, but I need to
say, and I think Bea will agree, and I think we are going to
be pushing really hard to move to where FDA recommended in
December in that range, because we think that is a realistic
range and we think it is justified, and we are not intending
to let up. Interim is the key word here.

DR. HOLLINGER: Thank you very much.

DR. SMALLWOOD: For the record, the vote on donor
exposure, there were 7 yes votes, 1 no vote, 1 abstention.
The industry representative agreed with the no vote. The
consumer representative agreed with the yes votes. Dr.
August would have voted yes. Dr. Piliavin would have voted
no.

DR. HOLLINGER: We will see you tomorrow morning
at 8 o'clock.

[Whereupon, at 5:45 p.m., the proceedings were
recessed, to be resumed at 8:00 a.m., Friday, September 19, 1997.

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