

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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

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Rima F. Khabbaz, M.D.
Jeanne V. Linden, M.D.
William J. Martone, M.D.
Beatrice Y. Pierce, R.N.
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TEMPORARY VOTING MEMBER

Paul R. McCurdy, M.D.

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P R O C E E D I N G S

Conflict of Interest

1 DR. SMALLWOOD: We will proceed with the meeting
2 at this time. Good morning and welcome to the 56th meeting
3 of the Blood Products Advisory Committee. I am Linda
4 Smallwood, the Executive Secretary. At this time, I will
5 read the conflict of interest statement as it pertains to
6 this meeting.
7
8

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

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

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

23 The following disclosures are presented: Dr.
24 Charles August has an unpaid association with the Medical

1 Advisory Board of the American Red Cross, South Florida
2 Division. The Agenda approved a waiver on June 11, 1996 for
3 his association.

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

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

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

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

21 Dr. Rima Khabbaz's employer, Centers for Disease
22 Control, Division of Viral and Rickettsial Diseases, has
23 unrelated CRADAs with two firms which could be affected by
24 the general discussions.

1 Dr. William Martone is a Federal Government
2 employee detailed to the National Foundation for Infectious
3 Diseases, a nonprofit organization. The Foundation receives
4 grants and/or donations from regulated firms. The grants
5 and donations are unrelated to the committee's discussions
6 and Dr. Martone receives no personal remuneration from these
7 grants and/or donations.

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

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

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

24 In the event that the discussions involve any

1 other products or firms not already on the agenda for which
2 an FDA participant has a financial interest, the
3 participants are aware of the need to exclude themselves
4 from such involvement and their exclusion will be noted for
5 the record.

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

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

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

19 [No response.]

20 **Welcome and Opening Remarks**

21 DR. SMALLWOOD: At this time, I would like to
22 introduce to you the members of the Blood Products Advisory
23 Committee. As I call your name, would each member please
24 raise your hand.

1 Dr. Blaine Hollinger, who will be Acting Chairman
2 for this meeting. Dr. Jerry Holmberg. Ms. Beatrice Pierce.
3 Mr. Benjamin Cheng. Dr. Rima Khabbaz. Mr. Corey Dubin.
4 Dr. Jeanne Linden. Dr. Charles August. Dr. Paul McCurdy.
5 Rev. Violet Little. Dr. William Martone. Dr. Jane
6 Piliavin. Dr. Joel Verter. Dr. Ness.

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

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

14 DR. EPSTEIN: Thank you very much, Linda.

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

20 Really, I want to thank these individuals for
21 their public service. We recognize that being a special
22 government employee and serving on an advisory committee
23 does entail personal sacrifices. We recognize that the
24 awards are not material, however, we value greatly the

1 contributions that you have made to decisionmaking, and we
2 assure you that the Government takes seriously its need for
3 outside inputs and for balance in the effort to reach sound
4 decisions in the public interest.

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

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

20 We will of course be reconstituting the committee
21 and it has not yet been decided what the membership will be.
22 I should mention, just so people are aware, that it is
23 possible for members to serve two consecutive two-year
24 terms, so some of you perhaps may not be off the hook just

1 yet, but we certainly recognize your efforts in the last two
2 years, and I just want to thank you.

3 DR. SMALLWOOD: Thank you, Dr. Epstein.

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

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

14 March 12th and 13th, 1998, will be the first
15 meeting in 1998; June 18th and 19th; September 17th and
16 18th; and December 10th and 11th. Again, these are
17 tentative, but we are trying to adhere as close as possible
18 to our regular schedule during these months.

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

22 That concludes my administrative remarks. At this
23 time, Dr. Blaine Hollinger will preside over the
24 proceedings.

1 Thank you.

2 DR. HOLLINGER: Thank you, Linda.

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

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

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

23 With that as an introduction, we do have a busy
24 schedule. By the way, I am also appreciative of all the

1 efforts that the FDA puts into providing us with background
2 information on these issues here, so that we can sort of get
3 up to speed, if you will, about trying to resolve some of
4 these very important issues that we are facing.

5 We will start off with Dr. Tabor.

6 **INADVERTENT CONTAMINATION**

7 **Summary of Previous Discussion and Introduction to Topic**

8 **Edward Tabor, M.D.**

9 [Slide.]

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

12 [Slide.]

13 As you will recall from your discussion in June,
14 inadvertent contamination is the presence in a plasma pool
15 or plasma product derived from a plasma pool of the unit of
16 plasma from a donor who was subsequently found to have an
17 exclusionary risk factor or a reactive screening test.
18 These are donors who were thought to have met all donor
19 acceptance criteria including negative tests on the donated
20 unit, or an inadvertent contamination can be a situation in
21 which a plasma pool is found to have an unexplained reactive
22 test on the pool itself, and this is a situation that is
23 arising more and more now that groups are interested in pool
24 testing.

1 [Slide.]

2 I think it is important to reiterate that
3 inadvertent contamination is very different from an adverse
4 reaction. In the case of an adverse reaction, the event is
5 defined by something that happens in the blood or plasma
6 recipient, and in that case, the material is recalled.

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

12 [Slide.]

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

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

23 [Slide.]

24 The recommendations that you, the committee, made

1 in June, the first recommendation was when notified of
2 inadvertent contamination of a fractionation pool with units
3 reactive for HBV, HCV, or HIV, FDA should immediately and
4 uniformly quarantine or recall all products as a first step,
5 and then determine regulatory action based on an assessment
6 of product risk, for instance, the impact of virus removal
7 or inactivation on the product in question.

8 [Slide.]

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

12 [Slide.]

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

16 [Slide.]

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

23 These unit issues could include situations where a
24 test was performed incorrectly or was recorded incorrectly

1 due to human error in the laboratory; a situation where a
2 donor sample was tested again later or at another location
3 or by another method; a situation which is becoming more and
4 more common now where a pool sample was tested later or at
5 another location by another method; a situation where a more
6 sensitive test becomes available after pooling has occurred;
7 or a situation in which the red cells from the same donation
8 have been found to transmit disease after pooling of the
9 plasma has occurred, but before the plasma derivatives have
10 been fully utilized.

11 [Slide.]

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

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

19 [Slide.]

20 Donor issues really involve the 23 donor questions
21 that are asked of donors at the time of donation. We
22 intended to have a copy of this in your packet. It
23 apparently was not included and you should receive one
24 sometime in the next hour or so.

1 These donor issues involve a number of situations
2 in which a risk factor or some causative donor history that
3 should have been picked up by the donor questions, is not
4 picked up, but is later revealed, and the situation might be
5 that in which a donor calls up the center later and says I
6 forgot to tell you, but I did have a history of such and
7 such a risk factor.

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

13 [Slide.]

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

19 [Slide.]

20 Secondly, marker-negative donors, those donors
21 whose plasma has been tested with the FDA-approved tests,
22 who also have no known risk factors, can still be infectious
23 for these agents, but nevertheless, the inactivation
24 procedures provide safety for the plasma obtained from them.

1 [Slide.]

2 Third, we believe that if we can determine the
3 range of viral load or risk associated with a specific donor
4 risk factor, that we can then determine what the risk is
5 associated with a specific inadvertent contamination episode
6 from a donor with that risk factor.

7 [Slide.]

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

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

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

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

1 to unit issues

2 [Slide.]

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

8 [Slide.]

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

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

19 [Slide.]

20 Finally, as you know, there has been a great
21 interest in PCR testing and other types of nucleic acid
22 testing, particularly with their applications to pools and
23 mini-pools of plasma, and we would like to ask whether the
24 committee feels that a negative nucleic acid test or other

1 additional assay applied either to the donor sample or to
2 the pool, or to the donor himself can be used to eliminate
3 the need to destroy a pooled product.

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

9 Thank you.

10 **Definitions and Operational Practice**

11 **Boyd Fogle**

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

22 [Slide.]

23 We will start with the definition again of recall.
24 Recall is defined by the Agency in 21 CFR Part 7, which are

1 formal guidelines for conducting recalls. These are used by
2 industry and the Agency. The definition is a firm's removal
3 or correction of a marketed product that the FDA considers
4 to be in violation of the laws it administers and against
5 which the Agency would initiate legal action, for example,
6 seizure. The point here is that the product is violative
7 and we would take action against the product.

8 [Slide.]

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

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

22 [Slide.]

23 There is also a definition of stock recovery.
24 Again, it is found in Part 7. This is a firm's removal or

1 correction of a product that has not been marketed or that
2 has not left the direct control of the firm, i.e., the
3 product is located on the premises owned by or under the
4 control of the firm, and no portion of the lot has been
5 released for sale or use.

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

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

21 [Slide.]

22 Now, those terms are defined, as I mentioned, in
23 our formal guidelines. In previous discussions, there have
24 been terms brought forward, such as quarantines and holds.

1 These are not defined within the context of the GMPs. They
2 are also not defined within the context of our recall
3 guidelines, but commonly accepted definitions for quarantine
4 include to exclude, to detain, or isolate, a strict
5 isolation imposed to prevent the spread of disease.

6 [Slide.]

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

16 [Slide.]

17 Operationally, within the context of GMPs, there
18 are the general principles of withholding from use
19 unsuitable products. This may also be based on the fact
20 that unsuitable components may have been used in products
21 that would pivot decisions within the context of GMPs for
22 testing and examination, retesting or reexamination, so that
23 decisions can be made as far as release for use in
24 distribution.

1 This may be initial distribution. It also may be
2 for redistribution, for distribution initially or something
3 is already in process, but yet you now have information, and
4 you may have placed a hold on it, so you may want to do
5 additional reviews.

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

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

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

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

24 [Slide.]

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

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

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

21 [Slide.]

22 These evaluations customarily include reviewing
23 batch production records, which give the manufacturing
24 history of the particular lot or other associated lots. It

1 may also include reviewing the history of source material,
2 which may include unit testing histories and donor testing
3 histories if there is a donor-specific issue.

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

10 [Slide.]

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

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

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

22 [Slide.]

23 We are also seeing that there may be additional
24 testing on a case-specific issue that would go back to

1 additional testing of donors or individual units or segments
2 from units that are available. There also may be additional
3 testing of pools and also final containers. There are
4 customarily medical evaluations and risk assessments that
5 are performed in these situations.

6 [Slide.]

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

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

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

21 [Slide.]

22 The conclusions that the Agency attempts to reach
23 is a determination of if a violation exists with respect to
24 the product and its manufacturing, a determination if the

1 violation is actionable. As you may recall, it goes back to
2 the basic definitions of recalls, market withdrawals.

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

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

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

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

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

17 REV. LITTLE: The end user?

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

24 DR. HOLLINGER: And the risk assessment factors

1 and conclusions are perhaps what the FDA might request or
2 might do regarding an issue?

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

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

11 DR. HOLLINGER: Mr. Dubin.

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

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

19 It would seem to me, it is obviously very helpful
20 in the middle of this discussion to have it up on the
21 overhead, because it gives us a chance to listen and think
22 about it, but I know, since I have read it, and reread it
23 regularly, usually, I go back to it before every BPAC
24 meeting, I think it is pretty important that the members of

1 the committee have regular access to that in their
2 deliberations because so many of the questions we are asked
3 to answer somehow relate directly or indirectly to those
4 regulations.

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

8 Thank you.

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

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

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

20 In the absence of a formal definition, it is hard
21 and difficult in certain situations to draw a line, but if
22 you look at the basic definitions, I think with a
23 quarantine, it gives a higher level of concern that there
24 may be some possible condition that could be transmitting

1 disease. I think quarantine gives a higher sense of urgency
2 versus a hold, but we have seen in practice that they are
3 used interchangeably.

4 DR. LINDEN: Thank you.

5 DR. HOLLINGER: Thank you very much.

6 **Donor Risk Factors, HBV and HCV**

7 **Robin Biswas, M.D.**

8 [Slide.]

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

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

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

24 [Slide.]

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

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

12 [Slide.]

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

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

22 The et ceteras, there is several there. One that
23 one could mention is a previous report of having tested
24 positive for a viral marker.

1 [Slide.]

2 Now, let us talk about HBV/HCV test-negative
3 donations from HBV/HCV infected donors. What sort of units
4 are these?

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

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

14 [Slide.]

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

22 For HCV in the window period, there are about 8
23 HCV test negative units per million units; for HBV it is 15.
24 As far as variants are concerned, at least using currently

1 licensed tests and in the U.S. setting, variants don't play
2 a role.

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

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

12 [Slide.]

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

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

22 [Slide.]

23 What I wish to do now is to discuss comparative
24 viral load by which I mean comparing the viral load in test-

1 positive units from infected individuals versus viral load
2 in test-negative units from infected individuals.

3 [Slide.]

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

7 Firstly, there are no usable cell cultures
8 available for HBV and HCV, and what I have up there only
9 quantitative nucleic tests available to assess viral load.
10 More accurately, one should say only nucleic acid tests used
11 in a quantitative fashion are available to assess viral
12 load.

13 [Slide.]

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

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

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

23 Most available tests are qualitative, not
24 quantitative. There are some tests that do specifically

1 address quantitative HBV DNA and HCV RNA, but there are
2 really very few. Most of the quantitative viral studies
3 analyze therapeutic efficacy only. Therefore the literature
4 that is available and useful to us is very, very limited
5 indeed.

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

10 [Slides.]

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

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

21 [Slide.]

22 In any event, all I want to show you is that when
23 you have a positive HBsAg test, the DNA load is more than
24 when the HBsAG test is negative.

1 [Slide.]

2 All I want to show you is, is that when there is
3 no HBsAG, when the HBsAG here, and also back here, is
4 negative, there is really very little or no HBD DNA compared
5 with when you have detectable HBsAG. There is HBV DNA.

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

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

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

19 [Slide.]

20 This slide of chronic Hepatitis B infection is
21 just meant to demonstrate the same thing, that when HBsAG is
22 positive, over here, there is more HBV DNA shown here
23 compared when the window period, where the HBsAG is
24 negative.

1 [Slide.]

2 In contrast to this, this depiction of a chronic
3 Hepatitis C case, from a review article by Harvey Alter,
4 shows that before the serologic test becomes positive, here,
5 before that becomes positive, in the window period, which is
6 this area here, in the window period, there are higher level
7 of HCV RNA than after the seroconversion.

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

12 [Slide.]

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

18 [Slide.]

19 This is just meant to show what I just showed you
20 more graphically with numbers, and it is a study by Rawal,
21 et al., and it shows the relative viral load in 17 HBV
22 infected donors. What you see here is that the mean of the
23 HBV DNA genomic copy numbers, the mean in the seronegative
24 window is considerably lower than then mean in the

1 seropositive units. However, do note that there is some
2 overlap here and here.

3 [Slide.]

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

8 [Slide.]

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

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

24 I would like to end by repeating what I indicated

1 earlier. Nucleic acid copy number by e RNA or DNA amount,
2 and degree of infectivity, has been shown sort of on a
3 limited basis, and studies are really needed to validate
4 this, and with the improvement in PCR, let's hope that that
5 happens.

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

9 DR. HOLLINGER: Thank you, Dr. Biswas.

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

12 [No response.]

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

18 I think we need to always consider a couple of
19 things, and that is, we don't know that much about the
20 replicative cycles and what is produced during the normal
21 replication in terms of infectious and noninfectious
22 particles. All we are measuring is virus, nucleic acid.
23 That doesn't necessarily correlate to infectivity, although
24 we think it does in many cases.

1 If you look at different viruses, for example, the
2 real viruses, the real viruses can have anywhere from 1 to 1
3 infectious particles to noninfectious particles -- I think
4 that is actually too low -- to maybe 1 in 5 during early
5 stages of infection.

6 For most other viruses, that rate can be 1 in
7 50,000 to 1 in 100,000, that is, 1 infectious particle to
8 100,000 noninfectious particles, some of which will not have
9 nucleic acid in capsids that are empty, or they will have
10 nucleic acid, but they will be defective.

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

18 DR. BISWAS: That is correct.

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

23 The other is can you comment a little bit -- I
24 know there is some information in which there seems to be,

1 at least anecdotally, I don't know if it has been reported
2 or not, but there seems to be some information about
3 individuals who are HCV/RNA-positive and anti-HCV-negative,
4 but do not seem to be in the window period.

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

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

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

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

21 DR. ALTER: [Off mike.]

22 DR. HOLLINGER: The other thing, Robin, I want to
23 comment about -- which I appreciate all this information, it
24 has really been good -- just again for the committee to also

1 realize that most of the studies you present, at least the
2 ones with HBV DNA, were done with hybridization technology,
3 and that is why the DNA looks like it comes later.

4 If you look with PCR --

5 DR. BISWAS: Absolutely.

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

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

17 DR. BISWAS: Right.

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

20 Those are my comments. Yes, Dr. August.

21 DR. AUGUST: I think this point may have come up
22 in the June meeting, but it bears on I think ultimately
23 clearing products or clearing units, and that is, that if
24 you take the most conservative assumption, and that is that

1 one particular equals one infectious unit, if you were to
2 find no viral RNA in a product or DNA, as the case may be,
3 could you then confidently assume that there was not going
4 to be infectivity and that you could release the product?
5 Is that a fair conclusion to draw?

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

8 DR. AUGUST: And repeatedly negative.

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

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

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

21 DR. HOLLINGER: Outside of the inactivation
22 procedures, which of course we have to remember are present
23 now in most cases, you are right. I mean these tests at the
24 very best will still miss perhaps as many as 100 to 1,000

1 copies or more per ml of sample, and while you can
2 concentrate large amounts to look at it, you still might
3 have infectious particles present.

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

8 DR. HOLLINGER: Yes, Jay.

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

14 DR. BISWAS: Which one are you referring to?

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

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

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

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

24 DR. EPSTEIN: Okay, so HBV --

1 DR. BISWAS: I am sorry. For the HBV, they were
2 acute, right, and for the HCV it was for the chronic.

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

9 DR. BISWAS: Using the antigen test.

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

13 DR. BISWAS: That is correct.

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

17 DR. BISWAS: Right.

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

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

24 DR. EPSTEIN: I would just comment to Dr. August I

1 do not think we could assert that PCR-negative means no
2 possible infectivity. That would be false reasoning. On
3 the other hand, I would say that what we would assert is
4 that it establishes an upper limit of the possible
5 infectious titer. In other words, if you know you have
6 negative PCR, infectious titer cannot be higher than some
7 value.

8 DR. HOLLINGER: Dr. Busch.

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

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

24 Just another comment with respect to the question

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

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

18 So, it looks to me to be real, but on the other
19 side of the coin, the look-back studies that have been done,
20 which number in the 30s or 40s, of recipients of prior red
21 cells from these donors have to date been consistently
22 negative. So, these people do not appear to have infected.
23 Now, whether they, in fact, were viremic at those earlier
24 time points is unclear.

1 So, these do seem to exist, but whether they are
2 infectious and whether they are just delayed seroconverters
3 versus atypical virus versus atypical seroconverters is
4 still unclear.

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

7 **Donor Risk Factors: HIV**

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

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

12 [Slide.]

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

20 [Slide.]

21 To look at what the risk is to the pool that
22 contains this unit with the donor risk factor, there is two
23 questions to be looked at - what is the risk that the
24 implicated unit is HIV infected, that is, what is the

1 likelihood of occurrence that there is virus in this unit,
2 and what are the estimates of viral load in that unit and in
3 the plasma pool that it is in.

4 [Slide.]

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

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

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

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

18 [Slide.]

19 These sources of risk have been evaluated in a
20 study called the REDS study, in which there is long-term
21 surveillance of over a million random whole blood donors
22 each year. The incidence rates of the markers of actually
23 converting to a confirmed HIV infection in donors is where
24 we can get an estimate of what the risk would be that a unit

1 from a donor who has some sort of risk factor, that that
2 unit may be infected.

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

6 [Slide.]

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

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

20 [Slide.]

21 Information for source plasma, I have really not
22 been able to get an update on this information. This is a
23 summary of data that was presented in the 1994 Workshop to
24 the Advisory Committee.

1 The topmost line summarizes the numbers from --
2 they were gleaned by Mr. Riordan in our group from license
3 application submissions. This is covering the time from
4 1984 to 1990 for donations screened by HIV-1 EIAs. Thirteen
5 were confirmed positive out of -- let me make a correction
6 here -- 11,214.

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

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

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

17 [Slide.]

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

22 Dr. Biswas referred earlier to a study by
23 Williams, et al., in the Journal of the American Medical
24 Association in March of this year, in which what they did

1 was sent out questionnaires to a subset of the REDS donors,
2 and they asked them a lot of different questions in this
3 questionnaire. The n for this, that is, the total of people
4 responding was 34,000. It was a good response.

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

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

14 [Slide.]

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

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

23 [Slide.]

24 That is where I focused my data collection

1 efforts. So in order to ask how to determine the viral load
2 in a marker-negative unit, I got the help of the staff at
3 Boston Biomedica, Inc., and Mike Busch also contributed
4 data, and what we have done is to review the viral load in
5 seroconversion panel samples, and in particular, the load in
6 p24 antigen negative, antibody negative seroconversion panel
7 samples.

8 [Slide.]

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

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

21 [Slide.]

22 In data that I have collected from numerous
23 sources, in particular, data presented at the AABB meeting,
24 Mike Busch et al., also data from screening of the BBI

1 seroconversion panels, from seroconversion panels from some
2 infected individuals who were not donors, and in all
3 publications I could find about viral loads measured in
4 units from seropositive blood donors.

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

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

17 [Slide.]

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

22 [Slide.]

23 I am going to show you three profiles from three
24 different seroconverting individuals. This is actual data.

1 In order to incorporate all the data on one slide, I used a
2 logarithmic scale to show viral load, and I am also talking
3 about signal to cutoff here. P24 and EIA reactivity is not
4 usually presented on a logarithmic scale, but anything over
5 a value of 1, this line here, is considered a positive
6 reaction in the assay.

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

15 [Slide.]

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

24 [Slide.]

1 The last profile I am showing, once again you are
2 seeing a similar profile. In this instance, possibly
3 because of the length of time between the donations, for
4 whatever reason, all of the units given in this profile
5 would be RNA negative when they are marker negative. That
6 is, the first day in which there is viral load, which is day
7 86 here, is also the first day at which there is p24
8 reactivity and antibody reactivity.

9 [Slide.]

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

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

22 In this case of the 66 samples, which I managed to
23 crunch the data for, we go up to about 3 times 10^6 as a peak
24 viral load.

1 I want to emphasize I have got the label on this
2 wrong, that these are antibody negative units, and what I
3 did was go through all the panels and pull out any sample
4 which had either a p24 reactivity or a detectable viral load
5 or both.

6 [Slide.]

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

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

19 The next panel shows p24 positive donations. They
20 are still antibody negative, but they do have p24, and you
21 can see a dramatic shift in the viral RNA levels. They
22 range from 10^4 to 10^7 copies per ml, and from then on, I
23 represent those samples that are EIA reactive. In this
24 case, they are almost all p24 reactive, too.

1 As you can see, the viral load stays about the
2 same, goes up just a little bit as EIA reactivity kicks in,
3 and then sort of follows what you would expect as the normal
4 curve during the peak viremic phase of infection.

5 [Slide.]

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

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

24 [Slide.]

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

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

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

21 If you take a typical source plasma donation of
22 800 ml's, that would lead to an 8 times 10^7 copies per ml
23 load going into the pool, which comes out to 8 copies per ml
24 in, for example, a 10,000 liter pool.

1 The worst case scenario is where someone who has a
2 risk factor, actually is seroconverting. I made it the
3 worst case by taking the highest possible peak load that we
4 have seen, which is 10^8 nucleic acid copies per ml.

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

14 [Slide.]

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

23 [Slide.]

24 To end, coming back to the point that was made

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

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

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

23 I think that is all.

24 DR. HOLLINGER: Thank you, Dr. Poffenberger.

1 Questions from the committee? Yes, Beatrice
2 Pierce.

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

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

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

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

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

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

24 DR. HOLLINGER: Dr. Poffenberger, what is the

1 longest time in a person who is known to seroconvert,
2 actually been shown to be infected, what is the longest time
3 period it has been between when the HIV RNA becomes
4 positive, what is the longest delay that you know of?

5 DR. POFFENBERGER: In infection?

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

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

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

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

19 DR. BUSCH: It really doesn't come from the
20 seroconversion panel. The best data -- and this requires
21 the known date of exposure and then serial samples to assess
22 seroconversion -- the best data is recently compiled by CDC
23 from health care worker infections where about 55 health
24 care workers over the last six or seven years have become

1 infected from needlestick accidents, and in analysis of the
2 sample data from those cases, the median is about 30 days
3 from exposure to seroconversion, but there were two cases
4 that did not seroconvert until after six months, at six and
5 seven months, and both of them were virologically confirmed
6 as the virus being identical between the source and the
7 subsequent infections that evolved in the seroconverters,
8 and there was actually a survival curve that showed, you
9 know, a consistent sort of declining rate of time to
10 seroconversion.

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

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

22 DR. BUSCH: There is data from a small number of
23 the -- well, from these non-seroconverters, these really
24 rare cases, they do appear to have high-titer viremia for

1 the duration of infection, and probably that is why they
2 progress so quickly in terms of CD4 decline in symptoms.

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

23 DR. HOLLINGER: Thank you.

24 Dr. August.

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

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

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

18 DR. POFFENBERGER: I would say that you really
19 have to take the rational approach. That is what we are
20 doing here, what is the risk, and this is the scientific
21 data. What I would like to say is what would bolster up our
22 confidence in following this rationale is the history of
23 transmission from products for HIV, and when you look at the
24 products that have, say, that lower level of 10^{11} log

1 reduction factor, how do they in fact transmit it over the
2 millions of doses that have been given, and I think the
3 safety record there is very, very good and does indeed
4 support the fact that this rational approach is giving us
5 the real facts. I would not say you can determine this to
6 an absolute black and white, yes, this is absolutely safe.
7 You can take your most rational approach.

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

10 Did you want to say something, John?

11 DR. FINLAYSON: Yes, not to put too fine a
12 logarithmic point on it, but I would propose that it's even
13 better than Dr. August says, because if you took not the
14 10^5 , which would be the usual worst case, but the 10^8 , which
15 would be the worst worst case that Dr. Poffenberger showed
16 up. By the time that went into a pool, which would be not a
17 particularly large pool, one was down to 8,000, and the
18 logarithm of 8,000 is going to be 3.9, and so that one has a
19 10 million-fold cushion there.

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

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

24 I have two caveats that I think we should

1 remember. One is -- and I think it is related to a question
2 that was asked -- the viral validation studies, to my
3 knowledge, are always done with lab strains, they are not
4 done with isolates from patients.

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

9 The other factor that came, and others have
10 brought up, is that the level of detection of these viruses
11 has a lower limit, so when you do a viral validation study,
12 they are always done with very high loads of virus, and what
13 you get as an answer is non-detectable virus often in the
14 test, and then you say -- if you started out with 10^7 and
15 you went down to non-detectable levels, and the non-
16 detectable is 10^3 , then, you can say, well, it is greater
17 than 10^4 viral removal, log removal, but that doesn't mean
18 that there is absolutely no virus there. There is a
19 possibility that with low levels of virus in there,
20 especially to start out with, that some of these methods may
21 not be as efficient. We are always looking at these
22 validation studies with high levels of virus.

23 The reason I am bringing this up is not because I
24 think there is a serious scientific chance that we are not

1 removing all the virus, but there is some chance and that
2 all the testing plus the viral validation has to be in place
3 to ensure the maximum safety for the system.

4 DR. HOLLINGER: Thank you.

5 Yes.

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

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

19 There is a lot of scientific evidence that
20 suggests that they are different in terms of the infectivity
21 and other properties and in terms of the antigen makeup.
22 So, these viruses, as far as I know, that are used for the
23 validation are all these stock viruses that have been
24 passaged for a long time, and I don't think in any way

1 relate to acute infection or chronic infection, and I don't
2 think you can make that relationship.

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

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

15 DR. HOLLINGER: Yes.

16 DR. BUSCH: The problem with trying to use
17 "primary isolates" or these plasma panels to assess
18 inactivation is that the viral titers in fact are
19 exceedingly low. In order to rigorously measure the 10¹⁰
20 levels of inactivation, you need to bump up viral titers up
21 to 10²⁰, 10²², which requires extensive in-vitro
22 amplification of these isolates.

23 We have recently done with Bob Coombs, cultures,
24 quantitative cultures on a number of these seroconversion

1 panels, and you can't even get a positive culture from these
2 plasmas until you have over 100,000 copies of RNA.

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

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

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

24 The truth is that there has not been an HIV

1 transmission since '86 in the United States, so I think the
2 proof is in the record that enormous numbers, well, hundreds
3 certainly, of high-titer antigenemic viremic plasmas have
4 been fractionated into pools, and have not resulted in
5 infectivity over the last decade.

6 DR. HOLLINGER: Thank you.

7 We will move then to the next speaker.

8 **Significance of Risk Factors Revealed by Surveillance**

9 **Miriam Alter, Ph.D.**

10 DR. ALTER: Thank you.

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

16 [Slide.]

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

20 There are variety of exposures that can be
21 associated with bloodborne virus transmission. For
22 Hepatitis B virus and Hepatitis C virus, these include
23 blood, blood products, organs, and tissues from infectious
24 donors.

1 Obviously, for Hepatitis B, this has really not
2 been an issue for a very long time. The opportunity under
3 most circumstances for HBV infection to be transmitted from
4 an infected donor are extremely remote given the sensitivity
5 and accuracy of long-time testing for HBV infection.

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

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

18 Other potential sources for HBV and HCV
19 transmission include contaminated instruments, equipment,
20 and supplies used for procedures involved in traditional
21 medicine, folk medicine, percutaneous procedures, such as
22 tattooing, body piercing, and even the use of commercial
23 razors, or even the use of razors in commercial
24 establishments.

1 For the most part, associations between these
2 types of activities and the transmission of HBV and HCV have
3 only been documented in countries outside of the United
4 States. There have been occasional episodes, clusters of
5 cases, of HBV infections associated with tattooing and
6 acupuncture in the U.S, and there have been no such
7 associations with HCV transmission.

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

11 [Slide.]

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

23 Transmission of HBV from infected sexual partners
24 or as the result of high-risk sexual activities involving

1 multiple partners is extremely well documented. In fact, as
2 you will see, sexual transmission of HBV or sexual exposures
3 account for the majority of the transmission of HBV in the
4 United States today.

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

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

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

24 Finally, infected health care workers fortunately

1 rarely transmit Hepatitis B to patients, although this has
2 been documented in the literature in the United States maybe
3 eight or nine times here in this country, but again it is
4 extremely rare and we do have recommendations for that
5 setting.

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

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

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

21 Patient to health care worker transmission has
22 occurred in the setting of accidental exposures to
23 needlesticks and other sharp injuries at a rate of about 2
24 percent, and finally, there has been one report of an

1 infected cardiovascular surgeon transmitting to his patients
2 from Spain. We have not documented such transmission in the
3 U.S.

4 [Slide.]

5 The overall prevalence in the United States of
6 either past or current infection is about 4 or 5 percent.
7 This slide summarizes the overall prevalence by age from the
8 National Health and Nutrition Examination Survey conducted
9 from 1976 through 1980. We have recently completed analysis
10 of NHANES III, which are the data collected from 1988 to
11 1994, and interestingly, there was little change in the age-
12 specific prevalence of even by racial/ethnic group.

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

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

20 [Slide.]

21 The most variation in the prevalence of HBV
22 infection is based on a variety of either ethnic,
23 behavioral, or lifestyle risk factors in the population.
24 Individuals who have immigrated from areas of high HBV

1 endonicity into the United States have extremely high rates
2 of HBV infections, 70 to 85 percent, and very high rates of
3 chronic carriage with HBsAG positivity actually as high as
4 20 percent.

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

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

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

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

22 [Slide.]

23 In looking at the trends in acquisition of HBV
24 infection in the last decade or so, we can see that while

1 the incidence of Hepatitis B reached a peak in the mid-
2 eighties, it has declined dramatically since then.

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

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

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

19 [Slide.]

20 Here, you can see the dramatic decline among
21 homosexual men in the mid-to-late 1980s, while there was an
22 increase in the number of cases among injection drug users
23 and among men and women who had either infected sex partners
24 or who were exposed to multiple partners.

1 The number of cases in all of these risk groups
2 has declined during the 1990s, and we certainly hope that it
3 continues. Again, we are focusing our vaccination efforts
4 on both injection drug users and other high-risk adults in
5 order to continue to achieve this downward decline.

6 [Slide.]

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

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

20 As you can see, most of these have a history of
21 high-risk exposures: 5 percent are drug related, and that
22 these individuals said they injected drugs in the past, but
23 not during the incubation period; 8 percent denied having
24 multiple partners, but have a history of other sexually

1 transmitted diseases; 1 percent have been in prison or jail;
2 10 percent have characteristics associated with low
3 socioeconomic levels, which suggests that they in fact may
4 have been exposed to high-risk behaviors or which they may
5 have failed to acknowledge or they had unrecognized contact
6 with an infected individual. So, all but 5 percent of the
7 recently acquired Hepatitis B in the United States can be
8 associated with high-risk behaviors or lifestyles or
9 occupations, most of which could be prevented with Hepatitis
10 B vaccine.

11 [Slide.]

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

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

1 where we have a very low frequency event.

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

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

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

19 [Slide.]

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

24 The prevalence does vary by racial/ethnic group

1 with the lowest rates among non-hispanic whites and the
2 highest rates among non-hispanic blacks and Mexican-
3 Americans.

4 [Slide.]

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

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

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

24 [Slide.]

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

7 Most of the decline among transfusion recipients
8 actually took place prior to the introduction of first-
9 generation testing and really had very little impact on the
10 overall incidence of disease since this group represented
11 less than 20 percent of the newly acquired cases in the
12 1980s.

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

17 Here, you can see the trends in the three most
18 common, what are thought of as the three most common risk
19 factors for Hepatitis C, and you can see that in terms of
20 the amount of disease associated with each of these factors,
21 there is very little associated with transfusions in the
22 last five years, and in fact, we have failed to detect a
23 case of transfusion-associated Hepatitis C in our
24 surveillance systems since 1994. It doesn't mean it doesn't

1 occur, it is just that it is at such a low frequency that we
2 can't detect it, whereas, the two most common risk factors
3 are associated with injection drug use and high-risk sexual
4 exposures.

5 [Slide.]

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

19 There has been one study in the U.S. which has
20 reported an association with a history of intranasal cocaine
21 use. This study was actually published from the NIH group
22 and was among volunteer blood donors who had denied any of
23 the risk factors on the history, had subsequently donated
24 and turned out to be anti-HCV positive, but, one, we don't

1 know what its contribution to transmission is and we don't
2 know whether the history of intranasal cocaine use is a risk
3 factor itself, such as through sharing of contaminated
4 straws, or whether it is an indication that both injection
5 drug use and non-injection drug use were actually practiced
6 by that individual. It is very rarely reported by newly
7 acquired cases of Hepatitis C in the absence of any other
8 percutaneous risk factors.

9 [Slide.]

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

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

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

1 characteristic.

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

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

17 [Slide.]

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

22 Again they include a variety of health care
23 procedures, a variety of percutaneous exposures, such as
24 tattooing, acupuncture and ear piercing, as well as male

1 homosexual activity or foreign travel.

2 [Slide.]

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

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

12 The prevalence of injection drug use in the
13 population is probably unknown. The National Institute for
14 Drug Abuse estimates it out about a half a percent of the
15 population, whereas, the study by Allen Williams, published
16 in JAMA, of donors, estimated it at about 5 percent who had
17 said that they had ever injected drugs in the past even
18 though they were actually negative for markers, but the
19 infection prevalence in this population is extremely high,
20 from 50 to 80 percent for B, and from 50 to 90 percent for
21 C. Even though the infection rates have declined
22 dramatically in this group, these individuals still
23 experience, those who are still susceptible, still
24 experience a high incidence of disease.

1 A history of transfusion is a little harder, it is
2 even harder to estimate. Again, there was a study published
3 by Murphy and colleagues in JAMA from the REDS group,
4 looking at the prevalence of these factors in the volunteer
5 donor population, and this again may be very different, as
6 pointed out by other speakers in the plasma population, 6
7 percent have ever had a history of transfusion. In the
8 current donor screening procedure, donors were only excluded
9 if they have had a transfusion in the prior 12 months. I
10 have no idea what the prevalence of HBV infection is in this
11 group. In the Murphy study, the prevalence of HCV infection
12 was 1 percent, and this was done among donors who were
13 identified during 1992 to '93, so I assume their transfusion
14 was before that.

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

22 About 9 to 10 percent of the U.S. population is
23 involved in health care employment. About 6 percent of them
24 are infected with HBV, have had HBV in the past. The vast

1 majority actually have now been vaccinated, and about 6
2 percent are infected with HCV.

3 Cocaine use, which may be an issue, which is an
4 issue that has been discussed I know among the blood
5 collection agencies in terms of whether or not to add that
6 as a risk factor, the prevalence of this behavior is about
7 14 percent in the population as estimated by NHANES III.
8 Again, 9 percent of these individuals have been infected
9 with HBV and about 10 percent with HCV.

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

15 [Slide.]

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

21 The prevalence of having an infected sex partner
22 in the population is also unknown. If we look at some of
23 the older studies published in the seventies and eighties of
24 the sex partners of volunteer blood donors, we find that

1 about 40 percent of them were infected with HBV. We don't
2 now what the prevalence of HCV is among the sex partners of
3 chronically infected individuals.

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

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

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

24 Thank you very much.

1 DR. HOLLINGER: Thank you, Miriam.

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

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

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

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

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

21 DR. ALTER: I am not familiar with the increase in
22 Hepatitis C in '92 and '93 among drug users, but as far as I
23 know, there has not been an increase in drug use. There
24 hasn't been a decrease in drug use either. Actually, what

1 we have seen is a decrease in the number of cases in drug
2 users for both Hepatitis B and Hepatitis C, although there
3 has been no decrease in drug use.

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

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

16 DR. ALTER: Thank you.

17 DR. HOLLINGER: Dr. Khabbaz.

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

22 DR. ALTER: That was Murphy's study. This was
23 published in JAMA, and it looked at donors. It asked a more
24 extensive history of all donors who came to donate during

1 '92 and '93 regardless of what their serology might have
2 shown, and 5 or 6 percent of them had a history of ever
3 having been transfused. If either Michael or Susan, who are
4 nodding their head, can elaborate on that, great. I don't
5 know anything else than that.

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

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

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

22 But, anyway, the prevalence you see among the
23 previously transfused donors was 1 percent. It was
24 significantly elevated relative to non-transfused donors, so

1 there was a significant association with C in prior
2 transfusion, but it was somewhat lower than one might
3 suspect.

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

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

14 DR. HOLLINGER: Charles.

15 DR. AUGUST: In the red, white and blue slide that
16 you showed correlating the incidence of I think B and C and
17 a number of events, it looked as if the incidence -- and I
18 think it was C or I guess it was B -- started declining
19 prior to anything that was identifiable, and that, for
20 example, the event initiating immunization for Hepatitis B
21 seemed not to change the slope of the curve, and I was just
22 wondering what you attributed the initial decline in
23 incident to in the first place. It sort of looks like the
24 top of a mountain, but there isn't any event that you could

1 point your finger at in saying this is why this happened.

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

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

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

13 DR. AUGUST: There it is.

14 [Slide.]

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

20 This shows there was this huge decline among
21 homosexual men and a substantial decline, as well, among
22 health care workers, but because health care workers
23 represent such a small percentage of all the infections, it
24 had no impact on overall incidence.

1 It is here that you can see that gay men
2 represented one of the highest numbers of cases during those
3 earlier years, and then that you have this 75 percent or
4 more decline in cases.

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

7 DR. ALTER: I could try that.

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

12 [Recess.]

13 **Illustrative Case Studies**

14 **Alice Godziemski**

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

19 [Slide.]

20 The first case study. The situation is that a
21 firm requests permission to distribute one lot of immune
22 globulin human. The plasma pool for this lot included units
23 of recovered plasma which tested nonreactive for all
24 required viral markers, but were collected from donors who,

1 after donating, reported to the collecting facility the
2 following postdonation information.

3 [Slide.]

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

13 [Slide.]

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

20 [Slide.]

21 Case Study No. 2 is that a firm requests
22 permission to release specific lots of plasma derivatives
23 prepared from plasma pools which contained units of source
24 plasma which tested nonreactive for HBsAg, but were

1 collected from donors who previously tested repeat reactive
2 for HBsAG. This case had seven units of source plasma that
3 were affected.

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

8 [Slide.]

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

16 [Slide.]

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

23 [Slide.]

24 The third case involves a firm that requests

1 permission to release specific lots of albumin prepared from
2 plasma pools which contain units of recovered plasma which
3 tested nonreactive for anti-HIV by EIA that were collected
4 from donors who previously tested repeat reactive for anti-
5 HIV-1 by EIA and had the following confirmatory test
6 results.

7 [Slide.]

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

15 [Slide.]

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

21 So, the outcome was that the continued use of the
22 plasma products was granted. In this case, also, three of
23 those donors that had the confirmatory testing results,
24 three of them had subsequent testing for reentry purposes.

1 They all tested nonreactive for HIV-1 by EIA with Western
2 blot indeterminates. Of the three, one had bands at P51 and
3 P55, another one at P51, and the third one at P17.

4 Those are the cases. Any questions?

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

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

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

16 [No response.]

17 DR. HOLLINGER: Okay

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

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

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

24 MS. GODZIEMSKI: I really don't know. I mean not

1 usually.

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

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

12 DR. HOLLINGER: Yes, Jane.

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

19 DR. GOLDING: I think there is one example or at
20 least one example that I recollect where the lots were not
21 released, and I thought we were actually still in the
22 process of discussing it. The situation was a donor donated
23 the product, denied any risk factors. His unit was part of
24 a pool. Later, on a subsequent donation, several months

1 later, the donor was found to be -- came back for another
2 donation -- was found to be positive.

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

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

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

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

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

24 MS. GODZIEMSKI: Yes.

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

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

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

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

22 MS. GODZIEMSKI: No, we don't.

23 DR. HOLLINGER: You would like that, Bill, is that
24 right?

1 DR. MARTONE: I was just wondering if that was a
2 standard operating procedure or not, or you just look at the
3 facts as we have them here and then make a determination.

4 DR. HOLLINGER: Dr. Khabbaz.

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

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

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

1 possibly because of having donated at another place.

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

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

17 DR. MARTONE: I think that sort of makes my point
18 about investigation of the donor, because in the example you
19 use, it is conceivable that someone acquired a case of acute
20 Hepatitis B and donated, was positive at that time, and then
21 previously had been negative, but at the time of the
22 donation was positive and then on retesting, you might find
23 that they have become a chronic carrier or that they had
24 resolved the infection, and at the time of the subsequent

1 donation, were HBsAg negative and antibody positive, which
2 would have allayed any concerns about that particular
3 donation going into that product pool.

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

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

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

22 Now, there have been several recent situations in
23 which the policies have come into question, and I think that
24 Dr. Golding mentioned one, which was a case in which a donor

1 who had failed to admit risk factors subsequently
2 seroconverted, had previously donated, and his other
3 products, namely, his transfusable component, did transmit
4 HIV, so we had a known contaminated collection, in fact, a
5 known window period collection with proven infectivity, and
6 we simply have not reached closure what to do with the
7 products that have been quarantined.

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

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

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

1 unusual threat.

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

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

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

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

23 DR. EPSTEIN: Well, currently, we are not
24 releasing products if there is a known infectious unit as

1 opposed to risk history. I would contend that there is an
2 inconsistency in the current assessment.

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

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

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

21 DR. HOLLINGER: Corey.

22 MR. DUBIN: I keep being struck by the sense that
23 we don't want to operate in a vacuum. I am concerned, at
24 least my own feeling is that to some degree we do that. I

1 think we have a total picture of a system that is dependent
2 on checks and balances at varying degrees and varying
3 places.

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

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

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

1 that were found.

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

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

13 DR. HOLLINGER: Reverend Little.

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

21 I would not want the message to get communicated
22 on any level that, well, okay, you know, if you weren't
23 aware of this or if you are not telling the truth, or
24 whatever, that's okay because in the end, something is going

1 to be inactivated. So, I am wrestling with that tension
2 right now, but thank you, Corey, because that helped.

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

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

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

22 On the other side of the coin, you recognize the
23 size of these pools, 10,000-member pools. I can't believe
24 there is ever a pool that does not, on subsequent followup

1 of the donors, evidence seroconversion for one multiple
2 viruses or have donors with risk, so I think the important
3 balance here needs to be the recognition that we are dealing
4 with enormous size pools -- and from prior discussion
5 probably potentially necessarily large-size pools -- and
6 that in the instance these viruses are so high, that
7 subsequent seroconversion, subsequent acknowledgment of
8 risk, if you really rigorously followed the donors who
9 contribute to any pool, I can't believe you wouldn't find
10 hundreds of donors who would, on subsequent followup,
11 donation, or interview, have risks.

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

18 DR. HOLLINGER: Thank you, Mike.

19 Anyone else in the audience? Yes, Jay.

20 DR. EPSTEIN: I just want to add one more point
21 about Dr. Martone's question about surveillance. I think
22 that if we thought that a product could not be distributed
23 without also doing surveillance, we wouldn't distribute that
24 product.

1 regulatory action based on an assessment of product risk?

2 [Slide.]

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

8 [Slide.]

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

15 [Slide.]

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

22 **Committee Discussion and Recommendations**

23 DR. HOLLINGER: Let's go back to that first
24 question, if you could. We will just deal with these

1 issues. This is the first question. I would like to have
2 comments from the Committee on this particular question.
3 Are there any specific comments? Yes.

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

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

21 And then the situation that Dr. Finlayson was
22 talking about evolved slowly away from it, and then we know
23 we have got two sides of an equation starting to build
24 towards a place where we are protected on all sides.

1 DR. HOLLINGER: Would you want to respond to that,
2 because I thought what you said was that you all have
3 standards, there are standards that you deal with, things
4 that you work on, but that the manufacturers don't
5 necessarily have specific standards of what they might do in
6 terms of looking for the donor, doing followup, and all this
7 other stuff. Am I correct in that?

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

12 I think what Mr. Dubin was asking is why do people
13 make mistakes, and gosh, as one who taught biochemistry for
14 35 years, I sure wish I knew the answer, but the situation,
15 as I would describe, is this. The FDA does put down
16 standards. It says, you know, you will interview donors and
17 you will have a screening program and you will have an
18 interview program which elicits these risk factors,
19 furthermore, you will test for this, and you will test for
20 this, and although we are aware of both "requirements,"
21 which are in the CFR, and recommendations which are put out
22 by memorandum, these are standard practice of the blood
23 banking and plasmapheresis industry.

24 So, those exist, and that is why we have a review

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

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

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

19 Did that help?

20 MS. PIERCE: That actually feeds into my concerns
21 because with acute PP standards and the triple safety net,
22 which is donor screening, donor -- well, donor questions,
23 donor screening, and then the inactivation techniques, in
24 this scenario here for Question 1, we are already talking

1 about when your first two steps of your safety net have
2 failed, and you are down to your third one.

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

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

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

21 Now, putting these two together, one is then faced
22 with what do you do when you do find out, and although there
23 are a number of instances where you don't, but when you do
24 find out that you have a donor, you have a situation where

1 one or more level of safety -- and do you just sit and say
2 while we have the other level of safety that's working, or
3 do you go back and make sure that that level of safety is
4 working and assess the situation. That is how I look at
5 this question.

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

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

16 DR. MARTONE: I would agree with Rima, and in
17 putting all this discussion into perspective, especially the
18 discussion about who we don't know about who is donating
19 these components, I guess all the four questions really are
20 going to boil down to how confident are we that if there is
21 something in there, the inactivation process is going to get
22 rid of it, for one, and that any testing that might be done
23 on the final products is a good test that would determine
24 whether there is any viable agent in that final product.

1 So, it seems to me that all these questions really
2 boil down to that final question, how good was the
3 manufacturer in ensuring that the GMPs were followed, and
4 that is going to be the FDA's responsibility to determine
5 that, and on subsequent testing of the product, is that
6 product safe, because it sounds like it is almost irrelevant
7 whether the person had a risk factor or was positive or
8 negative when they made that donation.

9 DR. HOLLINGER: I think I will bring this to a
10 vote, at least the first question here. The question you
11 have up there is straightforward, you all can read it.

12 How many of the Committee members, by a show of
13 their hands, are in favor of voting yes on Question No. 1?
14 Let me see a show of hands, please.

15 [Show of hands.]

16 DR. HOLLINGER: Those opposed?

17 [Show of hands.]

18 DR. HOLLINGER: Abstaining?

19 [Show of hands.]

20 DR. HOLLINGER: Our representatives. Paul?

21 DR. NESS: I vote in favor.

22 DR. HOLLINGER: Reverend Little?

23 REV. LITTLE: I abstain.

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

1 please, Linda.

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

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

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

15 Yes, Joel.

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

23 So, I find it hard to vote against any of this,
24 but I am not sure what we are doing when we are voting for

1 it other than saying it's like apple pie, but are the
2 techniques available that would then give assurance that
3 once it's released, that the technology is there to actually
4 say we know what the maximum level is.

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

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

23 REV. LITTLE: I absolutely agree with you. In
24 reality, I think the product is probably safe, but then as a

1 consumer, I get this picture, you know, of my son needing a
2 particular lot of blood product, and if faced with the
3 choice of one of the two, which one would I choose, would it
4 in my mind make a difference, and I have to say yes, it
5 probably would. But I agree with you, I think
6 scientifically it probably is safe.

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

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

18 DR. MARTONE: The question I have about this
19 question is what difference does it make -- and I ask this
20 to the FDA -- on your estimate of the maximum level of the
21 contamination whether it is 10^{-5} in that donor or 10^{-8} , is
22 there a cutoff that you are going to have, that you are
23 going to use, and if you are not going to use it, why should
24 that even be relevant?

1 DR. HOLLINGER: Let me come back and ask you. I
2 mean you have looked at this, too, and looked at some of the
3 issues. Do you have a feeling or does anybody on the
4 Committee have a feeling of what you would advise them?

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

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

13 DR. HOLLINGER: I think there was some data that
14 was shown -- you probably recall -- earlier about 10¹⁰ --
15 supposedly, reportedly 10¹⁰ and 10¹⁷ log reductions over a
16 variety of things, at least that is what has been reported.

17 It is sort of an open-ended question obviously,
18 asking the Committee, you know, an assessment of product
19 risk should take into account an estimate of the maximum
20 level of contamination could be associated with the risk
21 factor.

22 DR. EPSTEIN: I think what we are trying to get at
23 is a rational way to come to closure based on things we
24 could measure. I think that, for HIV, we have a simpler

1 situation because we have good assays for measuring virus
2 contamination by PCR, and we have a lot of data including
3 virus detection, but also transmission experiments,
4 culturability, animal studies, that have measured the
5 clearance.

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

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

19 So, for instance, if one could reach the point
20 where one could say that negative PCR means that there are
21 no more than, for argument's sake, 100 copies of viral
22 genome per milliliter, and if we know that inactivation is
23 in excess of, for argument's sake, 5 logs, could we then use
24 these principles to decide we have a safe product.

1 So, we are not really saying that we know all the
2 answers at this point in time. What we are really asking is
3 whether you endorse that kind of logic, and then, of course,
4 we will endeavor to do our best in each case.

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

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

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

20 DR. MARTONE: Maybe my question is simpler than it
21 sounded. Granted, we know what the maximum levels of
22 contamination could be based on the data we have here. Does
23 any of that make any difference for this particular
24 question?

1 In other words, let's assume that every instance
2 of notification could be a potential highest level of
3 contamination possible. Would that make you automatically
4 disqualify that product?

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

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

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

23 One product may be heated in a lyophilized state.
24 Another product may be exposed to a solvent-detergent

1 mixture. Another product may have a lower temperature
2 heating combined with nanofiltration. So, what we are
3 saying is that we would do a risk assessment, but it would
4 be on a product-specific basis.

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

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

9 DR. EPSTEIN: Oh, yes.

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

12 DR. EPSTEIN: That is what I would envision.

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

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

19 I think that it is a step forward to try to add to
20 the analysis, an estimate of potential contaminating titer
21 or a direct measurement, such as through PCR, and we see
22 that as a step forward that would kind of level the playing
23 field. In other words, we would be qualifying pools whether
24 we knew they were contaminated or we didn't know they were

1 contaminated, based on direct knowledge of an upper limit of
2 contamination in relation to viral inactivation. At that
3 point, we would have a consistent logic whether there was
4 inadvertent pooling of a positive unit, a high risk unit, or
5 no known unit, and we would be able to make the same levels
6 of assurance of safety.

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

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

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

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

24 DR. MARTONE: That is correct.

1 DR. HOLLINGER: Yes, I think that is what he said.
2 Let's go ahead and vote on that. All members of
3 the Committee who are in favor of this question, raise your
4 hand, please.
5 [Show of hands.]
6 DR. HOLLINGER: All those opposed?
7 [Show of hands.]
8 DR. HOLLINGER: Abstaining?
9 [Show of hands.]
10 DR. HOLLINGER: Joel, do you want to comment --
11 and I don't want to put you on the spot --
12 DR. VERTER: I felt I had to be consistent with
13 the first one.
14 DR. HOLLINGER: Okay.
15 Beatrice, anything?
16 MS. PIERCE: I agree. It is somewhat consistency,
17 but again it just goes back to my concerns about a lot of
18 issues that I voiced before.
19 DR. HOLLINGER: Corey, anything specific?
20 MR. DUBIN: I think, Blaine, it is coming down to
21 for me we have to pick and choose where we raise certain
22 issues, and there is a certain frustration that I know I am
23 voicing that I feel sometimes there is a bit of a
24 compartmentalization of things here, and I see that here

1 given some of the stuff we know about the last year and what
2 has happened with GMPs and some of the factors, and so I
3 have concerns. On some level, I need to follow those.

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

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

17 DR. HOLLINGER: Rev. Little, how would you vote?

18 REV. LITTLE: I would have to consistently
19 abstain.

20 DR. HOLLINGER: And Paul?

21 DR. NESS: In favor.

22 DR. HOLLINGER: Favor, okay.

23 Could you read the response?

24 DR. SMALLWOOD: The results of the voting are 8

1 yes votes, 1 no vote, 2 abstentions. The consumer
2 representative abstained, and the industry representative
3 agrees with the yes votes. I must also note that Dr.
4 McCurdy, the temporary voting member, was not in the room at
5 the time that the voting took place.

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

10 DR. McCURDY: I would have voted yes.

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

13 [Laughter.]

14 DR. McCURDY: Yes.

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

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

23 Dr. Linden?

24 DR. LINDEN: I don't understand the question, and

1 I would like to request that someone from FDA explain what
2 is meant by a "new scientific issue." Are you saying that
3 it raises no compliance issues, that the risk factor is not
4 something that would need a deferral, or does it mean
5 something other than that, because that is really going to
6 affect the answer.

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

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

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

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

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

1 scientific issue?

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

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

11 I think that the reason for that is that FDA has
12 been separating the issue and that what we have been talking
13 about is in the face of adequate GMP compliance, can we do
14 X, Y, Z. What you have been saying is, well, the record
15 shows that there isn't always adequate GMP compliance.
16 Well, when there isn't adequate GMP compliance, we recall
17 products, and, you know, that is the record that you are
18 talking about.

19 I mean you are looking at the record of recalls
20 and withdrawals and saying, well, look, here are instances
21 of failure of compliance, so, you know, how can we apply
22 risk assessment when there is failed compliance, but in
23 those instances, we do not release product in process, and
24 we do recall distributed product.

1 The thrust of this question is in June, the
2 Committee advised us always to quarantine first, and the
3 Agency has reacted to that advice and said, well, wait a
4 minute, you know, sometimes we have reason to believe that
5 compliance is not at issue, and in addition, there is no
6 novelty to this situation scientifically, what is the
7 benefit of a quarantine.

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

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

22 So, the question is does this mean that if a
23 manufacturer has shown good compliance with everything, that
24 someone is not going to go back and look specifically at

1 this lot, let's say you found out that there was a product
2 from someone, a donor, for example, or even if it was a
3 positive sample that is now in a pool or now been made into
4 a product, that someone is not going to go back and make
5 sure that in the manufacture of that specific product, that
6 there wasn't some breakdown along the way or some potential
7 breakdown?

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

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

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

22 So, for instance, if it was a heating process, and
23 the heating step is, you know, monitored with thermocouples,
24 and the thermocouples are located in 40 locations in a vat,

1 and there is surveillance monitoring of thermocouples, you
2 know, you could argue that, well, we aren't really sure,
3 unless we have gone back and determined that the company
4 monitored all its thermocouples and that indeed there was no
5 problem with that surveillance in that run or the preceding
6 or subsequent run.

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

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

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

24 On the other hand, if you are in an environment

1 where there is a record of good compliance, and where
2 recordkeeping suggests that there are no deviations, then,
3 perhaps the kind of 48-hour look at available records is
4 sufficient.

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

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

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

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

1 DR. HOLLINGER: Yes.

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

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

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

23 The situation with the collection devices and the
24 backwash of saline that impacted the viral testing, and the

1 most explosive of all, which will come up later, is the pool
2 size discussion where for 20 years, we sit, you know, in
3 belief that certain things are going on, and FDA seems to be
4 of that belief, and lo and behold, a congressional committee
5 steps in and holds a series of hearings, and these numbers
6 surfaces that are just shocking, and they are not only
7 shocking to hemophilia, all the other communities have been
8 calling on our 800 number to discuss this.

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

24 So, I think we need to be real clear on both sides

1 about where we are coming from.

2 DR. HOLLINGER: Corey, I think your comments sound
3 appropriate. Give us from your example what you would do
4 with this question. Is it a matter of timing? What things
5 would you suggest that perhaps would be beneficial here? I
6 guess that is the real question here.

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

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

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

24 DR. MARTONE: Let me voice the opposite opinion.

1 I am very uncomfortable with this recommendation. I am
2 uncomfortable because you are dealing -- in the first
3 instance, you are making the assumption, when you don't get
4 notification, that all the systems are in place, the company
5 has good GMPs, and you are issuing safe and good products.

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

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

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

22 DR. HOLLINGER: Thank you. Jerry.

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

1 seven-month investigation?

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

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

18 Now, if in that period we cannot determine that
19 there was adequate GMP compliance, investigations would be
20 ongoing for however long they take. So, I think the logic
21 is, you know, maybe we are communicating it backwards. We
22 are not saying we are going to render judgments in all cases
23 in 48 hours. We are saying can we get some reasonable
24 latitude during which if we can make a judgment, we can

1 avert quarantine. Otherwise, in all incidents -- I mean the
2 advice we got from this committee in June, all incidents
3 would trigger recalls and withdrawals. We think that is an
4 untenable position.

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

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

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

24 So, it is not possible to give you one uniform

1 answer. I mean the answer may be that a particular
2 manufacturer was recently and extensively inspected, and it
3 may be that another was not so recently inspected, but they
4 would all have been inspected. In fact, we have inspected
5 all fractionators distributing U.S. products since January
6 of '97, so that they have all had an inspection in that time
7 frame, 100 percent.

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

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

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

21 DR. HOLLINGER: Yes, Dr. Linden.

22 DR. LINDEN: It seems that if we vote yes on this,
23 what we are saying is that if properly performed, the viral
24 inactivation processes will completely eliminate the well-

1 studied lipid-enveloped viruses, and it seems that we are
2 saying it is therefore okay to dispense with the evaluation
3 that we just talked about in the risk assessment in
4 Questions 1 and 2.

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

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

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

23 DR. EPSTEIN: Again, the recommendation in June
24 was to make no distinction between in-house and distributed

1 product, so, you know, we don't have the luxury based on
2 that recommendation to consider holding distribution, and
3 not recalling distributed product.

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

12 DR. HOLLINGER: What would be the alternative?

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

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

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

1 DR. HOLLINGER: Paul.

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

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

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

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

22 The other thing is that the way it is worded gives
23 the implication that there isn't going to be any
24 investigation of the company that makes this product, and

1 that is the part I have the biggest problem with.

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

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

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

1 DR. HOLLINGER: Joel.

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

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

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

1 negative donors who have had some risk factors. I mean that
2 would be the other issue.

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

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

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

16 DR. HOLLINGER: Dr. Khabbaz.

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

22 DR. EPSTEIN: I would prefer that the question
23 apply both to risk history and positive unit. If the
24 Committee is uncomfortable lumping them for whatever reason,

1 then, certainly today's discussion was focused on risk
2 history, but I think that we are really dealing with similar
3 risk assessments in both kinds of incident.

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

8 DR. HOLLINGER: Say that again, Jeanne.

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

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

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

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

23 DR. LINDEN: We are talking about positive --

24 DR. KHABBAZ: This encompasses both.

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

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

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

19 DR. HOLLINGER: Yes.

20 MS. PIERCE: In terms of that, I guess one of my
21 concerns is that we are talking about risk factor here, but
22 in 48 hours, you are not going to be able to really
23 determine whether that risk factor actually equates a
24 positive unit or not, of it is just a risk factor, because

1 of window periods and things like that, and you are not
2 going to be able to get that additional information in 48
3 hours.

4 DR. HOLLINGER: Dr. Verter.

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

16 DR. EPSTEIN: That is correct.

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

21 DR. VERTER: Let's take it to an extreme, be
22 absurd. I will be absurd. If every one who contributed to
23 everything that is out there was swearing on a stack of
24 Bibles and anything that he held sacred, it would seem to me

1 everything out there would be recalled or quarantined from
2 what I have heard today.

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

17 Yes, please.

18 DR. KHABBAZ: Can I propose rephrasing the
19 question?

20 DR. HOLLINGER: How would you rephrase it?

21 DR. EPSTEIN: Jerry already proposed some
22 rephrasing.

23 DR. HOLLINGER: Yes.

24 DR. KHABBAZ: Rather than recent record, the

1 manufacturer has an excellent recent record -- what was the
2 wording that you used?

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

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

7 DR. HOLLINGER: Which is vague?

8 DR. MARTONE: "No new scientific or GMP issues."
9 I mean somebody sitting in an office could look at a report
10 and say, okay, there is no new scientific or GMP issues
11 here, let's get on with it.

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

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

18 DR. HOLLINGER: Dr. Linden.

19 DR. LINDEN: I still have the same problem that
20 unless the question is going to be rephrased to include the
21 risk assessment, I think to say yes to this is completely
22 inconsistent with having voted yes on Question No. 1, which
23 is that we said that there has to be an investigation to
24 assess product risk in order to determine regulatory action,

1 and here we are saying we are going to determine regulatory
2 action without doing that risk assessment.

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

7 Yes, Bill.

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

13 DR. EPSTEIN: Yes.

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

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

23 DR. MARTONE: But you would get a feel for that
24 while you were there, you would go there and you would look

1 at --

2 DR. EPSTEIN: Or maybe just from the lot release
3 record. I mean not everything requires going to the plant.

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

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

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

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

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

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

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

23 MR. DUBIN: Jay, I can substantiate that you have
24 called us late Friday night and worked through the weekend

1 and had conversations and the company has called.

2 DR. FINLAYSON: I must again confess that I have
3 not sat down and in cold blood -- bad pun -- read 21 CFR
4 211, however, according to GMPs, these same GMPs that tell
5 you that you have to keep records, and you have to have
6 sufficient illumination, and so forth, it also says thou
7 shalt have a quality controlled unit, and that quality
8 controlled unit shall do certain things, and among the
9 things that that quality controlled unit -- and we extend
10 that to quality control/quality assurance you shall do -- is
11 review the back records of every single lot before it is
12 ever turned loose.

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

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

20 So, it isn't that nothing is happening in the
21 company, and as Jay says, it doesn't matter whether it is
22 Friday afternoon, in fact, it seems that it is Friday
23 afternoon, that the risk assessment would begin at that time
24 on our part, as well.

1 But I sort of perceived that this role of the
2 company's quality control/quality assessment function was
3 not appropriately appreciated.

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

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

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

11 Yes, Paul.

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

20 The inspection is also totally random, so any
21 prudent manufacturer is going to be doing these things
22 continuously anyway. So, it seems to me that, you know,
23 within 48 hours, with a known inspection program, which
24 occurs at some frequency, that one could verify that, in

1 fact, this company is operating under control.

2 DR. HOLLINGER: Good point.

3 Jay, do you have that?

4 DR. EPSTEIN: I am almost there.

5 DR. HOLLINGER: Okay.

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

12 DR. NESS: In general, very little.

13 DR. HOLLINGER: Thank you.

14 [Overhead.]

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

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

22 DR. PILIAVIN: Why?

23 MS. PIERCE: Why? Because I think that the issue
24 comes up that some of this is random and that going on the

1 fact that they have a recent good record does not exclude
2 the fact that something can go wrong in the manufacturing
3 process.

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

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

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

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

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

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

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

24 DR. EPSTEIN: I think there was loose use of words

1 here. We would quarantine product under the control of the
2 manufacturer. The issue really is whether to act against
3 distributed product.

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

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

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

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

24 So, my feeling is that if you are going to

1 quarantine it at one level, to be consistent and I think
2 most ethical, you have got to quarantine it across the
3 board.

4 DR. HOLLINGER: Without recall?

5 DR. AUGUST: Without recall, but just --

6 DR. HOLLINGER: Just hold, quarantine hold.

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

13 DR. HOLLINGER: Yes, Bill.

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

19 DR. HOLLINGER: "Determined by suitable" --

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

22 DR. EPSTEIN: It could be epidemiologic also.

23 DR. MARTONE: Then, manufacturer and epidemiologic
24 just because you haven't explicitly stated yet in this

1 question the concept of investigating the manufacturer.

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

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

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

23 So, I mean you get to vote in favor or against,
24 but sort of that is the point.

1 DR. HOLLINGER: Let's call for the question then.
2 All those in favor of the question as currently written,
3 raise you hand, please, all those in favor.

4 [Show of hands.]

5 DR. HOLLINGER: All those opposed?

6 [Show of hands.]

7 DR. HOLLINGER: All those abstaining?

8 [Show of hands.]

9 DR. HOLLINGER: Paul?

10 DR. NESS: I would vote in favor.

11 DR. HOLLINGER: And Rev. Little?

12 REV. LITTLE: I would be opposed.

13 DR. SMALLWOOD: The results of voting for Question
14 No. 3. Four yes votes. Six no votes. Two abstentions.
15 The industry representative agrees with the yes vote. The
16 consumer representative agrees with the no vote.

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

22 [No response.]

23 DR. HOLLINGER: No discussion on this. I have a
24 problem with it. It just says, "on the donor or the pool."

1 It says, "Does the Committee agree that a negative nucleic
2 acid test or other additional assay on the donor or the pool
3 can be used to obviate the need to destroy a pooled
4 product?"

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

10 Bill?

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

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

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

24 DR. EPSTEIN: If I could comment, Blaine?

1 DR. HOLLINGER: Yes.

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

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

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

15 DR. HOLLINGER: Paul.

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

21 The way the question is sort of phrased implies
22 that it is only yes/no, which I don't think is your intent,
23 and so I think if we broadly interpret it, then, I certainly
24 would favor that these kinds of tests on the donor or the

1 pool should be used and may be useful additional information
2 in terms of making the appropriate medical and regulatory
3 decision.

4 DR. HOLLINGER: Let's bring this to a vote also.

5 All those in favor of this question, so signify by
6 raising your hand.

7 [Show of hands.]

8 DR. HOLLINGER: All those opposed?

9 [No response.]

10 DR. HOLLINGER: Dr. Ness?

11 DR. NESS: In favor.

12 DR. HOLLINGER: Rev. Little?

13 REV. LITTLE: Favor.

14 DR. HOLLINGER: Could you read the responses?

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

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

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

AFTERNOON PROCEEDINGS

[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

1 International Plasma Products Industry Association or IPPIA
2 in conjunction with American Blood Resources Association or
3 ABRA to improve the blood collection and manufacturing of
4 plasma products.

5 [Slide.]

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

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

16 [Slide.]

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

23 [Slide.]

24 The next standard that I have listed -- these

1 might not be quite in the order that IPPIA has, and we will
2 get to that later on -- is an inventory hold.

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

8 [Slide.]

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

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

22 It is important to remember that these voluntary
23 standards are above the minimum required by current
24 regulations and thus do, in fact, represent an advancement.

1 At the same time, they are not as complete as they might be,
2 and after the IPPIA presentation, the FDA will present its
3 commentary on these standards.

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

8 [Slide.]

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

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

24 These are just some of our concerns, but at the

1 same time, we urge you to keep in mind the positive aspects
2 of these proposals.

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

5 **Presentation of Proposal: IPPIA Representatives**

6 **Douglas Bell**

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

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

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

24 Before the technical presentations begin, I would

1 like to briefly outline for you the role of IPPIA and its
2 relationship with ABRA. It is also worth noting that the
3 IPPIA is affiliated with the European Association of the
4 Plasma Products Industry which represents the vast majority
5 of the commercial fractionation industry in Europe.

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

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

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

24 Because of the unique way source plasma is

1 collected and our membership being exclusive to the
2 "commercial" sector, our Voluntary Initiatives that exceed
3 FDA regulatory requirements do not apply to those that
4 exclusively collect or fractionate plasma recovered from
5 whole blood collection.

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

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

16 As a result, industry drafted four Voluntary
17 Initiatives that focus on minimizing the risk of "window
18 units." We determined that there were three primary
19 opportunities for window units to enter the manufacturing
20 process: units of plasma from previously untested, one-time
21 donors; previously collected negative units of plasma from
22 repeat donors who subsequently seroconvert; and units of
23 plasma collected from repeat donors who have tested negative
24 but do not return after their last donation.

1 We have developed an industry initiative to
2 address each of these theoretical threats from window units
3 and also developed a standard to institute new, more
4 sensitive testing technology to further close the window
5 period.

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

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

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

22 Now Jim Reilly will discuss the QPP program. I
23 would ask that you hold any questions until the end of our
24 presentation and that each of our speakers will remain in

1 the front to answer any of your questions.

2 Thank you.

3 **James Reilly**

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

5 [Slide.]

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

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

19 [Slide.]

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

24 First, the program was established in 1991. We

1 actually began discussions I think as much as two years in
2 advance of that for some portions of it. QPP has 380 of the
3 413 eligible centers -- the typo there should be 413, and
4 not 410. To place this in a more meaningful context,
5 roughly 1.5 million donors donate plasma 13 million times a
6 year. Of those, about 12 million of them are at certified
7 centers. It results in total in about 11 million liters of
8 plasma.

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

14 To put the worldwide market into perspective, the
15 11 million liters produced here in the U.S. is roughly 60
16 percent of the entire world supply, and it has been widely
17 recognizable.

18 [Slide.]

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

22 The employee training standards that we have were
23 upgraded once and the minimum educational requirements were
24 added to them when we did that.

1 The National Donor Deferral Registry -- which I
2 will explain in some more detail later -- has received
3 several relatively minor to major, depending on your point
4 of view, software upgrades since 1992, when it was entered
5 in as a pilot program. It has also more recently, on March
6 the 20th, 1997, received FDA 510(k) determination of
7 substantial equivalence, which would allow us to market it
8 as a device if the association so chose to.

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

16 [Slide.]

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

22 [Slide.]

23 First, facilities must have a formal training
24 program. The QPP provides guidance by dictating the

1 components of the program, such as initial, annual and
2 interim training; documentation; retraining; and that all
3 functions in the center are covered in the training
4 requirements.

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

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

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

22 As you know, the unknown is very difficult, if not
23 impossible, for us to quantify until it becomes a known, but
24 we believe these do help us in that endeavor.

1 The additional screening criteria we require
2 include increased emphasis on donor education of high risk
3 activities, exclusion for incarceration, and drug testing.

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

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

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

21 [Slide.]

22 Finally, each facility is required to submit
23 specific documents and data for review related to the
24 standards, and they are subject to both a biennial as well

1 as random inspections by third party.

2 [Slide.]

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

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

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

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

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

23 [Slide.]

24 Finally, before I turn the microphone over to my

1 colleague, Dr. Waytes, you should also be aware that we
2 don't view the QPP, the current voluntary standards, or any
3 of the industry's programs as stagnant. This slide is
4 simply a list of the initiatives we currently have in
5 various stages of discussion and implementation.

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

13 [Slide.]

14 Next, Dr. Waytes will describe several new
15 industry voluntary standards, which I think Mark was kind
16 enough to already lay out in summary. Two of these, which
17 are related to the plasma collection portion of the product
18 manufacturing process, will or have become QPP standards.
19 They are the use of plasma from non-returning applicant
20 donors from further manufacture, which became effective
21 actually in July of this year as a QPP standard, and the new
22 viral marker rate standard which will be based specifically
23 on confirmed positive viral marker tests from Qualified
24 Donors.

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

7 [Slide.]

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

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

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

23 [Slide.]

24 By definition, Applicant Donors are described as

1 all individuals presenting themselves who have not been
2 previously qualified as a donor in the past six months.

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

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

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

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

1 medical history screening questionnaire.

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

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

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

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

19 This standard also ensures that at least two
20 acceptable virus screening panels are performed on each
21 prospective donor, which reduces the probability of testing
22 error, and, to a lesser or greater degree, depending on the
23 interval between samples, reduces the window period for each
24 virus.

1 In summary, the use of plasma from one-time donors
2 is completely eliminated through this initiative. Through
3 this standard, industry is also able to retrospectively
4 assess the acceptability of initial donations with
5 subsequent interviews and test results.

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

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

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

21 All participating centers are committed to have
22 begun to perform confirmatory testing of anti-HCV, anti-HIV,
23 Hepatitis B surface antigen as of July of this year. From
24 this date, the confirmed reactive rates of Qualified Donor

1 units obtained at this each center will be collected for
2 each of the three viral markers.

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

11 [Slide.]

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

17 Retrospective data as collected prior to July of
18 this year from varying time periods ranging from 6 weeks to
19 6 months from all industry laboratories. This data
20 represents a total of 3.175 million donations collected from
21 nearly all industry plasma centers and is shown as follows:

22 [Slide.]

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

1 0.0112 percent.

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

10 [Slide.]

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

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

23 By holding all seronegative units in an inventory
24 hold, this standard provides manufacturers with the

1 opportunity to retrieve units from previously qualified
2 donors who seroconvert on a subsequent donation, or are
3 otherwise disqualified. Thus, window period units, as those
4 shown in this illustration, can often be prevented from
5 entering the manufacturing pools.

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

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

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

23 PCR testing. The fourth Voluntary Initiative is
24 the implementation of Genome Amplification Technology,

1 commonly known as Polymerase Chain Reaction or PCR. This
2 technology can further reduce the window period by
3 identifying potentially infectious units which fall below
4 the detection threshold of existing donor screening and
5 testing technologies. Each of the manufacturers is working
6 closely with the FDA and other affected parties to obtain
7 the required agency approvals necessary to implement PCR
8 technology as rapidly as possible.

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

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

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

1 based therapies.

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

5 I will turn the mike over to you.

6 **Douglas Bell**

7 MR. BELL: Thanks, Tom.

8 [Slide.]

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

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

21 In our testimony this summer before Congressman
22 Shays, Human Resources Subcommittee, we outlined seven
23 layers of safety in the manufacture of plasma-based
24 therapies. The uniqueness of fractionation allows for these

1 additional layers of safety. We believe that these layers
2 of safety are fundamental to achieving the level of safety
3 our patients expect and need.

4 [Slide.]

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

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

21 What we are pursuing -- and what we committed to
22 at Chairman Shays oversight hearing -- is a comprehensive
23 plan that builds upon the seven layers of safety. A
24 comprehensive plan that will review the existing initiatives

1 to measure their progress, assess the need for new
2 initiatives, and communicate to key individuals our
3 objectives and the progress that we have made.

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

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

13 [Slide.]

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

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

24 [Slide.]

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

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

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

18 As providers of plasma-based therapies we are, and
19 must continue to be, leaders in the commitment to safety.
20 It is a responsibility that we take very seriously. The
21 message we are sending through these voluntary initiatives
22 and our commitment to this comprehensive plan should be
23 clear: Industry is dedicated to continuous improvement, so
24 that the people who depend on plasma-based therapies for

1 their health and their very lives will know that those
2 therapies are safe, available, and effective.

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

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

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

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

19 DR. HOLLINGER: Thank you.

20 I think what we will do, if the Committee doesn't
21 mind, I think I will go on and have the FDA commentary on
22 the proposal first, and perhaps even go into the comments
23 from the group before making we can respond. Is that all
24 right with the Committee?

1 Why don't we have the FDA's commentary and then we
2 will move forward.

3 **FDA Commentary on Proposal**

4 **Paul Aebersold, Ph.D.**

5 DR. AEBERSOLD: My name is Paul Aebersold. I am
6 in the Division of Blood Applications. I will start the
7 commentary. There will be three speakers, as Dr. Weinstein
8 indicated.

9 [Slide.]

10 First, to comment on the inventory hold, I would
11 actually comment on all of the proposals. They are
12 definitely very positive steps to reduce the frequency of
13 window period donations from getting into the manufacturing
14 stream.

15 That is the underlying comment about the
16 proposals, but let me say about the inventory hold, that in
17 an ideal world, I think we all know what the inventory hold
18 would be. It would be a period of time that was longer than
19 the window periods for these three viruses, and any unit
20 would be released only when a donor subsequently returned
21 after the longest window period, 89 or 90 days, or something
22 like that, than the previously released unit older than that
23 age would be released.

24 This would mean essentially that only units would

1 be used for whom a subsequent test existed past the longest
2 window period. That is the idea situation. There is a lot
3 of impracticalities about it, not the least of which would
4 be that anytime a donor dropped out of the donor pool, since
5 they wouldn't be coming back, you would lose a number of
6 units.

7 In terms of a commentary on this, as probably the
8 ideal perhaps not being practical, the question would be is
9 the 60 days long enough to encompass the window periods. Of
10 course, again, there is no guarantee that a donor would be
11 returning before the product was released. As it stands,
12 the product would be released at 60 days whether or not
13 there was a subsequent test for qualified donors.

14 [Slide.]

15 We will look at the next slide. The applicant
16 standard. These are also, of course, under the 60-day hold,
17 inventory hold. Again, eliminating plasma for which the
18 donor never returns, not using that is a positive step based
19 on the numbers that were given that 95 percent of the
20 positive tests come from a small percentage of donors who
21 are the first-time donors, this would be expected to reduce
22 the number of window period donations entering the
23 manufacturing stream.

24 The business of qualifying the donor by two tests,

1 as Dr. Weinstein gave you a preview, that raises the
2 question of what time frame should be considered between
3 these two tests for a person to be considered a qualified
4 donor. I gathered -- I should say I am substituting for
5 someone who is on jury duty, and I am not in the plasma
6 collection business myself -- but my understanding is that
7 the time between donations could be two donations in a week
8 or something like that, and then the question that comes up
9 is, is this a suitable period, have you really learned that
10 much more about a donor to qualify that person because they
11 came back twice in a week, or are they twice as desperate
12 for money on the other side of things, would one want to see
13 a longer period between donations to consider someone a
14 qualified donor.

15 One could conceive perhaps that an absolute
16 quarantine or hold for the long window period time, although
17 maybe not practical for every donor, might be something that
18 could be considered for first-time donors to enter them into
19 the qualified pool, so that you would actually get a second
20 test past the window period donations before you would
21 consider them a qualified donor.

22 This would have a down side, of course. There may
23 be more plasma units that couldn't be used.

24 [Slide.]

1 The last part of the QPP program that I will say
2 anything about is the viral marker rate standard, and I
3 guess this is like apple pie, of course, one is in favor of
4 it. I guess the questions that the FDA would most likely
5 have to ask would be how is it handled if one of the
6 collection centers falls outside these bounds, how do they
7 take corrective action to ensure a better marker rate
8 standard or compliance in the future, how would they change
9 their donor recruitment, for example, if they fell out of
10 bounds, and, of course, in the memo that was in the BPAC
11 package, the question was asked what about first-time
12 centers, since they are going to have first-time donors, you
13 would expect their rates to be higher. So, we don't have
14 probably all of the information about how this program would
15 work for first-time centers or for centers what fall out of
16 compliance, and yet obviously, it is a very desirable thing
17 to hold the rate of positive donors down as much as
18 possible.

19 Dr. Hewlett will talk about the PCR testing.

20 **Indira Hewlett, Ph.D.**

21 DR. HEWLETT: Good afternoon.

22 [Slide.]

23 I am going to present a critique and an FDA
24 response on the aspect of the proposal that talks about

1 implementation of gene amplification technology.

2 [Slide.]

3 The IPPIA proposal does talk about implementation
4 of gene amplification technology, specifically, PCR testing
5 with an eye towards early detection of the infectious agent
6 and reduction of the window period.

7 They also are currently working with FDA to
8 implement testing. However, the proposal does not provide
9 any details on assay methodology, on the standards that will
10 be placed for PCR testing, and algorithms for testing, as
11 well as how donor notification of positive results will
12 occur.

13 [Slide.]

14 FDA's current perspective and thinking is that
15 nucleic acid testing is perhaps the most sensitive method
16 currently available for early viral detection. Nucleic acid
17 testing would result in reduced viral burden in blood and
18 plasma, and this is a good thing.

19 The plasma industry has proposed, however, testing
20 plasma pools rather than single donations for the presence
21 of viral nucleic acid. Part of the reason for this is that
22 pool testing may be the most practical at this time given
23 the state of the technology and the rapid evolution of this
24 technology.

1 [Slide.]

2 FDA believes and recognizes that plasma pool
3 testing implementation is in the best interests of public
4 health. We also believe that it is an interim step toward
5 single donation testing, which we hope will be the future in
6 terms of donor testing.

7 The test is considered to be a donor screen
8 because donors are being tested in the process of generating
9 plasma pools, and as a result and consistent with our
10 approach in the past with regulation of donor screening
11 assays, these tests will be evaluated under the IND/PLA
12 mechanism for licensure.

13 The purpose of the review under this mechanism is
14 to establish manufacturing consistency of the test, as well
15 as to establish the performance characteristics of the
16 assay.

17 [Slide.]

18 An integral part of pool testing would be donor
19 notification, and the issues here have to do with the public
20 health benefit that is derived from donor notification
21 including treatment and prevention of subsequent viral
22 transmission. Therefore, we believe that plasma pool
23 testing while being implemented should occur in concurrence
24 with procedures for donor notification and deferral, as well

1 as product retrieval.

2 [Slide.]

3 I am going to very briefly outline some of the
4 regulatory concerns in regard to the test methodologies, and
5 I have actually spoken in greater detail about this at a
6 previous meeting of this committee.

7 So, to summarize the issues, the key issues have
8 to do establishing a rationale for the pool size, taking
9 into account its impact on test sensitivity. Although FDA
10 has not yet defined a specific lower limit of detection, the
11 current thinking is that the lower limit should ideally be
12 below 100 copies per ml.

13 The test should also be evaluated for clinical
14 sensitivity and specificity in addition to analytic
15 sensitivity, and test sensitivity should be established for
16 viral variance, and this, of course, will be determined by
17 the design of primers and probes used in the assay.

18 [Slide.]

19 Other regulatory concerns include establishment
20 and evaluation of sample and reagent stability, the
21 reproducibility of the assay, the effect of interfering
22 substances in generating either false positive or false
23 negative results, which is of particular concern in a pooled
24 matrix.

1 In addition, the issue of controls is important
2 with pool testing, of course, and PCR testing, one has to be
3 concerned about controls for contamination, as well as
4 internal controls that would ensure that the assay has, in
5 fact, been performed as expected and described.

6 Other issues have to do with the establishment of
7 quality control methods that would monitor manufacturing
8 consistency.

9 [Slide.]

10 Finally, validation of the pooling matrix is, of
11 course, very critical. We have seen in our discussions with
12 industry a variety of pooling matrices and pool sizes, and
13 that this of course has to be validated including validation
14 of mechanisms that would allow tracing of positive results
15 back to the original donation and to the donor.

16 This type of setup, of course, would necessarily
17 involve software and instrument use, and validation of both
18 software and instrumentation should be provided by the
19 industry.

20 In addition, since this product or this type of
21 testing will fall under the IND mechanism for review, the
22 test methodology of course will fall into the category of
23 tests that would be under lot release requirements using
24 CBER panels.

1 [Slide.]

2 In the next couple of slides, I would like to
3 outline some proposed regulatory options that are under
4 consideration by the FDA, and this of course is an effort
5 that FDA has taken on to facilitate implementation of PCR
6 testing.

7 The first option is one where the blood product
8 manufacturer would take on full responsibility for the
9 testing. The manufacturer would submit the IND and the PLA,
10 and assume responsibility for the quality of the test.
11 Other manufacturers wishing to use the test would then file
12 PLA supplements for each product, and the test method would
13 be subject to lot release testing to monitor test
14 performance.

15 [Slide.]

16 In the second option, the blood product
17 manufacturer may choose to send plasma or pools to a testing
18 laboratory. The testing laboratory would submit then the
19 IND and the PLA toward licensure, and licensure would then
20 permit labs to test for multiple customers.

21 The blood product manufacturer would then submit
22 individual PLA supplements for each product, and the test
23 lab would then come under lot release surveillance.

24 [Slide.]

1 In a third option -- I do want to emphasize that
2 all of these options are proposed and are under discussion,
3 and comments will be solicited from the industry -- the
4 third option is one where the blood product manufacturer
5 develops an in-house test as a manufacturing control.

6 In this instance, any reactive specimens that are
7 identified would be tested by an independent laboratory, and
8 this would be set up in the framework of shared
9 manufacturing between the testing laboratory and the blood
10 product manufacturer.

11 The main concern and the important point here is
12 that the in-house test should be no less sensitive
13 analytically than the outside test lab method. The blood
14 product manufacturer and the testing lab then submit INDs
15 and PLAs, and the combined test method is then licensed as a
16 donor screen.

17 [Slide.]

18 In the last option, the blood product manufacturer
19 would use a test kit developed independently for pool
20 testing. The test kit manufacturer and the blood product
21 manufacturer would submit separate INDs and PLAs, and the
22 test is then licensed for the specific intended use, which
23 in this instance is pool testing, and for the use for which
24 adequate clinical data is provided. Again, the test kit in

1 this instance would be subject to lot release testing.

2 [Slide.]

3 In summary, FDA's view is that implementation of
4 nucleic acid testing in the form of plasma pool testing is
5 in the best interest of public health, although we see that
6 this is an interim step towards single donation testing in
7 the future.

8 As a validation, should be evaluated under the
9 IND/PLA mechanism, consistent with other donor screening
10 tests, since we have established at this point that this in
11 fact is a donor screening mode.

12 Finally, testing or implementation of plasma pool
13 testing is expected to occur in conjunction with donor
14 notification of positive test results.

15 I would like to conclude by saying that the
16 options that were presented, the last four options that were
17 presented are in fact part of a Federal Register notice that
18 is being drafted at the FDA and will be circulated for
19 comment, so what you are seeing here is in fact the current
20 thinking of the FDA in terms of plasma pool testing, and the
21 mechanisms that we have explored under the regulatory
22 purview that this set of products would fall under to
23 facilitate the implementation of PCR testing and gene
24 amplification testing for the testing of plasma pools.

1 Thank you.

2 I think the next speaker is Tom Lynch.

3 **Thomas Lynch, Ph.D.**

4 DR. LYNCH: Good afternoon.

5 [Slide.]

6 This subject, pool size limitations in
7 manufacturing plasma derivatives, is a subject that we have
8 brought before the Committee before, the most recently in
9 December 1996.

10 It may be useful to review that initiative now
11 before we go on to review the current IPPIA proposal. In
12 brief, FDA came forward with a system that has several key
13 features. Number one, in addition to suggesting that limits
14 should be proposed, we suggested that those limits be phased
15 in over a period of time.

16 Second, we proposed recognizing a difference
17 between products made from source plasma and those made from
18 recovered plasma, and set different limits for those two
19 categories.

20 Third, we suggested that the pool size be measured
21 in terms of donors rather than donations or volume.

22 Fourth, in doing this bookkeeping, we suggested
23 that donors contributing to the albumin that may be added as
24 a stabilizer excipient were even added to an in-process

1 material during manufacture, not be included in the final
2 total.

3 Fifth, recognizing that some products are
4 different from other products, we proposed a mechanism by
5 which exemptions might be granted for particular products
6 where the limits were either impractical or would adversely
7 affect the quality of a product.

8 This was debated rather energetically in December,
9 both the effectiveness of these measures and their impact on
10 product availability and cost were called into question.

11 The FDA undertook an information gathering process in an
12 attempt to assess actual manufacturing practices among the
13 nine largest plasma fractionators who hold U.S. licenses.

14 That process is ongoing, however, we have received
15 some preliminary data from the firms in question.

16 [Slide.]

17 Over the past month of six weeks, FDA has also
18 received a proposal from IPPIA to institute a voluntary
19 limit of 60,000 donors. Notably, this limit would apply
20 across the board to both recovered and source plasma. It
21 would include in the sum, donors who contribute to the
22 manufacturer of the active ingredient of a product, as well
23 as any stabilizing protein that may be added to it.

24 Finally, the proposal that FDA has received

1 specified that this limit would apply to the major products.

2 As I see it, this proposal does have two main
3 virtues. Clarity is one. It is a very simple because it
4 does not propose a complex multi-tiered program. The limit
5 is easily understood. Therefore, compliance with it, should
6 this limit be adopted, would be simplified.

7 Secondly, we may assume that this limit is
8 practically achievable since it comes from a major segment
9 of the industry itself. However, I would ask you to bear in
10 mind that not all U.S.-licensed plasma fractionators are
11 members of IPPIA, although those members do account for the
12 bulk of the market for plasma fractionated products.

13 [Slide.]

14 Just a brief side-by-side comparison points out
15 certain differences that are already fairly apparent. Both
16 FDA and IPPIA agrees that donors are an appropriate measure
17 of pool size for a variety of reasons, however, the number,
18 the gross numbers do differ in some respects.

19 However, those differences are not easy to resolve
20 because of, first of all, the FDA proposal initially
21 encompassed only the active component in any given product
22 whereas the current industry proposal includes the active
23 component and any excipient protein added.

24 The differentiation between sources and recovered

1 plasma that was part of the FDA program has been eliminated
2 in favor of a single limit, and while the FDA proposal
3 explicitly encompassed all plasma derivatives and the
4 industry proposal suggest perhaps only major products are
5 included, in fact, this may be a difference without a real
6 distinction, since most of the "minor" plasma-derived
7 products are manufactured from smaller pools. There is a
8 point of clarification there.

9 Finally, the time frame for implementation, we
10 initially suggested a three-month and 12-month period of
11 implementation. Of course, those limits have largely been
12 mooted by intervening events. Nonetheless, the time frame
13 for the current proposal is not clear, at least to me.

14 [Slide.]

15 In terms of evaluating the numeric limits, one
16 must consider separately products that are made with and
17 without albumin or other stabilizing protein in the process.
18 I will turn first to the ones that include albumin. That
19 would be intravenous immunoglobulin and anti-hemophilic
20 factor. These products are currently formulated with
21 albumin and of course would add, under certain
22 circumstances, to the effective pool size, the donors that
23 are represented in any given final container of product.

24 In this context, the 60,000 proposed limit is at

1 or near what I would term a hypothetical industry limit or
2 industry average as it exists today. By "hypothetical," I
3 mean that number of donors in a manufacturing pool that one
4 would arrive at by considering the average size of a plasma
5 pool from which the active ingredient was derived and the
6 average size of a plasma pool from which the excipient is
7 derived.

8 That is not always the case. In some cases, the
9 addition of stabilizer may increase the effective pool size
10 by a larger proportion, and in some cases, by lesser
11 proportion. It depends on the precise number of donors that
12 contributed to the particular lot of albumin used as a
13 stabilizer.

14 That notwithstanding, the 60,000 donor limit would
15 in fact reduce pool size by eliminating the occasional
16 exceptionally large plasma pool that a given lot of product
17 may be manufactured, and by eliminating the above average
18 pools, the fairly routine manufacture, that may occur above
19 the 60,000 donor limit.

20 [Slide.]

21 Turning to those products that are not formulated
22 with any stabilizer, the 60,000 donor limit appears to be
23 substantially above the average pool size as it currently
24 exists for most manufacturers, for most products.

1 Now, I hasten to point out that that is not
2 necessarily true for plasma derivatives manufactured from
3 recovered plasma, but with that caveat in mind, we are
4 looking at numbers substantially larger than current
5 industry practice on average.

6 Nonetheless, the occasional exceptionally large
7 pool does exist for these products, and the 60,000 donor
8 limit would eliminate those. It is a concern of ours that a
9 60,000 donor limit, however, would permit increases in scale
10 from what is currently practiced, and would ask whether or
11 not a cap at current levels would not be appropriate.

12 If it was decided that capping current industry
13 practice at its current level is an appropriate thing to do,
14 the issue of how to define that cap comes up, and this is
15 not an issue that we have resolved yet.

16 [Slide.]

17 Other unresolved issues regarding this proposal is
18 the time frame for implementation. We are not sure exactly
19 how soon this limit can be adopted, whether it is
20 appropriate to allow this restriction to be entirely
21 voluntary or whether it should be folded into some sort of
22 formal regulatory mechanism, such as a change to a product
23 license.

24 The exact scope of the proposal is also not clear,

1 whether it is intended to be restricted only to the "major
2 products," or whether all plasma derivatives should be
3 included, and finally, because this proposal derives from a
4 trade association that does not encompass all U.S.
5 licensees, it is not clear whether the non-members, the non-
6 IPPIA members, do in fact endorse this limit.

7 [Slide.]

8 Finally, we would ask whether or not a distinction
9 between source and recovered plasma is appropriate. We are
10 given to understand that it may in fact be possible to
11 maintain the use of recovered plasma at the 60,000 donor
12 limit. Eliminating the distinction that was proposed in
13 December of '96 would of course eliminate the issue of
14 whether such a distinction can be scientifically justified.

15 Finally, the question of whether or not FDA should
16 continue to evaluate this manufacturing issue and
17 contemplate additional measures in the future should those
18 become appropriate.

19 Thank you very much.

20 **Open Public Hearing**

21 DR. HOLLINGER: There are four additional speakers
22 in the open public hearing that want to speak on this issue
23 also, so I think we will have those four go ahead and give
24 their talks, but I would have you limit this to no more than

1 eight minutes a person. We have 30 minutes designated here,
2 and the first one will be by Kathy Miles Crews from the
3 Immune Deficiency Foundation.

4 MS. CREWS: Good afternoon. I am Kathy Miles
5 Crews. I am a member of the Immune Deficiency Foundation
6 National Board of Trustees, and I am President of the Texas
7 Gulf Coast Chapter. I am also the parent of an immune
8 deficient adolescent, and I have two brothers who have
9 primary immuno deficiencies. So, this is something that I
10 have lived with for a long time.

11 Growing up I watched my younger brother suffer
12 from chronic illness. Their physicians suspected that the
13 immune deficiencies that ran in our family were possibly
14 genetically linked. Concerned with this possibility, I
15 hesitated to have children. With the advent, though, of
16 IVIG, my brothers' quality of life changed for the better,
17 and I found myself rethinking the possibility of starting my
18 own family.

19 I married and with great anticipation my first son
20 Cody was born healthy. Four years later my son Clayton was
21 born, and within six months my worst fears came true. As a
22 carrier, I had passed a genetic disorder on to and had given
23 it to my second son. But at the age of eight months, he
24 began the IVIG therapy. This therapy has enabled Clayton to

1 grow into a very normal healthy adolescent.

2 IVIG has been instrumental in helping our family
3 live a very normal life, free of the fears of constant
4 recurring and life-threatening illnesses. However, in 1994,
5 we learned that the medication that kept him healthy had
6 developed some serious problems. Hepatitis C had been
7 transmitted through the use of IVIG. We were not able to
8 adequately obtain the lot numbers from the manufacturer
9 associated with the Hepatitis C virus. To this day, my
10 family is not sure of the lots that were affected by
11 Hepatitis C.

12 At that juncture, our family, along with thousands
13 of others, became very proactive in issues related to blood
14 safety. Issues related to recalls, withdrawals, and
15 notification became a paramount concern. This leads me to
16 the point I would like to make today.

17 Patients and physicians need to be notified
18 directly in the event of a recall or a withdrawal.

19 The Immune Deficiency Foundation's National
20 Patient Survey has revealed to us that over 20,000 patients
21 receive regular infusions of IVIG. Although we do not have
22 formal studies, as President of the Texas Gulf Coast
23 Chapter, I am in regular contact with 200 to 250 patients in
24 my area. I can therefore present what I believe to be a

1 typical scenario for immune deficient patients.

2 The typical patient does not record lot numbers,
3 and some are not even aware of the brand of IVIG they are
4 on. Patients who want to record their numbers and use an
5 infusion log sometimes are not able to do so because the
6 person who is giving the infusion does not know the lot
7 number.

8 In the event of a recall or withdrawal, the
9 product often stays in the pipeline and because the majority
10 of patients are not being notified directly, infusions of
11 withdrawn products occur frequently. The result is and will
12 continue to be that the patients, even the vigilant
13 patients, are likely to be infused with withdrawn products.

14 The Immune Deficiency Foundation is anxious to
15 join with other patient groups, the FDA, and industry in a
16 joint effort to provide prompt and direct notification of
17 product recalls and withdrawals to patients and physicians.

18 The IDF is currently working with the Alpha 1
19 Foundation, the National Hemophilia Foundation, and other
20 parties in an effort to develop a patient notification
21 program directed towards regular users of plasma products.

22 In essence, the system would encourage patients
23 and physicians who regularly use or prescribe plasma
24 derivatives to enroll in a voluntary registry or database.

1 It would be managed by a third party, as a means to permit
2 the plasma industry to directly notify patients and
3 physicians of all recall and withdrawals.

4 Without going into great detail on the specifics
5 of the program, let me just state five basic criteria which
6 must be met in any patient notification system.

7 1. Patient confidentiality. It must be
8 guaranteed. Patients will not enroll if they believe that
9 their confidentiality is going to be breached.

10 2. Any notification system must be industry wide.
11 Many immune deficient patients are having to switch from
12 brand to brand particularly in this time of shortages.
13 Patients should not have to be burdened with a multi-system
14 and also we should be provided with a single point of
15 access.

16 3. Direct and active notification of individual
17 patients and their prescribing physicians a must. Patients
18 must not be required to seek out this information on their
19 own initiative.

20 4. Patient and physician education must accompany
21 a more effective recall system to ensure compliance. We
22 must be ever mindful of the patient's fears in the face of
23 this information.

24 5. The FDA has the responsibility and should

1 oversee the implementation of such a system. At the
2 November 1996 workshop on patient notification, FDA
3 officials indicated that the preamble to the 1978 guideline
4 on recall does require industry to conduct effective recalls
5 to reach end users. IDF believes that the FDA has the
6 responsibility to enforce this implementation.

7 I would like to make the Committee aware that IDF,
8 the Alpha 1 Foundation, and the National Hemophilia
9 Foundation are currently working cooperatively to design a
10 program that meets these criteria.

11 Permit me to close with just two personal
12 observations.

13 My brother, Stephen, is now a practicing allergist
14 and immunologist. In his practice, he treats patients with
15 primary immunodeficiencies and he prescribes IVIG. To date,
16 he has never received a recall or withdrawal notification
17 from any manufacturer of IVIG. As a patient and as a
18 physician, and as a member of numerous medical societies, it
19 is shocking to me that he has never received direct
20 notification.

21 As a mother of a 13-year-old child, Clayton will
22 be infused with this product 17 times this year alone. The
23 present system makes me certain that one of his infusions he
24 will receive will have been a withdrawn and recalled product

1 without our knowledge or we are going to be notified too
2 late. In fact, this is a fact that I personally just cannot
3 accept. I urge the Committee to oversee the implementation
4 of a patient notification system to reach all users, all end
5 users.

6 Because of this morning's discussion, I am
7 compelled to point out that there are no formal CDC or FDA
8 sponsored health surveillances or lookback studies in the
9 primary immune deficient community, and I would encourage
10 CDC or FDA to contact the Foundation.

11 I would like to thank you for letting me voice my
12 concerns today. Thank you very much.

13 DR. HOLLINGER: Thank you.

14 We have two speakers for the National Hemophilia
15 Foundation. We can either have one that speak for eight
16 minutes or two that can speak for five minutes each, because
17 we only had one actually that asked to speak here.

18 One is Bruce Ewenstein -- I am sorry, Patrick
19 Collins, and the other Val Bias.

20 MR. COLLINS: Good afternoon. I am going to read
21 a prepared statement from Dr. Bruce Ewenstein, as well as
22 the rest of the members of the National Hemophilia
23 Foundation's Blood Safety Working Group of which Dr.
24 Ewenstein is a co-chair.

1 A rapid and effective notification system for
2 consumers of blood products that have been the subject of
3 market withdrawal or recall has been a long sought goal of
4 the National Hemophilia Foundation and remains one of the
5 agency's highest priorities.

6 The availability of timely and accurate
7 information is an absolute requirement for informed
8 decisions on the part of consumers and treating physicians
9 as they balance the risks and benefits associated with the
10 contemplated use of such products.

11 We believe that a primary notification system must
12 reach all concerned parties, should not require that
13 consumers seek out information, and must respect the
14 patients's right to privacy.

15 It remains our position that the posting of
16 updates pertaining to market withdrawals, recalls, and
17 ongoing investigations by toll-free telephone lines and
18 Internet web sites provides a valuable adjunct to, but not a
19 substitute for, an adequate primary notification system.

20 We agree with FDA's previously stated position
21 that the creation of such a system is the responsibility of
22 the manufacturers of these products. We also believe that
23 the FDA has the regulatory responsibility to monitor
24 industry performance and to enforce compliance with

1 established standards.

2 We propose the creation of a system comprised of
3 two complementary components that together would assure that
4 participating consumers and prescribing physicians receive
5 rapid notification of product withdrawals and recalls while
6 also providing written documentation of the manufacturer's
7 actions to all end users of these products.

8 We envision that the first of these components
9 involve the use of a single independent agency that would
10 issue telephonic and/or overnight mail notices to consumers
11 and prescribing physicians who voluntarily submit their
12 names. Medical necessity as well as recurrent shortages in
13 the marketplace require that many consumers receive products
14 from more than one manufacturer.

15 Often, these substitutions are made on short
16 notice. Thus, the NHF strongly encourages all of the United
17 States plasma product manufacturers to contract with a
18 single notification system, providing a single point of
19 access for all concerned parties.

20 The NHF is fully committed to working with the
21 manufacturers, other organizations representing regular
22 consumers of plasma products, such as the Immune Deficiency
23 Foundation and the Alpha 1 Foundation, and the FDA in the
24 selection of an appropriate agency. NHF is also committed

1 to promoting the voluntary use of this segment of the
2 primary notification system among our membership.

3 The second component of the primary notification
4 system would be designed to reach every consumer of a
5 product that has been the subject of a market withdrawal or
6 recall and to provide written documentation of these events
7 pertaining to these actions.

8 This notification should follow the path of the
9 product from manufacturer to end user and prescribing
10 physician. It may, be necessity, involve multiple segments
11 of the plasma product distribution network and a
12 considerable period of time may therefore be expected to
13 elapse between the withdrawal or recall decision and the
14 receipt by the manufacturer that all consumers of the
15 affected product have received written notification.

16 Nonetheless, it would provide that every consumer
17 of plasma products receive appropriate notices of potential
18 health hazards without requiring that these patients submit
19 potentially sensitive medical information to an agency not
20 directly involved in providing their medical care.

21 In closing, a primary notification system must be
22 implemented immediately in order for the end user to be
23 secure in the knowledge that he or she has been notified of
24 a withdrawal or recall. The status quo is totally

1 unacceptable as there is no certainty that the end user
2 becomes aware of the product withdrawal or recall. NHF
3 believes that it is the obligation of industry to rectify
4 this problem in an expeditious manner.

5 I thank you and I thank the Chair.

6 DR. HOLLINGER: Mr. Val Bias.

7 MR. BIAS: Good afternoon. My name is Val Bias,
8 and I am a person with severe hemophilia, Factor IX
9 deficiency. I have served as a past volunteer and currently
10 as a consultant to the National Hemophilia Foundation.

11 I would like to present NHF's response to the
12 IPPIA initiatives. NHF supports, in principle, the
13 voluntary initiatives proposed by IPPIA and ABRA to enhance
14 the safety of source plasma used in the production of pooled
15 plasma derivatives.

16 Many of the proposals have been discussed over the
17 past two years by industry, FDA, NHF, and others, as
18 measures to prevent inadvertent transmission of known
19 agents, and as importantly, to minimize the potential impact
20 of unknown emerging agents on chronic users of plasma
21 products. In fact, Immuno initiated many of these
22 initiatives for their plasma products two years ago.

23 The initiatives we received prior to today did not
24 include all of the scientific data to fully comment on their

1 merits. There is no doubt that these initiatives will
2 improve the safety of pooled plasma products. We look
3 forward to reviewing the more detailed plans when the NHF's
4 Medical and Scientific Advisory Council (MASAC) convenes at
5 the end of October. In the meantime, we would like to offer
6 some specific comments on each industry proposal:

7 Applicant donor standard. This calls for
8 preventing first-time donors from contributing to plasma
9 pools. This is a significant improvement in the safety of
10 plasma pools.

11 Viral marker rate standards. This measure will
12 provide for upper limits on antibodies for HIV, HCV, and HBV
13 in donor populations at each donor center. We need to know
14 what the limits will be, how they will be determined, and
15 what will occur if they are exceeded before we can comment
16 further.

17 Inventory hold. A 60-day hold will be implemented
18 for all plasma prior to processing. This measure, coupled
19 with not using plasma for first time donors, could provide
20 an enhanced removal window for period donations. However,
21 the window periods for HCV and HBV are frequently greater an
22 60 days, thus, some of the donors could contribute to the
23 pooled plasma. A hold of at least 90 days would make more
24 sense. Alternatively, the use of genome amplification

1 technology, PCR, would shorten the window periods
2 considerably, and would allow for a shorter hold period.

3 PCR testing. The detection of viral nucleic acids
4 would significantly decrease the window period for all
5 infectious agents transmitted via plasma. The preliminary
6 proposal did not specify which agents would be screened. We
7 would strongly urge HIV1 and 2, HAV, HBV, HCV, and
8 parvovirus B19 as the initial agents to be subjected to PCR
9 testing.

10 Furthermore, we support FDA requirements for donor
11 notification of positive tests. The methods for PCR testing
12 must have significant sensitivities and limits for
13 infectious materials in each pool needed to be established.
14 We know from Immuno's experience that PCR testing can detect
15 and eliminate HCV and HBV from pooled plasma, however, we
16 need additional information on the proposal before we can
17 comment further.

18 Donor exposure limitation. Industry proposes a
19 60,000 donor cap for plasma pools which make major products
20 including Factor VIII and Factor IX, albumin, and IVIG. We
21 use the term pool size to mean the number of donors
22 contributing to each lot of product, thus, all the
23 excipients and stabilizers need to be included in the total
24 figure if they come from pooled plasma. This proposal is

1 very disturbing to the health care providers who prescribe
2 and the consumers who use coagulation products for the
3 following reasons:

4 We were surprised, as seemed to be the FDA, at the
5 blood safety hearing convened on July 31, 1997, by
6 Congressman Christopher Shays, that up to 400,000 donors are
7 used in a single plasma pool. That is 27 times more than
8 the 15,000 donors which we were led to believe by industry
9 were the upper limits, and considerably greater than
10 industry acknowledged last spring when we queried each
11 manufacturer.

12 Industry offered at the Shays hearing to reduce
13 pool sizes by 40 percent. We support all initiatives that
14 will reduce plasma pool size and we continue to support FDA
15 goals that will eventually lead to donor pools of 15,000 in
16 the future.

17 In summary, the bleeding disorder community
18 welcomes these initiatives and once supporting data has been
19 reviewed by MASAC, we will support these initiatives if they
20 contribute significantly to safety.

21 As a person dependent on these products, I think
22 this is a step in the right direction that industry is
23 taking. I thank them and I thank BPAC for considering them.

24 Thank you.

1 DR. HOLLINGER: Thank you.

2 The next speaker is Christopher Lamb from the
3 American Red Cross.

4 MR. LAMB: Thank you very much, Mr. Chairman, and
5 members of the Blood Products Advisory Committee, for
6 allowing me the opportunity to speak with you about the
7 important issue of plasma derivatives safety. I am
8 Christopher Lamb, Vice President, Plasma Operations, of the
9 American Red Cross Biomedical Services under which our
10 plasma program operates.

11 The American Red Cross is the largest not-for-
12 profit provider of blood services in the United States,
13 collecting almost 6 million units of whole blood from
14 volunteer donors annually, or about 45 percent of the
15 nation's blood supply. Blood collected for transfusion is
16 made into specific components such as red blood cells,
17 platelets and plasma, which Red Cross distributes to over
18 3,000 hospitals in the United States.

19 In addition to these components, approximately 1
20 million liters of plasma recovered from our volunteer blood
21 donor units are annually processed, or fractionated, into
22 plasma derivatives. Approximately 800,000 liters are
23 fractionated at Baxter Healthcare's Hyland Division under
24 that company's FDA license, and approximately 200,000 liters

1 are fractionated by the Swiss Red Cross under its FDA
2 license. These plasma derivative products are distributed
3 under the Red Cross label to hospitals, hemophilia treatment
4 centers, and other intermediaries. The Red Cross itself
5 does not fractionate plasma.

6 Plasma derivatives manufactured for Red Cross
7 include Factor VIII Concentrate used by persons with
8 hemophilia, albumin used to restore plasma volume in
9 treatment of shock and burns, and immune globulins used to
10 treat immune disorders. Red Cross plasma derivatives
11 account for approximately 15 to 20 percent of the nation's
12 supply and are produced solely from voluntary, non-
13 remunerated donations.

14 1. Red Cross Initiatives to Improve Safety.
15 Before discussing specific initiatives to improve safety, it
16 is necessary to distinguish between recovered and source
17 plasma. Red Cross plasma derivatives are made from
18 voluntary whole blood donations. Plasma obtained when whole
19 blood is divided into components is called recovered plasma.
20 In contrast, plasma derivatives made by commercial companies
21 are manufactured principally from plasma obtained by a
22 procedure called plasmapheresis. Plasma obtained by
23 plasmapheresis is called source plasma, almost all of which
24 is collected from paid donors.

1 The amount of recovered plasma from a unit of
2 whole blood averages 250 ml. The amount of source plasma
3 obtained by plasmapheresis averages 700 ml. Therefore, an
4 initial pool of recovered plasma contains plasma from more
5 than two to three times the number of donations as the same
6 size pool made exclusively from source plasma.

7 The Red Cross has taken several steps to reduce
8 the number of donations in pools of recovered plasma. In
9 early 1996, we directed Baxter to initiate processes to
10 ensure that American Red Cross labeled AHF-M and IVIG were
11 derived from pools containing approximately 16,000 liters or
12 between 54,000 and 60,000 donations.

13 Since mid-1996, the majority of Red Cross AHF-M
14 and IVIG lots have been derived from pools containing fewer
15 than 60,000 donations. Importantly, this process ensures
16 that albumin used to stabilize these products is also
17 derived from the same pool, in other words, material from
18 different pools is not mixed together. Efforts will
19 continue with our contract manufacturers, Baxter and the
20 Swiss Red Cross, over the next year to reduce negotiated
21 validate pool size to similar levels for the production of
22 all products and batches intended for transfusion.

23 In addition, we are incrementally increasing the
24 volume of recovered plasma donations through improved

1 collection and separation techniques. Through these efforts
2 the average volume of recovered plasma per unit of whole
3 blood has increased from an average of less than 250 ml to
4 283 ml and we expect further improvements to follow. We
5 also intend to increase the amount of volunteer plasma
6 obtained by plasmapheresis to further decrease the number of
7 donors in Red Cross plasma pools.

8 2. Other Red Cross Efforts to Address Plasma
9 Derivative Safety. Pool size is only one of the elements to
10 consider in improving the safety of plasma derivatives. The
11 Red Cross is actively exploring new methods to inactivate or
12 remove potentially transmissible agent from blood and
13 plasma, such as gamma irradiation, iodine treatment, and the
14 use of high efficiency filters. These techniques can be
15 effective against both known and newly emerging threats to
16 blood safety. Dr. William Drohan of the Red Cross Holland
17 Laboratory recently reviewed these and other technologies at
18 a meeting of the FDA Blood Products Advisory Committee.

19 In addition, within the next year, the Red Cross
20 will also implement a highly sensitive testing technology
21 called polymerase chain reaction or PCR, to detect early
22 evidence of infectious virus in plasma to be processed into
23 derivatives.

24 Preliminary studies, which were presented to this

1 committee in March of this year, suggest that PCR testing
2 may prevent the transfusion of several hundred blood
3 components each year that may be infectious for Hepatitis C.

4 3. Efforts to Reduce Window Period Donations.

5 Please note that because whole blood donors can donate blood
6 at most once every 56 days and most repeat donors donate
7 twice a year, the likelihood of multiple window period
8 donations from a volunteer donor of recovered plasma going
9 into a pool are remote.

10 The American Red Cross is committed to providing
11 the safest blood from volunteer donors. We participate in
12 epidemiology studies, such as REDS, which was referenced
13 here earlier today, and ARCNET, an American Red Cross
14 program that track viral marker rates and assess the risk of
15 transfusion associated with transmission of viruses.

16 The results of our studies are published in peer-
17 reviewed articles and journals, such as the New England
18 Journal of Medicine. A review of data related to the
19 reduction of HCV and HIV risk shows substantial improvements
20 since 1985. With regard to HCV, risk has been reduced from
21 1 in 200 in 1985, to a risk of 1 in 103,000.

22 With PCR we anticipate reducing the window period
23 currently estimated at 59 days, by between 20 to 40 days.

24 With regard to HIV, the risk has been reduced dramatically

1 from 1 in 3- to 4,000 prior to 1985, to 1 in 225,000 in
2 1990, and 1 in 675,000 after introduction of HIV p24 in
3 1996.

4 PCR testing might provide incremental improvement.
5 However, the experience with HIV p24 testing perhaps offers
6 some additional insight in assessing the potential for
7 improvement. Since introduction of that test, there have
8 been 2 antibody negative/antigen positive cases out of
9 approximately 18 million tests in the volunteer sector.
10 This is much lower than expected and suggests that there are
11 in fact far fewer window-period donors than previously
12 thought in the volunteer donor population.

13 4. Regulatory Issues. The Red Cross blood and
14 plasma programs are regulated by the Food and Drug
15 Administration. We are inspected by FDA Office of
16 Regulatory Affairs and by several other governmental and
17 professional organizations. Since 1993, the Red Cross has
18 been operating under a consent decree agreed to by the Red
19 Cross and FDA that is designed to improve our operations in
20 several key areas.

21 We have essentially completed all requirements of
22 the consent decree. For example, we have consolidated our
23 50 testing laboratories into nine new standardized state-of-
24 the-art facilities that test all blood donated to the Red

1 Cross.

2 We have also developed a powerful quality
3 assurance program that is the model for the industry. The
4 FDA has been very tough but fair throughout this process.
5 The Red Cross is now a stronger, better managed, more
6 efficient organization because of these efforts.

7 5. Creutzfeldt-Jakob Disease. The American Red
8 Cross takes all potential threats to blood and plasma safety
9 very seriously, and we have moved aggressively to expand the
10 body of scientific information related to CJD.

11 We have several research studies underway at our
12 Holland Laboratory and in collaboration with Dr. Paul Brown
13 at NIH and Dr. Robert Rohwer at the Veterans Administration.
14 The Red Cross has committed over a million dollars in
15 research studying possible links between CJD and
16 transfusion, probably more than any other private
17 organization.

18 The Red Cross is also conducting a CJD "lookback"
19 study under the direction of Marion Sullivan at the Red
20 Cross Holland Laboratory in collaboration with CDC. We have
21 studies 179 recipients of blood transfusions from donors
22 subsequently diagnosed with CJD. These recipients have been
23 followed for up to 25 years following transfusion. None of
24 the recipients has died of CJD or shown any signs of

1 illness.

2 These data are encouraging, however, until there
3 is further convincing evidence of non-transmissibility, the
4 Red Cross will continue to quickly withdraw plasma
5 derivatives following receipt of post-donation information
6 from a donor or a donor's family about a risk of CJD.

7 Conclusion. The American Red Cross is committed
8 to providing an adequate supply of blood components and
9 plasma derivatives that meet the highest standards of
10 safety. Red Cross plasma derivatives have proven to be safe
11 and effective. We are proud of our volunteer donor
12 tradition and believe this also contributes to a high
13 quality starting material as suggested by the recently
14 published Government Accounting Office report.

15 We have taken steps to insure this safety by
16 reducing the number of volunteer recovered plasma donations
17 in pools for fractionation. These steps are part of a
18 larger program of initiatives -- unique to volunteer
19 recovered plasma -- to improve safety by an aggressive
20 quality assurance program, focused research programs, and
21 improved donor screening and testing.

22 Thank you, Mr. Chairman.

23 DR. HOLLINGER: The last speaker that has asked to
24 speak is Wayne Swindlehurst from the Committee of 10,000.

1 MR. SWINDLEHURST: Mr. Chairman, members of the
2 BPAC, I am Wayne Swindlehurst. I am a person with
3 hemophilia, severe Factor VIII deficient. I am also the
4 Vice President of the Committee of 10,000.

5 I come here today on behalf of our Board of
6 Directors. We have reviewed and considered the IPPIA.
7 While we are pleased to see voluntary initiatives on the
8 part of industry, we question these proposals and are not
9 sure whether certain aspects of these proposals will impact
10 the safety equation in a substantial fashion.

11 First of all, we are somewhat surprised at the
12 pool size proposal given what we have learned over the last
13 two months. If industry is proposing to increase baseline
14 pool size, yet we remember that over the last 20 years, we
15 have been led to believe that we were infusing products
16 produced from plasma of up to 20,000 donors.

17 This was the accepted standard that we, the
18 consumers, Congress, the FDA, and others were led to believe
19 was operative. To our shock, we recently learned that we
20 had been fed a line for over 20 years. Given this, it is
21 not hard to understand our dismay at first understanding
22 this 20-year cover-up and then being presented with this new
23 limit, which we know represents a smaller size than many of
24 the previous pools.

1 Our board is unanimous in its opposition to this
2 standard and again state that its only justification is
3 industrial economies of scale. We are also unsure as to the
4 real efficacy of the inventory hold given what FDA has
5 raised about window period.

6 We want a serious attempt to address the dangers
7 of the window period transmission, not just a window
8 dressing. We support PCR testing, but need much greater
9 detail regarding standards and parameters if we are to
10 seriously consider this part of the proposal.

11 In closing, we again call for a new approach on
12 the part of the manufacturers. We look toward a time when
13 our relationship evolves into one of trust and cooperation.
14 It is clear given the recent revelations regarding pool size
15 that industry is yet to be ready for this new era of
16 cooperation. We continue to look forward to a future where
17 we can all -- industry, consumers, Congress, FDA -- can all
18 work together in a climate of mutual trust and respect.

19 Thank you.

20 DR. HOLLINGER: Thank you.

21 Is there anyone else during this open public
22 hearing that wants to speak?

23 [No response.]

24 DR. HOLLINGER: Not having seen anybody, we will

1 take a break now until 4 o'clock. It is 3:36. We will be
2 back here at 4 o'clock to continue the discussion of the
3 Committee.

4 [Recess.]

5 **Open Committee Discussion**

6 DR. HOLLINGER: The meeting will come to order.

7 Dr. Weinstein will present the two questions that
8 are up here. I would like to comment that recipient
9 notification, although it is really critical and we need to
10 discuss it, that is not one of the topics for discussion
11 today. Donor notification is part of this, but recipient
12 notification is not, and that is an issue that we will
13 probably have to deal with in the future. So, keep that in
14 mind as we discuss these things today.

15 **Presentation of Questions**

16 DR. WEINSTEIN: For each separate voluntary
17 standard, should the FDA recommend this voluntary standard
18 as an interim measure? If the standard is not recommended,
19 what further action should be taken?

20 **Committee Discussion and Recommendations**

21 DR. HOLLINGER: Thank you, Mark.

22 Basically, obviously, if the answer to the first
23 question is yes, then, we are not going to deal with the
24 second question. If it is no, then, we deal with the second

1 question.

2 I think I want to just feel out the Committee for
3 just a minute because I think I know where we are going to
4 go initially with this, so I would like to see a show of
5 hands on the first question about should the FDA recommend
6 the voluntary standard as presented completely by the IPPIA
7 without any changes, would they recommend this voluntary
8 standard as an interim measure.

9 How many would be in favor of that from the
10 Committee? Raise your hands. The whole package as it is.

11 [No response.]

12 DR. HOLLINGER: How many would be opposed to it?

13 [Show of hands.]

14 DR. HOLLINGER: So we can move to the second
15 question, which is if the standard is not recommended -- I
16 think what they are asking here, if the standard is not
17 recommended, what further action should be taken.

18 So, I think we need to discuss this. Yes, please,
19 Jane.

20 DR. PILIAVIN: It says for each separate voluntary
21 standard. I think we can do it more easily. We could say
22 yes, yes, no, no, or whatever it comes out, and then all we
23 have to do is work on the parts we don't like.

24 DR. HOLLINGER: Thank you for picking that up.

1 That is a very important point. Let's then look
2 at each of the voluntary standards.

3 DR. PILIAVIN: The first one is not using the
4 plasma from first time donors for which I would like to give
5 a rousing yes.

6 MR. DUBIN: It's inventory.

7 DR. PILIAVIN: Inventory? What happened to that
8 other first one?

9 DR. HOLLINGER: No, the first one is absent donor
10 standard, plasma for one time donors, on page 1, the group
11 that is widely acknowledged as the most likely to be at risk
12 will not be used to make plasma-based therapies. Only
13 donations from those individuals who test negative and
14 complete the full donor interview process on two separate
15 and sequential occasions, and on each and every subsequent
16 occasion, will be used.

17 Now, tied into that has to do with the question
18 which they discussed, has to do with the timing for those
19 subsequent donations or the separate and sequential
20 occasions, I believe, which is a critical one and which they
21 wanted to deal with.

22 Any questions or comments, please, about that
23 first standard? Yes.

24 DR. AUGUST: I think we have to deal with the

1 issue of the timing of the two separate and sequential
2 occasions. It was pointed out to us that if those happen to
3 be just a few days apart, they could then hold the material
4 for 60 days and you wouldn't really have learned very much
5 or assured much in the way of safety.

6 DR. PILIAVIN: But you would have depending on how
7 fast they can do the testing, you would have at least
8 learned whether they are safe on the basis of testing.

9 MS. PIERCE: I think that if the first donation
10 does not exclude the person, being that it is negative, but
11 the fact that it might be in the window period, the donation
12 then actually will qualify that one that is negative, but a
13 potential window period really should be taken 60 to 90 days
14 after, when you would be pretty much out of the window
15 period.

16 DR. PILIAVIN: No, they don't do that with other
17 people.

18 MS. PIERCE: No, but what I am saying that is what
19 I say as the fallacy here, because you have a second
20 donation that is going to qualify your first donation, but
21 it can be -- what was it -- three days after your first
22 negative donation you can have a second negative donation,
23 which would still be in the window period, it is something
24 that may have a window period of 60 to 90 days, and it would

1 qualify both donations as being acceptable.

2 DR. PILIAVIN: No, that is not true.

3 MS. PIERCE: Yes, it is.

4 DR. PILIAVIN: They still will not use, they will
5 not use the first one. The person comes back. By then, the
6 testing has been done.

7 DR. HOLLINGER: Let's find out. Why don't you go
8 ahead from the group.

9 DR. PILIAVIN: Then, that second one goes into a
10 hold for 60 days, just like everybody else's donation.

11 MS. PIERCE: Right, but then there is nothing at
12 the end of the 60 days, there is not another test at the end
13 of the 60 days.

14 DR. HOLLINGER: Why don't you go ahead and see if
15 you can elaborate on that a little bit.

16 DR. LYNCH: The purpose of the applicant program
17 is to only accept donations from donors who have committed
18 to repeat participation. The purpose of this was not to
19 close the window period, but to select a totally different
20 population of donors who we call qualified donors, who have
21 taken it upon themselves to come to the center on two
22 separate occasions and have shown that commitment.

23 Obviously, all collectors of blood and plasma
24 would like to ideally get all of their product from

1 committed donors who are healthy, who we know, who come on a
2 regular basis.

3 As one measure of that commitment, we would like
4 two visits to the center. Now, what this does is it
5 eliminates any donor who wants to come in once to validate
6 high-risk behavior, for example, by getting some free viral
7 testing, and this is a problem throughout the industry and
8 the volunteer blood industry.

9 To discuss the specifics, any qualified donor who
10 returns, even that first unit and the second unit, and every
11 other unit, will be held in the inventory hold for a period
12 of not less than 60 days.

13 DR. HOLLINGER: On the two separate occasions,
14 what is the least time interval that you will accept that
15 person? If I come in today and then come back and see you
16 tomorrow, that is perfectly okay with you?

17 DR. LYNCH: No, because that is shorter than the
18 time allowed by federal regulations.

19 DR. HOLLINGER: And what is that time?

20 DR. LYNCH: A two-day period is the absolute
21 shortest period of time.

22 DR. HOLLINGER: So, if I come in today and come
23 back on Saturday, that is perfectly okay?

24 DR. LYNCH: Absolutely. If you come today to

1 donate, you come back again on Saturday to donate, we see a
2 commitment that we feel much more comfortable with than if
3 you only came in today, and we never saw you again. We find
4 that as being a critically important determination for risk.

5 DR. HOLLINGER: Joel.

6 DR. VERTER: I guess I have some confusion and a
7 suggestion. I think it is clear that we all support that if
8 it is a single time donor, that person shouldn't be
9 accepted, and I think the confusion is that they are trying
10 to do too much in this one suggestion.

11 If we could separate that out and say that we
12 support that part, I haven't seen enough data today to tell
13 me whether the 60 days is enough for all the viruses that we
14 are talking about. The idea of someone coming back three or
15 four days later and then how that would do is not clear to
16 me from this, so that is the issue.

17 I think there is two important things here, one
18 which the Committee can probably agree to, and one in which
19 there is confusion.

20 DR. HOLLINGER: Paul.

21 DR. McCURDY: I am assuming from this that
22 somebody could come back twice in a week for four times in
23 two weeks, and then disappear and seroconvert or whatever,
24 and 60 days later, those units would then be usable. I mean

1 assuming they make a four-donation commitment in two weeks.

2 DR. LYNCH: Remember we are looking at a series of
3 initiatives, and no single initiative is going to eliminate
4 all risk. In the series of initiatives, we have the
5 applicant donor standard, then, we have the inventory hold,
6 and you are correct, that if somebody comes four times in
7 two weeks, two weeks later seroconverts to HCV, then, how
8 would we identify those units?

9 We do the PCR testing of the manufacturing pools
10 or however each company wants to arrange their PCR testing,
11 so there is a followup with the PCR testing. The PCR test
12 itself closes that window period to some degree.

13 DR. McCURDY: Could I ask one question? Do you
14 really mean PCR testing in every instance or do you mean
15 genomic amplification which the most common is PCR? There
16 are other techniques that have perhaps similar sensitivity.

17 DR. LYNCH: Let's call it genomic amplification
18 although I believe most companies will be going with PCR.

19 DR. HOLLINGER: And the companies right now would
20 have the option of doing donor testing on individual units
21 versus doing pools?

22 DR. LYNCH: The reason I was as vague and the
23 IPPIA standards at this time are as vague as they appear to
24 be is that every individual company is currently discussing

1 their specific programs under an IND/PLA situation with the
2 regulatory authorities.

3 It was determined that we would involve this PCR
4 or genomic amplification testing. Each individual company
5 will do it in cooperation and as approved by the FDA in
6 their own FDA-approved way.

7 DR. HOLLINGER: Rev. Little.

8 REV. LITTLE: Two questions for clarification. Am
9 I understanding correctly that the idea of the applicant
10 donor is not so much addressing the issue of window period
11 as it has to do with motivation or with the consistency in
12 their donating? That's the first part.

13 The second part is, are the donors aware of this
14 or do they come back for a second time on their own, or do
15 you say this is part of what it takes to be a donor here?

16 DR. LYNCH: Here again, that is a center-by-center
17 and company-by-company matter. You are absolutely correct
18 in that the donor applicant program, we believe guarantees
19 that we will not manufacture any products from units
20 accepted from one-time donors. We consider a one-time donor
21 who comes to the center and who we never see again to be an
22 extremely high risk donor, and the main thrust of the donor
23 applicant program is to not accept plasma from one-time
24 donors.

1 DR. HOLLINGER: Corey.

2 MR. DUBIN: A basic statement, just to kind of
3 maybe keep the focus. If it's a duck and it quacks, it's a
4 duck. These are still paid donors, and I understand the
5 concept behind a one-time paid donor who is in the door and
6 out, but I think Dr. McCurdy made a really important point.
7 You know, it is hard for me sitting here as an end user
8 knowing the difference, and the studies in Europe and
9 elsewhere that have been done on paid versus unpaid donors,
10 to listen to this almost as if we are talking about some
11 kind of altruistic commitment from a donor who has got the
12 check, and I just want to remind people that we are still
13 talking about paid donors.

14 Now, that doesn't mean I am totally opposed to
15 where you are going as maybe an improvement over where you
16 have been, but I would like to keep the terms pretty clear
17 because we are still not talking about your average
18 altruistic donor that walks into the local Red Cross in
19 Santa Barbara at tri-counties and gives blood.

20 You know, I have got friends that go in every
21 month and give blood. They don't get a check, they don't
22 get anything, period. So, I kind of want to keep that --
23 remind people of that.

24 DR. LYNCH: And I do want to --

1 MR. DUBIN: Let me finish, I am not done, and I
2 want to go back to what you were saying that we don't want
3 to make more out of this, this isn't a window period thing,
4 and we don't want to try and make this a window, the hold is
5 a window period thing, and we will come to that.

6 So, I agree we ought to keep them focused on what
7 it is.

8 DR. HOLLINGER: Go ahead.

9 DR. LYNCH: I just want to say that I really
10 believe that the altruistic element is a major component of
11 the donors that we have in the center, that we can keep
12 coming back on a regular basis. Every company compensates
13 for time and travel, a certain amount on each visit, and I
14 think that certain helps for that kind of commitment. I
15 think I would expect it, too, but I really believe that our
16 donors do keep coming back with a sense of altruism. I
17 think we would not be able to have the quality of the donors
18 that we do have if it wasn't for that.

19 DR. HOLLINGER: Can I ask a question just because
20 I am not sure -- what is compensation like? Give me an idea
21 of how much they are compensated for donating plasmapheresis
22 or a range. Give me a range.

23 MR. REILLY: I will try to address that and some
24 of things that Corey said.

1 The rate is let's say roughly somewhere between 10
2 and \$20, it is company-specific and may vary for a variety
3 of reasons.

4 With regard to the paid donor issue, nobody has
5 said that they are not paid, and we are not implying that
6 they are not. What we are talking about, though is a
7 program that takes advantage of the donor population that we
8 have and looks at the uniqueness of the situation and the
9 opportunities that we have to improve the product.

10 Although two days does not seem like a
11 particularly long period of time, if you look at the data
12 that Tom presented before, what it shows is that our
13 experience is that those donors that come in initially are
14 where we see the risk, both in real test results and then
15 presumably in potential for window units.

16 So, what we have done is we set in place a
17 mechanism that says until the donor comes back and makes
18 that commitment that he is going to repeat, because our
19 experience is that they don't just come back once, they come
20 back repeatedly, they either come in only once or they come
21 in repeatedly for a number of times.

22 So, with that experience in mind, let's find a way
23 to take that at-risk unit and move it out of the
24 manufacturing process, and that is effectively what we have

1 done.

2 DR. HOLLINGER: Jane.

3 DR. PILIAVIN: I have an empirical question for
4 you. The example that was given is of someone's concern
5 about the effectiveness of Item 2, which we are not going to
6 talk about, but let's say you have someone who comes in
7 twice a week for three weeks, and then you never see them
8 again.

9 Have you ever done any studies that indicate
10 anything about the viral markers in those folks, like on the
11 last time they give? Is it more likely or less likely that
12 they will have a viral marker of some sort than people who
13 stay long enough, so that you can have the whole window
14 period go by? I know it would be real hard to do.

15 MR. REILLY: That is one of the problems, is what
16 is long enough to know. Eventually, every donor stops
17 donating. How do you decide what's long enough that you --
18 we know that there is a major gap between donation one and
19 two, beyond. From two, beyond, the gap seems to be -- our
20 experience is that it is less or nil.

21 DR. PILIAVIN: But I mean you have already thrown
22 out a lot of the people on the first go. You don't know
23 whether they would have come back.

24 DR. LYNCH: I think the data you are asking for, I

1 think is very pertinent, and I think as all of the companies
2 adopt the PCR testing and as the individual donor who
3 contributed that unit is identified, the data will be
4 available then to answer those questions that you have.

5 DR. MARTONE: Let me try and get something
6 straight. The person comes in the first time. Do you draw
7 a unit of plasma and then hold it, and then if they come in
8 again, you will use it, or do you not draw anything on them
9 the first time except for their baseline lab studies?

10 MR. REILLY: The standard would allow for you to
11 do either. From the practical point of view, they draw the
12 unit and they would hold it until the donor returns.

13 DR. MARTONE: How long would you hold that unit?
14 Sixty days?

15 MR. REILLY: Well, that varies from company to
16 company. I would presume they are going to hold it at least
17 two days.

18 DR. MARTONE: Well, when are they going to throw
19 it out?

20 MR. REILLY: We have not set an ultimate cutoff of
21 how long they have to hold it, but I don't know that that is
22 necessarily relevant to the safety question if the donor
23 comes back in two days or 12 months or 6 months.

24 DR. MARTONE: Well, I think it is just relevant to

1 my understanding as to what is going on.

2 DR. HOLLINGER: But you wouldn't use it if it's a
3 first time donor, is that correct, if it's marker negative?

4 DR. LYNCH: That's correct.

5 DR. HOLLINGER: Regardless.

6 DR. LYNCH: That's correct.

7 DR. HOLLINGER: You are just drawing it because it
8 is easier. You presented some earlier data that showed that
9 in your qualified donors -- I am assuming these are donors
10 who have been negative, that you had rates that ranged from
11 2 to 12 per thousand dollars, and that seems pretty high to
12 me. I mean you presented that very early, 0.005, 0.019,
13 0.012, I think it was.

14 DR. LYNCH: These are percentages.

15 DR. HOLLINGER: I know they are percentages. So,
16 0.005 is 5 per thousand, if my percentage is right -- oh,
17 it's 5 percent, not 0.005, sorry about that. So, it is 5
18 per 100,000. Okay. And the HCV would be 12 per 100,000, 1
19 per 10,000. Okay. So, it is pretty low at that level, but
20 surprisingly, there are still people within that group that
21 are seroconverting during followup. Is that higher than you
22 would expect ordinarily?

23 MR. REILLY: We don't know what the norm would be.
24 This is what our numbers are. We don't have a comparable

1 data set to assess it against.

2 DR. HOLLINGER: Thank you.

3 Yes, Jay.

4 DR. EPSTEIN: I think that there is an underlying
5 confusion in that the marker rate in a first time donor and
6 the marker rate in the repeat donor do not mean the same
7 thing. The marker rate in the first time donor represents
8 prevalence in the population from which the donor is drawn.
9 The marker rate in the repeat donor represent incidence in
10 the population from which the donor is drawn.

11 Now, the confusion is whether having eliminated
12 the first time donor, you have then selected for a lower
13 incidence subpopulation, and that is by no means clear.

14 In other words, it may be that repeat donors still
15 are representative samples of the same underlying
16 population, and I think that what Jane was trying to get at
17 is that if you were to be able to measure incidence in those
18 rejected first-time donors, you could learn whether or not
19 there is a difference comparing them to your repeat donors,
20 but that is the think we will never know if we simply defer
21 them.

22 I think the other point of confusion -- and this
23 point needs to be very clear -- that the scheme that is
24 being prevented in no way rules out a window period

1 collection in the donor who re-presents as a repeat donor,
2 because there is no control over the interval of testing.

3 However, I think the point that is being made by
4 the industry is that an individual who is screened once for,
5 you know, examination and risk factors, and then comes back
6 again and is again screened by examination and risk factors,
7 the argument would be that that is an individual less likely
8 to actually have risk factors, and I think that if there is
9 any benefit at all to rejecting the first time donor, it is
10 not the fact that you are rejecting the marker positives,
11 and it is not merely the fact that you are rejecting a
12 first-time donor. It is the belief that you are selecting
13 for donors who truly don't have risk factors based on being
14 screened twice, and I think that that is really how to frame
15 the issue.

16 We are simply getting confused comparing marker
17 rates.

18 MR. REILLY: Thank you, Jay. I think you probably
19 stated it better than we have.

20 DR. PILIAVIN: Just for the record, I do have one
21 set of data that I took in Poland where, at least in the
22 time I was doing it, back in the eighties, they had a blood
23 collection center in Warsaw where you could come in and
24 either give blood for free or give blood for money.

1 It was the same personnel. It was like a
2 controlled experiment except you don't randomly assign the
3 people to conditions, and I was collecting questionnaire
4 data from all of them. It is indeed the case that the paid
5 donors answered my altruism questions in a very similar
6 manner to the way that my unpaid donors answered the
7 questions, and, in fact, some people said that when they
8 could afford it, they gave for nothing, and when they needed
9 the money, they took the money.

10 Now, this is a completely different system, but it
11 is just to sort of underscore the idea that people who do
12 accept money for giving blood products don't necessarily
13 have no altruistic motivations at all. I mean they are
14 probably of a different nature and not as strong, but they
15 are there, they choose this way to make money rather than
16 some other way.

17 MR. REILLY: And there have been some discussions
18 of, for instance, marker rates as a measure, that have shown
19 relative comparability.

20 MR. DUBIN: What year, Jane, were you in --

21 DR. PILIAVIN: This was in the eighties.

22 MS. PIERCE: Just to clarify, the first time a
23 donor comes in, does not actually donate a unit, but does
24 enough to be tested on that. The second time they come in,

1 and donate, if they do not come back again, that second-time
2 donation will be used, because of the testing done on the
3 first one?

4 MR. REILLY: Presuming that all of the testing,
5 all the screening criteria were in fact met.

6 DR. HOLLINGER: Let's vote on this question in
7 terms of this particular standard, the applicant donor
8 standard, which basically says that they won't use one-time
9 donors, and the issue still is open about the separate or
10 sequential.

11 I would like to see how many are in favor, though,
12 of the way this standard has been presented, how many of
13 those are in favor of the way it is so stated? Please raise
14 your hand.

15 [Show of hands.]

16 DR. HOLLINGER: All those opposed?

17 [Show of hands.]

18 DR. HOLLINGER: Any comments, Paul?

19 DR. McCURDY: I just think, taken by itself, the
20 applicant donor, particularly one who may donate just a
21 couple of times before he moves on, he or she moves on, I am
22 not sure that that really does much.

23 By itself, I can't see that, and I am not sure
24 that it adds anything to some of the other standards that

1 are there.

2 DR. HOLLINGER: You would feel more comfortable if
3 the donor stayed around for at least a period of time, more
4 than just a couple of times or three times?

5 DR. McCURDY: I would like to see testing done at
6 an interval, so that you wouldn't be testing almost the same
7 circuit of blood. I mean every two days or twice a week or
8 a couple times in two or three weeks, that is essentially
9 testing the same blood volume.

10 DR. HOLLINGER: What would you put as a number?

11 DR. McCURDY: I haven't given enough thought to
12 it, but I suspect that the inventory hold issue,
13 particularly if one of the goals is window period, I think
14 if the 60-day hold were coupled with the repeat testing, as
15 is done for I think some biologic products, not blood.

16 DR. HOLLINGER: I think Jane's comments initially
17 are very pertinent. I would hope the industry would take
18 this into account. It is critical, and Jay also mentioned
19 that, too, is that it really is important. If you have
20 people who come in for a short time, as you mentioned, three
21 weeks, six weeks, or something like this, that that blood is
22 evaluated in comparison with a large amount of data which
23 you already have to see where these are truly at higher risk
24 than your regular donors.

1 MR. REILLY: One of the paths, if you will, we are
2 going down is I guess a continually expanding data set to
3 start to make these kind of decisions from. We are in the
4 middle of collecting the first set, and we will be able to
5 figure out exactly what means to us and how to proceed into
6 the future.

7 DR. HOLLINGER: Paul, I am sorry, I didn't mean to
8 ignore you and Rev. Little. How would you vote from the
9 industry?

10 DR. NESS: Yes.

11 REV. LITTLE: Yes.

12 DR. HOLLINGER: Yes for consumer.

13 MS. PIERCE: I just wanted to clarify. These four
14 standards are a package, is that correct? These four
15 standard are being implemented as a package, not as
16 individual --

17 MR. REILLY: We have adopted them as a package.

18 MS. PIERCE: Right.

19 MR. REILLY: But they all have sort of individual
20 implementation deadlines. This one, in fact, was adopted in
21 July.

22 MS. PIERCE: I guess that is what I was
23 considering when I saw the applicant donor, is that then you
24 go to inventory hold, and that somewhat modifies the

1 applicant donor.

2 MR. REILLY: They all have some interrelation, but
3 they can be developed independently, and they have value
4 independently, but collectively, they have a greater value.

5 DR. HOLLINGER: Let's move on to the one on the
6 inventory hold.

7 DR. SMALLWOOD: I will read the vote.

8 DR. HOLLINGER: Yes, please, I am sorry.

9 DR. SMALLWOOD: On the IPPIA Standard No. 1,
10 applicant donor, the vote was 10 yes votes, 1 no vote, no
11 abstentions. The industry representative and the consumer
12 representative both agreed with the yes votes.

13 DR. HOLLINGER: Thank you.

14 The inventory hold is the next one, which has
15 stated that, "All donations will be held in inventory for a
16 period of at least 60 days. During this time, if a donor
17 seroconverts and subsequently tests positive or is otherwise
18 disqualified, the earlier donation" -- and I presume that
19 earlier donations should really be in there -- "can be
20 retrieved from inventory and destroyed."

21 Comments, please. Yes, Dr. Linden.

22 DR. LINDEN: I think we have already heard some
23 comments in regard to the concern that this is only a hold,
24 it is not really true quarantine and retesting as is done in

1 some other industries, such as the tissue industry where
2 living donors are retested and I believe also blood donors,
3 when the blood is used for stimulation.

4 In the semen donor industry, there is six-month
5 quarantine and retesting, and in most cases, the donors are
6 given a strong incentive to return for that final test
7 because a portion of their payment for their donations is
8 withheld.

9 Is there a reason why that type of strategy would
10 not work here to induce the donors to come back after be it
11 60 days, 90 days? I know there is some discussion on that
12 point, as well.

13 MR. REILLY: There is probably a fairly subjective
14 decision, but my guess would be the amount of money involved
15 isn't nearly enough to stimulate somebody who has decided to
16 move on in their life, and not donate any longer.

17 DR. HOLLINGER: Jane.

18 DR. PILIAVIN: Another empirical question. Have
19 you any idea what proportion of the plasma donors do indeed
20 hang around for over 60 days?

21 DR. LYNCH: Shall I talk on our own experience?

22 DR. HOLLINGER: Yes.

23 DR. LYNCH: On our own experience -- and this is a
24 little bit dated plasma which we are in the process of

1 updating right now -- it is better than half.

2 DR. PILIAVIN: Actually, the only people for whom
3 this helps are those who are around after the window period
4 has been closed, and you can test them again. Otherwise, it
5 doesn't help.

6 DR. LYNCH: Oh, not at all. Actually, anyone,
7 even 60 days after a donation if somebody seroconverts
8 during that time, remember, a window period isn't a set data
9 that everybody has the same window period. There is a broad
10 range of time, and if at anytime during that minimum of a
11 60-day period, either from seroconversion to one of the
12 three major viruses, a surrogate test like elevated ALT or a
13 number of things, we could identify this person as a high
14 risk person, we can go back and retrieve units, and this not
15 only has value for the three viruses that we are
16 specifically testing for, but actually for any known or
17 unknown virus that might be associated with high risk
18 behavior.

19 DR. HOLLINGER: Charles.

20 DR. AUGUST: It seems to me that if you wanted to
21 set that time period in a biologically meaningful way, you
22 would have to do a couple of things. The first is you would
23 have to define window periods in terms of mean and standard
24 deviation for the three viruses that are of interest, as

1 well as for the assay that you were going to use, be it
2 antibody, antigen, or a nucleic acid by PCR, and then
3 knowing that data, you would have to decide to set your
4 holding period in terms of a second or a third perhaps
5 standard deviation above the mean to encompass everybody
6 that you would like or to encompass a certain percentage of
7 the people that you would like to eliminate.

8 Obviously, you would like to eliminate everybody,
9 but you might not be able to do that, so you might have to
10 take the second standard deviation at the 95th percent
11 confidence limit or the third standard deviation for the
12 99th or even go out another one depending on whether it
13 would involve an impractically long holding period.

14 But this kind of information, it seems to me, is
15 what is required to make what you now have as a 60-day
16 holding period, more meaningful and relevant to the issue of
17 excluding infected units than it now seems to be.

18 DR. LYNCH: I would like to respond to that.

19 Actually, when the 60-day minimum unit or
20 inventory hold was established, it was with the belief and
21 understanding that this is a meaningful and an achievable
22 goal at this time. The nice thing about these voluntary
23 initiatives is that they are not static, they are not carved
24 in stone, they are completely, all the time being

1 reevaluated and can be changed.

2 Your point about the window period is important
3 because this inventory hold period has to be taken into the
4 context that we are following this up to nucleic
5 amplification testing or PCR testing, and we will as time
6 goes on get a lot more information based on the numbers and
7 the types of donors that we are identifying beyond the
8 window period with this testing.

9 And you are absolutely right, as this information
10 comes across, we as an industry and as individual companies
11 get more information from the PCR testing results, we can
12 always go back and reanalyze how meaningful and how valid
13 was the 60-day period, is there some value to extending it,
14 and if there is, that would be certainly taken under
15 consideration.

16 DR. VERTER: Again, I applaud the industry for
17 coming forth with standards and also the attitude you just
18 expressed, but I wonder if someone from FDA could clarify
19 something for me and maybe the committee.

20 The question is should the FDA recommend this
21 voluntary standard as an interim measure. What is the
22 intent of that?

23 DR WEINSTEIN: This would become part of the GMP,
24 it would be put into a guidance document, and it would be

1 made enforceable under our GMP guidance once it had gone
2 through good guidance practices, notice, and comment period,
3 and all members of the organization would be expected to
4 follow the given standard, and it would no longer in a sense
5 become quite so voluntary. There would be more FDA
6 overseeing of making certain that this was being carried
7 out.

8 On the negative side of this, the recommendation
9 standard being adopted at this time would be put in place
10 when we can see now that there is, from your questions,
11 insufficient data to actually demonstrate that these claims
12 would have effectiveness on the safety of the products.

13 It is our impression that they would in many
14 cases, but we would not have the data here to clearly
15 support this, and one might imagine that industry would
16 advertise that these things are in place, and there would be
17 perhaps an indication that they are effective safety
18 measures.

19 In a sense we can see, yes, there are positive
20 outcomes of these voluntary standards, but at the same time,
21 there are, as you are raising these questions about their
22 true effectiveness in input of the safety of the product, so
23 those are what an FDA recommendation might mean.

24 DR. VERTER: I kind of understood the word

1 "recommendation," it was the interim that I needed some
2 clarification on.

3 DR. WEINSTEIN: The interim is just the
4 acknowledgment that these are a process, that they are
5 changing here, but what we are saying here we accept them
6 now. We are taking them now at this point in time without
7 asking for this additional data and validation of the
8 processes that are being proposed.

9 MR. REILLY: If I could just make a brief comment.
10 One of the things that may come out of this is probably
11 somewhat obvious. In some cases there is good data to
12 support precisely what and why we did things. In other
13 cases, the data is not as precise.

14 What we have tried to do is to say we know
15 instinctively that these things will make a difference, so
16 have not let, if you will, the pursuit of perfection stand
17 in the way of implementing anything at all. So, we have
18 tried to take measures that we could take quickly, that made
19 sense, that we could demonstrate at least some minimum
20 level, of not a full level, of effectiveness.

21 MS. PIERCE: My concern here is that just holding
22 for the period of 60 days without some additional test
23 further apart from the donations doesn't really give you the
24 information whether or not someone is in a window period.

1 I guess my other question is what is the rate of
2 repeat donors who will come back maybe the fourth and fifth
3 time, but would be out of the window period for an earlier
4 donation. Say they come back in 30 to 60 days.

5 MR. REILLY: Let me take the first question. The
6 inventory hold was not intended to absolutely close all
7 window units out. It was a practical standard which allows
8 us, for donors that we have identified as seroconverting, to
9 go back and, if you will, ensure that at a minimum we can
10 get the window units from those donors we have identified.

11 From those donors who have dropped out of the
12 program for whatever reason, and we don't have a test result
13 on, we are not suggesting that the 60-day inventory hold has
14 done anything about those window units.

15 MS. PIERCE: I guess that is what I am asking.
16 How many then would you catch the seroconversion on before
17 the test or whatever donation?

18 MR. REILLY: The data that we put up before is the
19 percent of seroconverting qualified donors. So, those are
20 the donors who, whether it is for the second donation or the
21 hundredth donation, they have seroconverted and for that
22 percent that -- I think HIV was, what, 0.005 -- that is the
23 number that we are able to retrieve from that inventory.

24 DR. PILIAVIN: Beatrice, when I asked him a

1 question earlier, I don't know if this is part of what you
2 are asking, he said that roughly half of the plasma donors
3 are still around that long after their first donation. It
4 will help with like roughly half of them.

5 DR. HOLLINGER: But that really creates, too, I
6 mean I look at the other way, half are not, which means it
7 creates a two-tier system. You have a tier which says those
8 who are going to be around, we are going to look at you, and
9 if you seroconverted, we are going to discard all your
10 previous donations.

11 Then, you have got this other half here, you are
12 saying we aren't going to look at you, because you didn't
13 give one in 60 days, so we will look at it in the pool maybe
14 we aren't going to look at them individually, and the
15 question is should they be looked individually if they are
16 not going to be around in 60 days.

17 In my opinion, I think the 60 days is too short
18 personally, I think it ought to be 90 or 100, and the issue
19 is what do about people who are not going to be around for
20 those periods of time, rather than pool those, should those
21 be looked at individually for any evidence of disease by
22 perhaps some of the more sensitive measures, and perhaps I
23 would even permit those to be pooled if they are not large
24 volumes, and looked at in a small concentration, if you

1 will, 1 out of 100, or 1 out of 50 rather than -- I mean I
2 would be even happy with that. That would make me even more
3 secure to look at them in that way in terms of cost savings.

4 DR. KHABBAZ: The range, the inventory hold says
5 for a period of at least 60 days? Is there an upper time
6 that is considered? Let's say after 60 days, somebody has
7 not been back, but then they are back at 70 or 80 days, is
8 it at least intended to allow keeping the hold longer?

9 MR. REILLY: A company could decide to hold
10 longer. The minimum would be 60.

11 DR. HOLLINGER: That's a good point, Rima, because
12 then the question is do you hold indefinitely, how do you
13 know these are people that are not going to come back, and
14 that you are going to pool.

15 Theoretically, then, you probably couldn't pool
16 anybody as you would read this, because you are saying it
17 says at least 60 days, so then you come up a year from now,
18 if they are not back in a year from now, you go back and use
19 those first six units, at what point do you decide that you
20 are going to use those six units if these people are never
21 going to come back versus waiting until they come back for a
22 second time?

23 I think they will use them, too, I think you are
24 right, but the question is at what point do you say you are

1 not going to use that because we haven't seen this man after
2 90 days, let's say. It's a good point.

3 Could you respond?

4 MR. REILLY: I think one thing that we need to be
5 clear on is the way the standard works. It is, in effect, a
6 rolling 60 days from date of collection. So, if the donor
7 donates 60 days later, if he was a qualified donor, in other
8 words, it was at least his second donation, 60 days later
9 that unit could be pooled.

10 DR. HOLLINGER: Regardless of whether he is there
11 or not, whether he has come back in 60 days?

12 MR. REILLY: That is correct.

13 DR. HOLLINGER: Jay.

14 DR. EPSTEIN: It is very clear that the inventory
15 hold is not a quarantine and release strategy which would
16 capture a window period unit. Having recognized that, it
17 seems that the key question is what is your estimate for the
18 percent of window period units that would be caught, and I
19 have not heard an answer to that.

20 It would require a fairly sophisticated analysis
21 of the interval at which repeat donors return, and you would
22 have to then stratify against that the different window
23 periods of the different conditions for which you screen,
24 and I have not heard that that analysis has been done, but I

1 think it would be very clarifying to me, and I assume to the
2 committee, if such an estimate has been made and what the
3 result is.

4 DR. LYNCH: I think the estimate that has been
5 made are the amount of the PCR reactivity of the small
6 minipools that have been done by some companies. This would
7 basically tell you how many donors seroconverted and you did
8 not remove by an inventory hold if it was your policy to do
9 PCR testing after the inventory hold. So, that data is
10 available. I am wearing an industry hat right now, and it
11 would be inappropriate for me I think to discuss independent
12 company data, but those numbers have been presented
13 publicly.

14 DR. EPSTEIN: I mean I think that that is what we
15 are all looking for here is an answer to that question, and
16 so it would be illuminating if anyone here knows the answer
17 and knows the estimate, because I think that it is obvious
18 that the answer is non-zero. Certainly, there will be some
19 seroconverters who come back within 60 days, so it is non-
20 zero.

21 On the other hand, it is also obvious that it
22 can't possibly be 100 percent because 60 days is -- for two
23 reasons -- one, that is less than certain window periods,
24 such as for Hepatitis C or Hepatitis B, and also because not

1 all donors will come back within that hold period.

2 So, you know, we know it is non-zero, and we know
3 it is not 100 percent, and I think the issue is in order to
4 have a feeling for whether it a benefit worth recommending
5 from a regulatory point of view, we would like to know how
6 good is it, and I have not heard any estimate.

7 DR. MARTONE: I agree with that. It would seem
8 that the recommendation is almost pointless if you are not
9 going to do something after 60 days other than hope that you
10 might catch somebody who comes in, and those numbers I would
11 suspect to be fairly small.

12 On the other hand, if you could give us an idea of
13 how many repeat donors would be coming in and getting
14 retested for another unit, therefore, you would know that
15 this one got through most of the window period and could be
16 released, you might tier your strategies and say, okay, we
17 are going to use this one, we don't know anything about the
18 person, they haven't come back, and those are the ones we
19 will do PCR testing on if we are going to do PCR testing on
20 a fraction of units rather than pools.

21 DR. HOLLINGER: I think that's right, you know,
22 without knowing a number, you know, I certainly would feel
23 better if I am going to do a PCR testing even on a pool, I
24 would require a pool of a much lower number for those

1 patients who did not come back after 60 days in this rolling
2 type of thing than I would, say, on the final pool, if you
3 will, for a fraction, and so on, just for that reason, until
4 we have some information about this estimate that was
5 discussed.

6 DR. LYNCH: I could answer some of that, actually,
7 some of the data that has been published, and it's data that
8 is a couple of years old, based on one manufacturer's
9 findings.

10 PCR testing of minipool testing, if broken down to
11 a per-unit basis, would be about 1 to a million for
12 Hepatitis B, there was none for HIV, and it was
13 approximately 1 per 50,000 at that time for Hepatitis C.
14 This is again older data that has been published, so I feel
15 comfortable releasing it.

16 As far as how many units are followed up by a
17 subsequent donation, as I said earlier in my presentation,
18 97 percent in one survey, 97 percent of units that were
19 entered into the inventory hold were followed up by at least
20 one subsequent donation. There is at least at a minimum of
21 one additional time when that donor could come in, be
22 requestioned, be retested, and I think that adds value to
23 the confidence that you have in that unit of plasma.

24 MR. REILLY: We are trying to take some notes

1 about where your concerns are with these standards. As they
2 go into place, allows us the capacity then to look at what
3 kinds of questions emanate and what data would then be
4 supportive of the position that we have taken.

5 DR. HOLLINGER: The numbers, it was like 1 in a
6 million for B, and obviously, the numbers must be larger
7 than that, because you quoted that it was something like it
8 was 5 out of 100,000 of your qualified donors are found to
9 be HBs antigen positive sometime later.

10 MR. REILLY: But we have removed all of them and
11 their previous units.

12 DR. HOLLINGER: You have removed them, but there
13 must be others that are coming at the same time. I mean
14 these were discovered, so they must have had a PCR-positive
15 unit somewhere in that period of time if they were a
16 qualified donor, and later you found that to be HBs antigen
17 positive.

18 MR. REILLY: But the inventory hold that was in
19 place allowed them to remove those previous donations which
20 had tested negative.

21 DR. HOLLINGER: Which had tested negative.

22 DR. LYNCH: In other words, although these are
23 individual initiatives, the value is synergistic with one
24 initiative with another, taking an inventory hold along with

1 the PCR testing. Couple that with the donor applicant
2 standard. These are more than additive, they are
3 synergistic on each other.

4 DR. HOLLINGER: If I can go back, you say that
5 they were removed, but on the other hand, you told me that
6 after 60 days, this is going to be dumped into the pool, so
7 you really -- if a person comes back 90 days later, they may
8 have had two or three that you didn't remove, and you may
9 have found then now to be HBs antigen positive, but since
10 you said it is a rolling type of thing, they would have had
11 transfusions that would already have been dumped in that
12 could have been positive in that time period.

13 MR. REILLY: Correct, if it exceed the 60 days, it
14 could well have been added.

15 Yes, please, Jeanne.

16 DR. LINDEN: I would like to just take a slight
17 different tack. I think everybody here agrees that the
18 absolute ideal situation would be to have a true quarantine
19 and retest where there would be holding for a period of
20 probably at least 90 days, and coming back and retesting 90
21 days after the last donation, because, of course, this will
22 only help you for your earlier donations, the last donations
23 just before they stopped donating aren't going to have much
24 of a check on them.

1 I would certainly encourage the industry to try to
2 pursue some sort of incentive program to try to get people
3 to come back for a blood test, but I think that we are not
4 in an ideal situation. Firstly, for recovered plasma, this
5 isn't doable at all. I mean this doesn't even apply, and
6 think actually, the industry is to be commended for
7 voluntarily having taken the step to even address this at
8 all. It is not the ideal, but I think it is actually a
9 pretty good first step. It is better than what was done
10 before. It is a step in the right direction, and maybe one
11 can build on that looking at the experience perhaps with
12 this type of approach, seeing how many things are caught.

13 The other thing is, of course, the role of PCR.
14 If the window period is shorter, then, a shorter hold time
15 is going to be more successful in more cases.

16 MR. REILLY: To be really frank and honest with
17 you the cost and logistics far exceeded what we thought they
18 were.

19 DR. LINDEN: I actually am very concerned about
20 shortages. We right now have a shortage, that I am aware of
21 at least, of 5 percent albumin and I.V. gamma globulin, and
22 in the past we have had a lot of shortages of different
23 products that have actually caused problems for us as public
24 health agencies.

1 I think if we make demands that are too
2 unrealistic and, you know, cutting out half of the
3 donations, then, you are going to have potentially real
4 supply problems, and I think, you know, maybe looking at
5 incremental steps is perhaps a realistic way to go.

6 DR. HOLLINGER: I think the albumin problem was
7 one for some bacterial contamination from a major supplier.
8 Is that correct? It may be different. It is an important
9 issue.

10 I guess we could vote on this. It sounds like
11 there is a lot of -- yes.

12 DR. McCURDY: It seems to me apriori, I would be
13 more comfortable with a shorter period and a retest than I
14 would be with a longer period and no retest. I suspect that
15 that kind of approach, varying those is modelable, that is,
16 I think you can probably -- there are data around that could
17 be used to model that and see what the losses are.

18 I would guess that if half of your donors are
19 around, as somebody pointed out, half of them are not, and
20 if you lost half your one to three or four-time donations in
21 the process, that might be much too costly in product and
22 dollars to do. But, as I said, without seeing modeling
23 apriori, I would be more comfortable with a whole period
24 with a retest, a so-called true quarantine than I would with

1 a longer period and no retest.

2 MR. REILLY: The supply frankly, as well as
3 logistics, but supply is a rather substantial part of that
4 equation, and I don't remember the precise data, but several
5 years ago, someone did take a look at how would you impose a
6 full-scale quarantine, and it was a fairly rough
7 calculation, so I can't maybe stand on it with great
8 firmness, but the most conservative estimate they came out
9 with, I think, if I remember right, was a roughly 90-day
10 quarantine would result in an ongoing loss of 50 percent of
11 collections, in other words, 50 percent of every unit you
12 ever collect forever would be trashed.

13 DR. McCURDY: How about a 30-day hold?

14 MR. REILLY: I don't know what the 30-day would
15 do.

16 DR. McCURDY: I think if you had a model that
17 worked, then, you could plug in all sorts of different
18 numbers and come up with something that might be useful and
19 doable. Maybe not.

20 DR. LYNCH: If I could just add a little bit more
21 information, I was reminded, talking about what percentage
22 in an inventory hold program, what percentage of units that
23 are removed because of the program, are removed at what
24 period of time, and I was informed by one of the member

1 companies who had looked into that, is that 90 to 95 percent
2 of the units that are removed from inventory hold, even a
3 long inventory hold, are removed during the first 60 days.
4 So, as you go beyond 60 days, the yield of units being
5 removed is further and further decreased.

6 DR. HOLLINGER: I will call for a question here,
7 if I can.

8 Rev. Little?

9 REV. LITTLE: I just wanted to sort it out a
10 little bit. I am glad to see that industry is doing
11 something like that, but I am still confused about if this
12 is an FDA recommendation, does there need to be more data
13 before it is a recommendation, or is it a recommendation
14 just based upon it seems a good thing to do?

15 DR. HOLLINGER: I think the issue is where these
16 standards should be as an interim measure, understanding
17 that there will probably be -- well, will clearly be --
18 changes as it goes along, as more information is obtained,
19 hopefully, they will ask for those.

20 Yes, Bill.

21 DR. MARTONE: I just think we should be given more
22 information about this before we could endorse it. Either
23 way, I mean it is either going to beneficially get rid of
24 some bad units or it's going to do nothing, and I don't have

1 a good feel. I mean you are asking industry to do something
2 here, and I don't see the strong positive benefit in terms
3 of data.

4 I guess what I would ask for is more information
5 on this point.

6 DR. HOLLINGER: I guess the question then would
7 come up would this a better interim -- I am just asking the
8 question now -- would it, at least as an interim measure
9 versus doing nothing -- yes?

10 DR. MARTONE: Is doing nothing the same as doing
11 this?

12 DR. HOLLINGER: I guess that would be the issue.

13 MR. REILLY: It is probably worth saying that the
14 industry is committed to this.

15 DR. MARTONE: Okay, but tell me why, so I can be
16 committed to it, too.

17 MR. REILLY: What we have tried to provide is what
18 data we do have and what logic we applied or reasoning we
19 applied to the development of the standards to date.

20 DR. MARTONE: Well, I can see the initial donor
21 deferral issue, but I can't see the 60-day hold. Maybe you
22 presented data, and I just forgot it.

23 MR. REILLY: Well, let me maybe contrast it
24 against the existing situation. The existing situation is

1 that there is no minimum requirement, and that as fast as
2 you could get the plasma to the plant and pool it and
3 manufacture it, it is used.

4 What this does is it guarantees you at least 60
5 days at which point you could retrieve the units.

6 DR. MARTONE: How many of those units are you
7 going to retrieve?

8 DR. LYNCH: I presented that data in my
9 presentation. Out of 300,000 units over a five-month period
10 by one company, I believe it was 2,555 units were retrieved
11 as a result of 330 or 331 donors subsequently being
12 identified by seroconversion, by surrogate testing, or by
13 post-donation information.

14 DR. MARTONE: In that 60-day period?

15 DR. LYNCH: That was a 90-day inventory hold.

16 DR. MARTONE: That was a 90-day.

17 DR. LYNCH: Yes.

18 DR. MARTONE: I just missed that part of the
19 presentation.

20 DR. LYNCH: So what I am saying is, if I were a
21 consumer of a blood product, I would find a lot of comfort
22 that these 2,555 units from donors who were subsequently
23 identified as being at potentially higher risk were removed
24 from the plasma pool.

1 DR. MARTONE: That was a 90-day hold and you said
2 something a little bit earlier that -- is it 95 percent of
3 those would have been caught in 60 days?

4 DR. LYNCH: Yes.

5 DR. MARTONE: Okay.

6 DR. LINDEN: I have one other question. When this
7 concept was introduced, was it with the intention
8 specifically of partially closing the window period and
9 catching some of these units, or was it also significantly
10 an opportunity to interdict pools that you might otherwise
11 have to destroy because of post-donation information that
12 comes up later if the processing were to occur right away?

13 MR. REILLY: It provides us benefit on both sides,
14 but I think the first was our impetus.

15 DR. HOLLINGER: I am going to call for a question
16 on the inventory hold. All those who agree with the
17 proposal as an interim measure, so signify by raising your
18 hand.

19 [Show of hands.]

20 DR. HOLLINGER: All those opposed?

21 [Show of hands.]

22 DR. HOLLINGER: All those abstaining?

23 [Show of hands.]

24 DR. HOLLINGER: Paul?

1 DR. NESS: Favor.

2 REV. LITTLE: Abstain.

3 DR. HOLLINGER: Abstain.

4 DR. SMALLWOOD: Votes on the inventory hold as an
5 interim measure, there were five yes votes, three no votes,
6 1 abstention. The industry representative agreed with the
7 yes vote. The consumer representative abstained. Those
8 votes represent the remaining members that are here. Two
9 members left.

10 On that particular question, Dr. August's response
11 was yes at 90 days. Dr. Piliavin's response was as follows:
12 that she believes that the viral marker standards are vague,
13 but liked the idea. Again, as Dr. Linden suggests, it is a
14 step in the right direction.

15 DR. HOLLINGER: Is there a yes, no, or abstained?

16 DR. SMALLWOOD: She did not indicate.

17 DR. HOLLINGER: I think, Jay, what you can hear
18 from that is that there are some things -- and I think you
19 picked up on all those obviously.

20 Let's go on to the next section which has to do
21 with viral marker rate standard. It is manage the quality
22 recruitment and retention of the donor population at the
23 centers. The voluntary standards establish a maximum
24 allowable viral marker rate incidence of disease in the

1 plasma donor population. Each donor center will be required
2 to maintain a viral marker rate for anti-HCV, anti-HIV, and
3 HBsAG below a set limit as part of its QPP certification.

4 Comments? Yes, Jay.

5 DR. EPSTEIN: It wasn't clear to me from the
6 presentations whether the marker rates used to set limits
7 would include the first time donor rates. We understand the
8 units are discarded, but are you using only the repeat donor
9 rates or are you using the combined rate, what rate are we
10 using?

11 MR. REILLY: The existing standard was based on
12 the combined rate. The new standard that is in the
13 voluntary standards is to be based uniquely on the qualified
14 donor rate, which would be the equivalent, if you will, of
15 the donor, so the units that are used in the manufacturing
16 process.

17 DR. MARTONE: Can I ask a question?

18 DR. HOLLINGER: Yes, you may.

19 DR. MARTONE: How do you respond to the important
20 FDA statement on the bottom of page 2 here in the handout,
21 that CBER has received reports of some centers using two or
22 more testing laboratories and only reporting the results
23 from the laboratory with the most favorable outcomes? I
24 think that is an important point that I would like

1 addressed.

2 MR. REILLY: I haven't seen that report, but as we
3 administer the QPP program, we obviously asked them to
4 report that data to us to evaluate their compliance. At
5 least when we are aware of it -- which I believe is all the
6 time -- we get the data in total, and to the best of our
7 knowledge, we have not found a situation where they are
8 doing that.

9 DR. HOLLINGER: Is there someone from CBER here
10 that could comment on that specifically?

11 MR. REILLY: CBER raised that with us once before
12 as a hypothetical that could occur. To the best of our
13 knowledge, it has not and we are aware of some dual
14 laboratory situations.

15 DR. MARTONE: They say they received reports.
16 What would you do to a place if you found out they were
17 doing that?

18 MR. REILLY: I think we would take action to
19 decertify them from QPP.

20 DR. HOLLINGER: Paul.

21 DR. NESS: A comment and a question. In view of
22 Dr. Epstein's comments about the difference between the
23 prevalence of infection which might be determined by first
24 time donors and the incidence of infection which may be

1 subsequent donors, it would seem that the standards would be
2 better if they covered both, first time, nonqualified
3 donors, and qualified donors. I would think that would
4 really be the ultimate way of looking at it.

5 The second question would be they said they were
6 going to come up with some sort of standards, and if you
7 don't make the standards, then, there would be a corrective
8 action. I wonder what kind of corrective action they would
9 think of doing.

10 DR. LYNCH: I will take the first question and
11 then pass the second one on to Jim.

12 When it was decided as to define the donor group
13 to base the standard on, the decision was made on finding
14 the most meaningful and relevant data, and it was obvious to
15 us that the most meaningful and relevant data to the safety
16 of our manufacturing pools is to look at the viral rate of
17 every unit collected from every donor who was qualified to
18 contribute to the pool.

19 We feel strongly that this is the most meaningful
20 data to collect and compare.

21 MR. REILLY: The other side of the question was
22 what kind of enforcement action. At the moment, we are
23 transitioning through all the standard from one to the
24 other. The current enforcement action is if they are not in

1 compliance, they are decertified.

2 The future standard is very refined, and there are
3 a number of new issues that have come up from it, and there
4 may be action levels in between the initial noncompliance
5 and actual decertification, but ultimately, if they cannot
6 come into compliance, they would be decertified.

7 DR. HOLLINGER: What does decertification entail?

8 MR. REILLY: What does it entail?

9 DR. HOLLINGER: Yes.

10 MR. REILLY: It seems simplistic in its nature
11 that we simply would not allow them to advertise or take
12 advantage of the fact that they have been certified as QPP.
13 What that means to them, though, is that nearly ever
14 fractionator in the world has now made QPP certification a
15 specification in their contract, so they are effectively out
16 of business.

17 DR. HOLLINGER: Thank you.

18 Paul.

19 DR. McCURDY: I am curious as to what the purpose
20 of this is. It occurred to me initially that the purpose
21 was to see how well you select your donors, because if you
22 select them well, you will get them with a low marker rate,
23 but that would be first time donors mostly, because those
24 are the ones that you are selecting initially.

1 I was wondering what the purpose of this is, what
2 do you expect to gain out of it.

3 MR. REILLY: I think that is what Tom was sort of
4 alluding to. Maybe I will try and say it a different way.
5 It is about the quality of the donor. It is about the
6 quality of the donor that we have retained and we are going
7 to use in the manufacturing process.

8 In other words, if you will consider it as an
9 additional part of the screening, if you will. We go
10 through all kinds of screening questions and tests before we
11 tell somebody or before their unit is considered to be
12 acceptable, we have simply added yet another screening
13 barrier to the unit being acceptable.

14 So, that is the quality of the donors that we
15 ultimately retain and consider acceptable.

16 DR. MARTONE: Based on that, I would say that you
17 don't have too much control over who walks through your door
18 the first time, so I don't see why that should be included
19 in this minimum standard here, but you do have control over
20 who you follow up and retain, and there I think are in the
21 standard.

22 MR. REILLY: And that is why we set the standard
23 where it is, because that is what we are trying to measure
24 is who we retain.

1 DR. MARTONE: I thought you said you would include
2 the first entry.

3 MR. REILLY: No.

4 DR. MARTONE: You are not going to use that.

5 MR. REILLY: We are not going to use that.

6 DR. MARTONE: Okay.

7 DR. HOLLINGER: And new centers that come aboard?

8 MR. REILLY: Effectively, that makes no
9 difference. New centers are always in with a whole new
10 donor population, so we are only measuring what they decide
11 to retain.

12 DR. HOLLINGER: Thank you.

13 Let's go ahead and vote on this one. All those in
14 favor of this particular standard as written, so signify by
15 raising your hand.

16 [Show of hands.]

17 DR. HOLLINGER: All those opposed?

18 [Show of hands.]

19 DR. HOLLINGER: Abstaining?

20 [Show of hands.]

21 DR. HOLLINGER: Three, three, three.

22 Paul?

23 DR. NESS: Favor.

24 REV. LITTLE: Abstain.

1 DR. HOLLINGER: Okay.

2 DR. SMALLWOOD: Results of voting on No. 3 viral
3 markers. Three yes votes, three no votes, three
4 abstentions. Industry representative agrees with the yes
5 votes. The consumer representative would abstain.

6 DR. HOLLINGER: Oh, yes, we have two others. Just
7 a second. There may be tie-breaker here.

8 DR. SMALLWOOD: Dr. August would have voted no,
9 too vague so far as criteria definitions are concerned. I
10 believe I misunderstood Dr. Piliavin. She agreed with the
11 viral marker standards, but they are vague, but she likes
12 the idea, so yes.

13 MR. REILLY: If I could just make one comment.
14 The vagueness is really a circumstance of timing. We are,
15 if you will, right literally in the middle of collection of
16 the data and setting of the rates and assessment of that, or
17 we would have provided you enormously more definitions.

18 DR. HOLLINGER: Thank you.

19 Yes, Jeanne.

20 DR. LINDEN: Am I allowed to clarify my no vote,
21 which is to say I really support the idea. The only reason
22 I voted no was I thought it was too vague and would not want
23 to see this imposed as a standard the way it is, but I would
24 encourage further work in this area to develop something

1 more specific.

2 DR. HOLLINGER: Thank you for comment.

3 Anybody else want to ask for forgiveness?

4 [Laughter.]

5 DR. HOLLINGER: Let's go on with the PCR testing.

6 All plasma used in the manufacturing process must test
7 negative through genome amplification testing for HIV and
8 Hepatitis C. Procedures such as PCR are more sensitive than
9 the antigen or antibody detection methods currently employed
10 to screen collected plasma.

11 Comments? I just have a question. Why just HIV
12 and Hepatitis C, and not Hepatitis B included?

13 MR. REILLY: If I recall back from the debates
14 that we had, I think it was a sense of trying to prioritize,
15 if you will, which ones to attack first, because it wasn't
16 practical to do them all at the same time, and B is
17 actually, if I remember correctly, on the list, but just
18 farther down on the priority.

19 DR. HOLLINGER: Do you recommend vaccination for
20 your plasma donors that come in, so you don't even have to
21 worry about B in the future at all?

22 DR. LYNCH: No, our donors are not routinely
23 vaccinated.

24 MR. DUBIN: Clearly, they haven't considered it.

1 DR. HOLLINGER: It would certainly seem
2 appropriate.

3 While we are waiting for Bill to come back, let's
4 go and just read the other part and we will come back and do
5 this -- oh, here is Bill.

6 We are here to vote on this as written. All those
7 in favor of the standard for the PCR testing, so signify by
8 raising your hand.

9 [Show of hands.]

10 DR. HOLLINGER: All those in favor that the plasma
11 used in manufacture must test negative through genome
12 amplification testing?

13 [Show of hands.]

14 DR. HOLLINGER: Let's do it again.

15 DR. McCURDY: Blaine, I am making the assumption
16 that some of the objections about the completeness of
17 information in here, exactly how they are going to do it,
18 and validating the test are going to be taken care of.

19 DR. HOLLINGER: Yes.

20 MS. PIERCE: But the only concern is that is why
21 we have gotten all these yes/no, because people have made
22 those assumptions differently on the different questions.

23 DR. HOLLINGER: Let's ask Jay for a clarification.

24 MR. REILLY: Jay, I am hoping is going to say the

1 same thing I am. Basically, the ambiguity in this standard
2 really is that it has to be a cooperative effort with an IND
3 and PLA between FDA and each individual manufacturer, so
4 literally, all those questions that Indira went through have
5 to be answered before anybody can implement it.

6 DR. EPSTEIN: Yes. The point of Dr. Hewlett's
7 presentation is that FDA will be exercising close regulatory
8 control over such systems that may be implemented. The
9 question really on the table is should we go further and
10 recommend it rather than leave it to a voluntary evolution.

11 DR. HOLLINGER: Will you be including B or not?

12 DR. EPSTEIN: I think that it is clear that the
13 earliest developments will be for HIV and HCV. I think we
14 look forward to closing as many windows as possible and
15 screening for as many agents as we can, especially those for
16 which there is not viral inactivation where you could make
17 an even stronger case for doing it than for agents where
18 there is viral inactivation, but the scientific development
19 has followed the path of HIV, HCV first, so that's at hand.
20 We might want the others, but the technologies are not yet
21 developed.

22 DR. HOLLINGER: Part of this will also include
23 whether you are going to test single donors or pools and of
24 what size.

1 DR. EPSTEIN: Well, I think the immediate proposal
2 is pool testing. FDA's point of view, which represents our
3 current thinking, is that pool testing should be regarded as
4 an intermediate control strategy to be followed as
5 technology permits with single unit testing.

6 DR. HOLLINGER: Corey.

7 MR. DUBIN: If they come back to you guys and say
8 they want single unit testing done, are you prepared to do
9 that?

10 MR. REILLY: I think what has been offered up and
11 what people are working with FDA on is a variety of matrixes
12 which allow you to, not necessarily test the unit, but test
13 a matrix and work back to the donor when you find the
14 positive.

15 The net result, Corey, is yes, the donor would be
16 identified.

17 MR. DUBIN: Thank you.

18 DR. HOLLINGER: So, once again, all those in favor
19 of the interim standard or the standard for interim
20 evaluation as written, so signify by raising your hand.

21 [Show of hands.]

22 DR. HOLLINGER: All those opposed?

23 [No response.]

24 DR. HOLLINGER: Abstaining?

1 [No response.]

2 DR. HOLLINGER: Paul?

3 DR. NESS: Yes.

4 REV. LITTLE: Yes.

5 DR. HOLLINGER: All right.

6 DR. SMALLWOOD: No. 4. PCR testing vote
7 unanimous, 9 yes votes. The consumer and the industry rep
8 both agreed with the yes vote. Those that left, Dr. August
9 would have voted yes and Dr. Piliavin would have voted yes,
10 as well.

11 DR. HOLLINGER: Thank you. We are now down to the
12 last one, and not necessarily the easiest one, donor
13 exposure limitation. Plasma pool size measured by total
14 number of donors will be limited to 60,000 for all major
15 products, both source and recoverable of blood including
16 Factor VIII, Factor IX, albumin and IGIV.

17 This measurement takes into account the
18 composition of starting pools, the combining of
19 intermediates from multiple pools, and the use of plasma
20 derivatives of additives or stabilizers in the manufacturing
21 process.

22 Comments?

23 DR. LINDEN: Before we get into a lot of
24 discussion, I actually have a question for the industry.

1 The Red Cross speaker mentioned the concept on the excipient
2 albumin of using the same lot from the same pool. Is that
3 something that the source plasma industry is committed to or
4 are you intending to just say, well, as long as it's less
5 than 60,000 that's okay, and it's okay to double it by
6 adding these additional donors?

7 MR. BELL: Each, the answer from manufacturer to
8 manufacturer will differ, but the important distinction that
9 I think Dr. Lynch made there is that our 60,000 donor limit
10 includes the excipient to the equation, so some
11 manufacturers may be pursuing it in that manner, others may
12 not, but the assurance is that including the excipient in
13 the manufacture of the products, there will not be donor
14 exposures to exceed that 60,000 donor limit.

15 MR. DUBIN: Two things I want to say, and the
16 first comment is probably not directed at the two of you
17 because you guys are in the public policy side, but I have
18 just come off a week of hundreds of phone calls from out of
19 my community.

20 I will just use myself as an example. I have a
21 four-decade relationship with all four of the major
22 companies. My oldest is with Baxter because I was one of
23 their first guinea pigs for Factor VIII. My father was very
24 close to the original president. We have a long-standing

1 relationship in the Dubin family. We believed for four
2 decades what we were told, that the exposure factor and the
3 risk factor was somewhere between 12- and 20,000 donors per
4 pool.

5 Those numbers were given to the United States
6 Congress over the years, they were given in this committee,
7 and understand I am the soft end of the reaction out there,
8 not just in hemophilia. I get calls from other user
9 communities who, after raking me over the coals a little
10 about sitting on the BPAC, and not knowing this, or did you
11 know it, we got down to some serious discussion.

12 So, this is a tough discussion for us because
13 everything has changed. All of a sudden, you know, 60 looks
14 better than 120, or 60 looks better than 200, and there is a
15 process going on now that we have to reassess it, and that
16 is why I am trying to isolate you guys out of this critical
17 part of the comment.

18 But we are pretty angry about it, and it's not too
19 good a way to treat your customers, first of all, and it's
20 not something that is really too smart to do for four
21 decades when we are in a period now when we are trying to
22 pull out of a very rough period between us and build some
23 kind of working relationships for the future, which we keep
24 talking about, and we are still talking about.

1 This didn't help those of us who are at the front
2 line of trying to recreate the environment or the ground
3 between us. That said, let me get on to the specifics. We
4 were very pleased at FDA's December '96 recommendations,
5 5,000, 20,000 short term, long term. We thought those were
6 intelligent numbers to go move towards and we still haven't
7 seen anything that tells us these numbers are nothing more
8 than based on economies of scale and not safety, and until
9 we see hard evidence that that is not the basis, this is the
10 position we will continue to take, and I think it will be
11 unchanged, and I think you will find most of the
12 organizations on the user side are somewhere in this end of
13 the continuum.

14 MR. BELL: If I could address the comment, that is
15 a good point that Corey brings up, and we don't take it
16 critically. I have been involved in the discussion and
17 debate of pool size at least for the past two years through
18 BPAC and other forums.

19 In our cursory review, and as you know, it taxes
20 your memory to go back and recollect who was saying what,
21 when, and what was the context of the debate. When we did a
22 cursory review of the BPAC transcripts, you can see over the
23 course of time how the debate unfolded and changed. At the
24 very inception of the debate, at least as industry was

1 responding, we were looking at the question of what are your
2 pool sizes in the context of what is the volume of the pool.

3 As it continued to unfold, there seemed to be more
4 and more questions about we were focusing on donor, donor
5 exposure, and then another portion on the debate unfolded,
6 something that we met a learning curve on, which is, well,
7 not only is it the size of the pool that is important, but
8 it is the excipient that you use when you manufacture it,
9 but which creates additional donor exposures, if you will.

10 So, really, when we look back on the debate, it
11 really has significantly changed from the very beginning of
12 time to the point it is at now. So, I think that is an
13 important point to recollect or as the transcripts would
14 reflect the way the debate was unfolding. I think that is
15 important.

16 I think also, the second point is that the numbers
17 can be inflammatory when you look at them in the context of
18 different products and different donor exposures for
19 different products.

20 In the context of the four major products which
21 our commitment over the summer to Congressman Shays was, is
22 very different from some of those other products which
23 require increased volume to create the small capacity of
24 product that is actually sold. So, that is why we had to

1 put it in the context of only the four major products, and
2 keep those donor exposures in check.

3 DR. VERTER: Originally, I was going to vote no on
4 this, but I have decided I am going to vote yes, and this is
5 the rationale. I was going to vote no because it seemed
6 inconsistent with what we did in December and certain other
7 philosophies that have been expressed.

8 On the other hand, what I have heard today is this
9 may be of marked benefit and change in procedures that have
10 been going on for 20 years, that no one knew about, even
11 though they thought they knew about it. And it's voluntary,
12 and the FDA, I assume would continue to interact with these
13 groups. Furthermore, I don't recall seeing them in
14 December, although I would have to go check my notes, and I
15 certainly didn't see them today, as to what as the rationale
16 for 5 or 20 or 60 or 420, and so it seems to me until we see
17 some data, this might be the best good interim step that
18 this committee can take. So, for that reason when the vote
19 comes, I am going to vote yes.

20 MR. BELL: That's an excellent point because what
21 we saw, even as Corey reflected, in the testimony in
22 Congress, Dr. Zoon did an excellent job of really weighing
23 the benefits and detriments of pool size that clearly there
24 is no convincing argument for one or the other, but it is

1 something that clearly needs to be explored and considered
2 as we move forward, and I think in recognition of that, the
3 industry has put forward this voluntary initiative.

4 DR. HOLLINGER: Joel or the rest of the Committee
5 members, would you make a distinction between recovered
6 plasma and source plasma, as the FDA has wanted to, based
7 upon the volume size, recovered plasma being about a quarter
8 or a third the volume of the source plasma in there or not?
9 I think that is the other issue here besides -- and I agree
10 with you, I think one number that is lower is better than
11 all the others. The issue I think also is where there
12 should be a distinct difference between recovered and
13 source.

14 MR. DUBIN: I have to ask a question. I mean if
15 this is voluntary, all right, then, how do we know they are
16 doing it? The BPAC can vote to recommend that we agree with
17 this 60,000 number, but we haven't held them to anything, we
18 haven't changed anything. They have simply come to us and
19 said -- and I want to add something else -- this is in part
20 damage control. Let's understand what's happening.

21 They took a beating up on the Hill and came back
22 and did some damage control. Now, if that damage control
23 has some substance, you guys might have some impact on even
24 my thinking, but I don't see any guarantees that what we are

1 really about to do if we vote yes is create the conditions
2 where they are going to meet this standard, and this is what
3 the standard becomes.

4 DR. MARTONE: My understanding of it is that they
5 will monitor this, and if they don't comply, they will be
6 decertified. Is that incorrect?

7 MR. BELL: This standard is exclusive from the QPP
8 certification program, which is an ABRA program, and this is
9 an IPPIA voluntary initiative.

10 DR. MARTONE: So, this is just like a guideline
11 that you don't monitor.

12 MR. DUBIN: Right.

13 MR. REILLY: The QPP is specific to plasma
14 collection, so this is really a manufacturing plant
15 standard.

16 DR. MARTONE: So, this is a guideline that you
17 will not monitor.

18 MR. REILLY: I think that is in part or at least
19 on the surface correct, but maybe Jay could weigh in on
20 this.

21 DR. EPSTEIN: I think that if this becomes
22 recommended by FDA, there is, first of all, the expectation
23 that industry will adopt it. We would then be in an
24 enforcement posture, in other words, we would monitor this

1 and take enforcement actions. So, that is why it is
2 material to FDA whether we ought to recommend these limits.

3 Now, of course, really the options are accept
4 these limits with the various limitations, you know, such as
5 that it is not stratified by product, it is not stratified
6 by source plasma versus recovered plasma, but recognizing
7 that it is a step forward and that it is an upper limit
8 where there were no upper limits before, and that is
9 inclusive of excipients, which we hadn't really come to
10 terms with before, and, you know, take this and go forward.

11 But the implication of an advisory committee
12 recommendation is that FDA would move forward and recommend
13 that these become the enforceable industry limits.

14 DR. MARTONE: In that case, what my recommendation
15 is, is to endorse the concept of limitation of pool sizes
16 and leave it up to you guys to decide how large or small
17 those sizes should be rather than take some pool size limit
18 from this guideline, so I would change the question.

19 DR. HOLLINGER: You would vote no on it.

20 DR. MARTONE: I would vote no on this particular
21 question, but what it really means is yes to an FDA
22 limitation on pool size.

23 DR. HOLLINGER: Yes, Beatrice.

24 MS. PIERCE: I have two questions, but the first

1 one has to do with the statement that was made at the July
2 31st meeting with the Shays Committee, and that was that
3 pools could be decreased by 40 percent.

4 Now, from the numbers that we have here, 40
5 percent in some cases would definitely be below 60,000, and
6 I guess that's -- why 60,000, and not 40,000 or lower?

7 MR. BELL: That's a good question. The answer is
8 this. The numbers that we were debating in the context of
9 for all major therapies, let's not include anything but
10 albumin, IVIG, Factor VIII, Factor IX, were pools sizes that
11 were approximately the 100,000 range, and what we said is
12 that we could, as an industry, without detrimentally
13 affecting safety, efficacy, or the availability of these
14 products, decrease it from that 100,000 level 40 percent to
15 the 60,000.

16 In addition, the other point that I guess you
17 raise is that this is a 60,000 cap, an absolute cap, so
18 manufacturers are at, at least that level or below that
19 level, and will continue to be below that level, and we will
20 work forward from there.

21 DR. HOLLINGER: Paul.

22 DR. McCURDY: As I understand it, we are being
23 asked to accept or not accept this as an interim measure,
24 and I think as an interim measure, it's probably a

1 reasonable approach.

2 I think it is probably better than nothing. I
3 don't know what the right number is, I have a feeling it
4 probably is lower than this, but with the idea that it's an
5 interim measure, I think I can support this.

6 DR. HOLLINGER: Let's not forget that there are
7 many companies here who have much smaller numbers in here
8 than 60,000, and I don't think that they are going from -- I
9 would hope not -- from 23,000 to 60,000 because of this
10 measure, but they could.

11 DR. KHABBAZ: If we vote to recommend the
12 standard, can we also take a vote on an additional separate
13 comment that the FDA work on setting up a lower standard?

14 DR. HOLLINGER: I think we could, but I think that
15 the FDA probably hears all this. Am I right, Jay, that if
16 one votes -- I mean it would depend on how you are hearing
17 this -- or should there be an additional vote? I guess
18 there could be an additional vote.

19 DR. EPSTEIN: Well, I mean we had your
20 recommendation last December that we move toward even
21 smaller limits, and we wouldn't expect to stop here, but the
22 question is, is this a point at which we can have a policy
23 with respect to current industry practice. That is not
24 going to be the end of the story. An interim policy, would

1 you support this as an interim policy? That is the
2 question.

3 MR. DUBIN: Jay, how long an interim policy?

4 DR. EPSTEIN: Well, I can't answer that.

5 MR. DUBIN: Ballpark?

6 DR. EPSTEIN: The trouble is that it will take
7 time to investigate the feasibility of driving the numbers
8 even lower, and that process has been started, but, you
9 know, it isn't over until it's over.

10 DR. HOLLINGER: Corey, let me just say we have two
11 Committee members who might be leaving here soon, so we are
12 going to have to come to a decision because we have a quorum
13 right now. If one person leaves, we don't have a quorum
14 anymore.

15 MR. DUBIN: And what have we got, about two
16 minutes left?

17 DR. HOLLINGER: We have actually no time left from
18 when we said we were going to be finished.

19 MR. DUBIN: All right. Let me throw my one
20 sentence out and I will get the heck out of the way and we
21 can vote.

22 DR. HOLLINGER: Go ahead.

23 MR. DUBIN: The bottom line for me, if we vote for
24 this, this cannot be the end. We are going to keep

1 agitating like crazy, and the last thing I want to say is
2 forget I have hemophilia, forget who all of us are. At what
3 point do people get outraged about the truth?

4 At what point does it matter that for four decades
5 people don't tell the truth, and then we come to this
6 meeting and we act as business as usual, and at that point
7 for me, it just becomes a question of it's going on all over
8 our society as far as I am concerned.

9 DR. HOLLINGER: Beatrice, go ahead.

10 MS. PIERCE: Real quick, I would like somebody
11 from the FDA to comment on the fact that the FDA
12 recommendations for numbers do not include excipient donors,
13 whereas, the 60,000 does, and considering that that is
14 mainly from albumin, those excipient donors which has a very
15 safe record, can you speak to that point, the value of
16 having excipient in there?

17 DR. EPSTEIN: FDA has certainly recognized all
18 along that it is donor exposures that we seek to control,
19 not just volume or scale of manufacturing, and there is no
20 question that one has to include all downstream pooling
21 procedures including the addition of excipients in
22 formulation as contributors.

23 We knew that of course in December. However, at
24 that point in time, we had only a very sketchy knowledge of

1 what the downstream processes were, and the impact that they
2 were having on the pool sizes, so we took the point of view
3 of starting down that path by setting limits to the upfront
4 fractionation pool, but with the definite notion that we
5 would come back with discussion of downstream pooling and
6 use of excipients.

7 So, really, it was never an either/or situation.
8 It is just that you have in front of you a more limited
9 initial FDA proposal, and now, if you will, the paradox that
10 if you have a larger number, but a more inclusive system in
11 the current IPPIA proposal, but there is no question that
12 FDA's goal in this is to drive the total donor exposure as
13 low as possible.

14 DR. HOLLINGER: Thank you. Let's not always
15 forget in the final here, that these products are very safe
16 right now, and that what we are really trying to do is make
17 things even safer as such.

18 Yes, Paul.

19 DR. NESS: Just one quick comment. I understand
20 the emotionalism and the fact that people are unhappy that
21 they may not have thought they heard the truth, but we have
22 heard I think pretty convincing evidence today that there is
23 a major -- that the levels of contamination are relatively
24 small, that the systems of inactivation have many logs of

1 protection over those levels of contamination, seven or
2 eight logs we heard, and we are talking, we are arguing here
3 about small arithmetic differences which are maybe two to
4 sixfold.

5 I am impressed by the medical impact of really
6 lowering donor exposure for these agents. Therefore, I
7 would vote no if I had a vote.

8 DR. HOLLINGER: We will vote on the question of
9 the donor exposure limitation as stated.

10 All those in favor of the standard as set --

11 MR. DUBIN: Are we voting to have FDA recommend
12 this just so I am clear?

13 DR. HOLLINGER: Yes, that is correct, as an upper
14 limit.

15 DR. McCURDY: Interim measure.

16 DR. HOLLINGER: Interim measure, yes.

17 All those in favor of the donor exposure
18 limitation as stated, raise your hand.

19 [Show of hands.]

20 DR. HOLLINGER: All those opposed?

21 [Show of hands.]

22 DR. HOLLINGER: Abstaining?

23 [Show of hands.]

24 DR. HOLLINGER: Paul?

1 DR. NESS: Opposed.

2 DR. HOLLINGER: Opposed. Rev. Little?

3 REV. LITTLE: I would vote yes. Can I say why?

4 DR. HOLLINGER: Yes.

5 REV. LITTLE: I am voting yes because it's an
6 interim measure and it's something, but I have to tell you I
7 am sitting here and I am really feeling outraged because I
8 feel that, you know, for so long the truth hasn't been told,
9 and in a sense now it's almost being -- I don't want to say
10 rewarded -- but held up as, well, look, this is being done,
11 so I do hope that this is clearly seen as an interim
12 measure. I don't think that number is acceptable, but as an
13 interim measure I am voting yes.

14 DR. HOLLINGER: Thank you.

15 DR. MARTONE: I voted no because I am unconvinced
16 that that is the optimal upper limit for the number.

17 DR. HOLLINGER: You think it should be higher or
18 lower, in your opinion, or you just don't know?

19 DR. MARTONE: I think we have been hearing from
20 the FDA it should be much lower, and I think this committee
21 voted for a higher limit based on -- nothing.

22 MS. PIERCE: Let me qualify why I said yes, and it
23 is with a lot of mixed emotions, but it is yes to get the
24 process going, to get it moving toward 60,000 with the

1 intention that this is not the end, and it should be rapidly
2 moved even lower.

3 DR. HOLLINGER: I think Jay is hearing that.

4 Yes, Corey.

5 MR. DUBIN: And I have to say the same reason. If
6 I think a majority of our guys our getting product out of
7 pools over the 100,000 range, 60 obviously is a slight
8 improvement. I didn't want to vote yes. It is pretty clear
9 I did because I do think Jay is listening, but I need to
10 say, and I think Bea will agree, and I think we are going to
11 be pushing really hard to move to where FDA recommended in
12 December in that range, because we think that is a realistic
13 range and we think it is justified, and we are not intending
14 to let up. Interim is the key word here.

15 DR. HOLLINGER: Thank you very much.

16 DR. SMALLWOOD: For the record, the vote on donor
17 exposure, there were 7 yes votes, 1 no vote, 1 abstention.
18 The industry representative agreed with the no vote. The
19 consumer representative agreed with the yes votes. Dr.
20 August would have voted yes. Dr. Piliavin would have voted
21 no.

22 DR. HOLLINGER: We will see you tomorrow morning
23 at 8 o'clock.

24 [Whereupon, at 5:45 p.m., the proceedings were

1 recessed, to be resumed at 8:00 a.m., Friday, September 19,
2 1997.]

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