

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FIFTY-FOURTH MEETING
OF THE
BLOOD PRODUCTS ADVISORY COMMITTEE

8:07 a.m.
Thursday, March 13, 1997

Potomac Rooms I, II and III
Quality Suites Hotel
3 Research Court
Rockville, Maryland 20850

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PAUL MIED, PH.D.
EDWARD TABOR, M.D.
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ALSO PRESENT:

DR. CELSO BIANCO, America's Blood Centers
JOHN BOYLE, Immune Deficiency Foundation
JAN BULT, European Association of the Plasma Products
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DR. MICHAEL BUSCH
DONALD COLBURN, National Hemophilia Foundation
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P R O C E E D I N G S

(8:07 a.m.)

DR. SMALLWOOD: Good morning and welcome to the 54th meeting of the Blood Products Advisory Committee. I'm Linda Smallwood, the Executive Secretary.

At this time I will read the conflict of interest statement regarding this meeting.

This announcement is made a part of the record to preclude even the appearance of conflict of interest at this meeting of the Blood Products Advisory Committee on March 13 and 14, 1997.

Pursuant to the authority granted under the committee charter, the Director of the FDA Center for Biologics Evaluation and Research has appointed Dr. Paul R. McCurdy as a temporary voting member.

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

Dr. Benjamin Cheng's employer has received an educational grant from two different regulated firms. Both

1 grants are unrelated to the committee discussion.

2 Dr. Blaine Hollinger serves as the principal
3 investigator on an unrelated grant awarded by a firm which
4 could be affected by the general discussion.

5 Dr. Carol Kasper, in her capacity as the
6 Medical Vice President, World Federation of Hemophilia, is
7 responsible for organizing the 1997 annual meeting which
8 involves soliciting regulated firms for financial support.

9 Dr. Rima Khabbaz' employer, the Centers for
10 Disease Control, Division of Viral and Rickettsial
11 Diseases, has an unrelated CRADA with a firm which could be
12 affected by the general discussions.

13 Dr. William Martone has reported that his
14 employer, a nonprofit organization, receives a donation and
15 two unrelated grants from regulated industry. He receives
16 no personal remuneration.

17 Dr. Paul McCurdy is employed by the National
18 Heart, Blood, and Lung Institute. As a part of his
19 official government duties, he supervises staff who serve
20 as the project officer for a contract from the North
21 American Biologicals, Inc. for HIVIG and two other
22 contracts to develop nucleic acid based assays for HIV and
23 HCV RNA. Dr. McCurdy is not involved in the day-to-day
24 operations of the contract.

1 Ms. Beatrice Pierce has reported that she spoke
2 at the National Hemophilia Association and the Kentucky
3 Chapter of the National Hemophilia Foundation. The agency
4 approved a waiver on June 11, 1996 regarding her
5 association with the NHF.

6 Dr. Scott Swisher has an association with the
7 New York Blood Center. The agency approved a waiver on
8 June 11, 1996 for this association. In addition, Dr.
9 Swisher consulted with an unrelated firm on platelet
10 substitutes. Neither the firm nor the topic is related to
11 the committee discussion's today.

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

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

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

1 At this time I would just like to make a few
2 announcements and introduce the committee.

3 The first announcement is that on March 17,
4 1997 there will be a public meeting on the proposed
5 approach to regulation of cellular and tissue based
6 products, and this meeting will be held at the Parklawn
7 Building in Rockville, Maryland. The meeting will be from
8 8:00 a.m. to 4:30 p.m., and there is information, the
9 Federal Register notice, and a registration sheet you may
10 find outside on the desk.

11 At this time I would like to introduce the
12 members of the Blood Products Advisory Committee. As I
13 call the name of the members, would you please raise your
14 hand?

15 Dr. Scott Swisher, chairman; Dr. Blaine
16 Hollinger, Dr. Jane Piliavin, Dr. Joel Verter, Dr. Carol
17 Kasper, Dr. Scott Holmberg, Ms. Beatrice Pierce, Dr. Susan
18 Leitman, Dr. Rima Khabbaz. We have a new member to our
19 committee, Dr. Jeanne Linden. Dr. Paul McCurdy, the
20 Reverend Violet Little, and Dr. Paul Ness.

21 For the proceedings for this meeting, Dr. Gary
22 Friedlaender will be absent. Dr. Martone will be absent
23 today, and I am assuming that the other members will be
24 here shortly. I believe Dr. Charles August just came in.

1 As you may notice on the agenda, we do have a
2 full agenda today. However, if you will notice, our
3 meeting does appear to be shorter than it has been during
4 the past. However, during the open public hearing, we do
5 have a significant number of speakers, and I will ask that
6 those speakers would please adhere to the time that I will
7 allot to you. Before the open public hearing, I will make
8 an announcement based upon the time where we are in the
9 agenda. So, if you would please govern yourselves
10 accordingly.

11 I would also just like to let everyone know
12 that there are no facilities here for lunch in this hotel.
13 So, you will have to go away from the hotel. We are sorry
14 for that inconvenience.

15 At this time we will have committee updates. I
16 will now turn the meeting over to Dr. Swisher and he will
17 proceed from there. Thank you.

18 DR. SWISHER: I too would like to make a couple
19 of observations. One is that we are moving northward. I
20 hope we are able to stop short of the Arctic Circle --

21 (Laughter.)

22 DR. SWISHER: -- which is a little bit far from
23 National Airport.

24 The other observation is that the sound system

1 here is not up to our usual poor standard.

2 (Laughter.)

3 DR. SWISHER: So, I want to make sure everyone
4 is very careful to use a microphone and to speak right into
5 it.

6 I too would like to welcome Dr. Jeanne Linden
7 to the committee. Dr. Linden is Director of the Blood and
8 Tissue Resources Program of the New York State Department
9 of Health and is very experienced in this area, brings an
10 area of expertise to the committee that I think will be
11 very welcome. Thank you for joining us.

12 I think the next item will be our committee
13 updates. Dr. Weinstein, would you proceed with those?

14 DR. WEINSTEIN: The first update item will be a
15 discussion of criteria for clinical validation of fibrin
16 sealant as a hemostatic agent and for clearance of devices
17 that manufacture such products.

18 The Food and Drug Administration is developing
19 guidance regarding requirements for fibrin sealant as a
20 hemostatic agent and for clearance of devices that
21 manufacture such products. This FDA guidance, which will
22 be published for comment in the near future, will describe
23 recommendations for licensure of fibrin sealant products.
24 The intent of this initiative is to clarify FDA's

1 expectations regarding the clinical evaluations to
2 demonstrate efficacy for licensure of commercial fibrin
3 sealant products. FDA would intend to apply similar
4 criteria to assess medical devices labeled for preparing
5 hemostatically effective products, for example, from
6 autologous blood.

7 The rationale for modification of FDA's review
8 criteria for fibrin sealant will now be stated. Fibrin
9 sealant has never been approved in the United States.
10 However, fibrin sealants made from various sources of
11 fibrinogen and bovine thrombin are in wide use now as part
12 of medical practice. These formulations are not
13 standardized, consistent, or made by methods validated to
14 ensure their safety, purity, and potency, such as steps to
15 inactivate or remove viruses. Public health this more
16 likely to be harmed if this conditions is allowed to
17 persist than if regulated commercial products were
18 available.

19 Fibrin sealants have not been licensed
20 previously in the United States in part because clinicians
21 have been reluctant to conduct controlled clinical trials
22 where the use of fibrin sealant is already a de facto
23 standard of care. There are also situations which the use
24 of fibrin sealants may be of benefit, such as to control

1 bleeding in a confined or nearly inaccessible area, where
2 some sponsors feel that a prospective controlled clinical
3 trial may put the patient at significant and unnecessary
4 risk.

5 To facilitate the licensing of fibrin sealant,
6 the FDA intends to propose considering for review surrogate
7 endpoint studies that demonstrate only local hemostatic
8 effectiveness of a fibrin sealant, as opposed to systemic
9 or long-term medical benefits. An example of such a study
10 would be one that compares the hemostatic effectiveness of
11 fibrin sealant to the standard of care at a donor skin
12 graft site.

13 We will continue to encourage well-controlled
14 clinical trials for other than hemostasis, such as wound
15 healing. Thus, manufacturers who can demonstrate the
16 clinical efficacy of their fibrin sealant preparations for
17 specific indications will be able to label and promote
18 their products for these indications. Approval for a
19 specific indication will signify that the FDA has approved
20 a clinical trial and the specific formulations of the
21 product that may have been tailored for that indication.

22 The following points summarize the proposed
23 revised considerations to be used by CBER to assess
24 clinical trials of fibrin sealants.

1 Number one, in the past it was recommended that
2 fibrin sealant be tested in a setting and under conditions
3 where it might normally be expected to be used in clinical
4 practice. The basis for this concept has not changed.
5 However, a simple demonstration of hemostatic effectiveness
6 may suffice for approval for the indication of topical
7 hemostasis.

8 Secondly, CBER recommended that the product be
9 tested against a placebo such as saline or a currently
10 licensed topical hemostatic product. The basis of this
11 concept has not changed. However, CBER now considers that
12 an appropriate control might be a placebo, an approved
13 product, or the current standard of care. Sponsors should
14 be prepared to justify the appropriateness of the chosen
15 control.

16 Thirdly, previously the agency had considered
17 that efficacy of a product should be shown both by evidence
18 of improved hemostasis and by demonstration of clinical
19 benefit through measurements such as decreased blood
20 component use, shortened operative time, improved wound
21 healing, reduction of infections, or less need for re-
22 exploration. Currently it is felt that evidence either of
23 accelerated hemostasis or other clinical benefit may be
24 considered, depending on the indications claimed.

1 Fourthly, where there is more than one active
2 component in the combination of thrombotic product, the
3 contribution of each component had to be demonstrated by
4 testing the combination of the product against the major
5 single component as, for example, fibrinogen and thrombin.
6 Note that CBER intends to propose that such studies can be
7 performed in appropriate animal models rather than in human
8 subjects.

9 In summary, to facilitate approval of fibrin
10 sealants as hemostatic agents, the FDA intends to consider
11 for review endpoint studies that demonstrate hemostatic
12 effectiveness in a manner analogous to topical hemostatic
13 agents reviewed as medical devices. Such studies still
14 would contain not only suitable design, but also
15 appropriate statistical analysis. An example of a study
16 which the agency believes would reflect clinical benefit
17 would be one that compared hemostatic effectiveness of
18 fibrin sealant to the standard of care or placebo at an
19 oozing surface or anastomosis.

20 Many of the medical devices that are currently
21 licensed have been approved on the basis of time to
22 hemostasis. Endpoints such as blood loss and so forth
23 could still be evaluated and could serve alone as primary
24 endpoints depending on the nature of the study. Clinical

1 trials, either pre or post licensure, may be valuable for
2 refining the use of fibrin sealants' topical hemostasis.
3 Such studies could explore, for example, additional
4 clinical settings or alternative product compositions.

5 FDA would continue to encourage well-controlled
6 clinical trials. Thus, manufacturers who can demonstrate
7 the clinical efficacy of their fibrin sealant preparations
8 for additional indications besides topical hemostasis would
9 be able to label and promote their products for these
10 corresponding indications. Approval for a given indication
11 would signify that the FDA had evaluated the clinical trial
12 and the formulation of the product that was used for that
13 indication.

14 As noted, FDA will solicit comments on this
15 proposed policy through a Federal Register notice.

16 DR. SWISHER: Are there any questions from the
17 committee for Dr. Weinstein on this issue?

18 (No response.)

19 DR. SWISHER: If not, thank you and we will
20 move on to discussion of factor IX from Dr. Lynch.

21 DR. LYNCH: Good morning. I want to give a
22 brief introduction to a new U.S. potency standard for
23 factor IX. The previous standard designated FN2 was, in
24 fact, manufactured in 1978 and came into play as a standard

1 in 1981 and served in that role for about 13 years. In
2 1992 we noticed that the potency of that standard had come
3 down about 30 percent. Moisture had gone up to
4 approximately 8 percent, and we decided it was time to
5 replace FN2 with a new standard.

6 The undertaking was in fact a joint one between
7 FDA, the World Health Organization, and the European
8 Pharmacopeia. We have ended up with what by all rights is
9 a true international standard which was developed and
10 calibrated through international cooperative operation.

11 The first stage of the process was to select
12 the material that would become the standard from a panel of
13 four candidates. Just to give you a little background of
14 what we had to choose from, we started out with four
15 materials. Three of them were high purity factor IX
16 preparations and one was a prothrombin complex concentrate.

17 We evaluated these things basically on the
18 basis of reproducibility in a laboratory assay. This was a
19 one-stage or APTT coagulation assay, clotting assay.

20 Just to give you a flavor, two other criteria
21 were the stability of these preparations, and this is an
22 example of a short-term study. You can see that two of the
23 preparations numbered 1 and 2 were considerably better than
24 the other two.

1 And purity. This is a Western blot of the four
2 candidates. Clearly candidate number 2 is the most intact
3 of the four. This in fact was selected for further
4 development as the standard. 25,000 vials of this material
5 were donated by Centeon Corporation. This is their
6 Mononine product.

7 An international calibration study was then
8 initiated to determine the value to be assigned to this
9 product. Thirty-seven laboratories and 17 countries
10 cooperated with this calibration, and the final results
11 were reported out to the WHO during the summer of 1996.

12 The study was coordinated by the National
13 Institutes of Biological Standards and Controls in England
14 and the Center for Biologics Evaluation and Research, the
15 Division of Hematology, here in the U.S.

16 This just gives you an idea of the data that is
17 generated in a study like this. This was actually quite a
18 successful calibration. You can see the range of values.
19 This is a rather narrow scale. You can see the range of
20 values and only a few obvious outliers. So, the
21 consistency of the results was really quite good.

22 There are a couple of extant standards that we
23 are attempting to replace and the potency of the candidate
24 material was assessed by all of them. That is why the

1 slide is so complicated.

2 In the course of the study, we compared the two
3 predecessor international standards, and it turned out that
4 there was a 5 or 6 percent discrepancy, which is actually
5 very good agreement. In assigning the final potency, both
6 of these values were taken into account, and the final
7 assigned value is a composite of both.

8 The Expert Committee on Biological
9 Standardization adopted this material in October of 1996,
10 and an assigned potency of 10.7 international units per
11 milliliter was assigned to the material. This standard is
12 currently available from the Division of Product Quality
13 Control at CBER, from NIBSC in England, and from the
14 European Pharmacopeia. I will leave the address from which
15 this standard can be obtained from FDA at the front desk
16 for anybody who is interested.

17 I'll entertain any questions.

18 DR. SWISHER: Any questions from the committee
19 on the presentation by Dr. Lynch?

20 This kind of study gives an opportunity to look
21 at the variabilities that are brought in not so much by the
22 material as by the technology with which the measurement is
23 made. I must say the dispersion of these values is a
24 little wider than I might have expected.

1 Do you want to comment on that, or am I living
2 in an unreal world?

3 DR. LYNCH: My guess would be that a biological
4 assay like this would have a precision of no more than 10,
5 15 percent under the best of circumstances. The final
6 value that we obtained, depending on the method of
7 calculation, was plus or minus 5 to 7 percent. I think we
8 were all very satisfied with the precision of this study
9 and the reliability of the results. So, it's certainly
10 more variable than your classic chemical assay, but for a
11 bioassay, I think we're doing okay.

12 DR. SWISHER: It's probably a pretty good
13 lesson to retain in our heads as we look at other kinds of
14 assay procedures and the kinds of variability that are
15 really inherent.

16 DR. LYNCH: I would agree with that comment.

17 DR. SWISHER: We may have false expectations of
18 some of the assay systems.

19 DR. LYNCH: I think it's something that a
20 clinician may take into account perhaps under some
21 circumstances when evaluating what the potency on the label
22 of a product is. Sure.

23 DR. SWISHER: The next update is Dr. Paul Mied,
24 HTLV-II.

1 DR. MIED: Thank you, Dr. Swisher.

2 This is an update for the committee regarding
3 FDA recommendations for donor screening for antibodies to
4 HTLV-II.

5 In November 1988, FDA issued a memorandum to
6 all registered blood establishments which recommended
7 testing donations of whole blood and cellular components
8 for transfusion for antibodies to human T-lymphotropic
9 virus type I, or HTLV-I. This recommendation, which was
10 concurrent with licensing of the first kit to detect
11 antibodies to HTLV-I, was made because HTLV-I was
12 identified as the etiologic agent of a number of disorders,
13 including adult T-cell leukemia and HTLV-associated
14 myelopathy tropical spastic parapareses, or HAM TSP.

15 HTLV-II is a virus closely related to HTLV-I,
16 sharing approximately 60 percent sequence homology.
17 Consequently, antibodies to HTLV-II frequently are cross-
18 reactive for HTLV-I antigens. Currently licensed screening
19 assays are unable to distinguish the two viruses. In fact,
20 it appears that approximately half of the HTLV infections
21 detected among blood donors are due to HTLV-II.

22 In March 1993, the Blood Products Advisory
23 Committee was asked to consider a claim for the detection
24 of antibodies to HTLV-II for a test that contained an HTLV-

1 I viral lysate and a recombinant form of the HTLV-I p21e
2 protein. This request was made based on the cross-
3 reactivity of antibodies to HTLV-II for HTLV-I antigens.

4 In the absence of an HTLV-II antigen based
5 comparator test, the committee felt that HTLV-II antigen
6 must be present in the kit to allow a labeling claim for
7 the detection of HTLV-II antibodies. The committee did not
8 vote at that time to recommend that blood donors be
9 routinely screened for antibodies to HTLV-II because
10 evidence for the involvement of HTLV-II in disease, while
11 accumulating, was not strong enough to warrant a
12 recommendation.

13 In addition, a recommendation for screening was
14 considered by the committee to be not appropriate in the
15 absence of a licensed screening test for antibodies to
16 HTLV-II.

17 In December 1996, the Blood Products Advisory
18 Committee again considered the question of whether to
19 recommend routine screening of blood donors for antibodies
20 to HTLV-II. At that time, a test kit was under review by
21 FDA that met the criteria set forth by the committee in
22 March 1993 for a labeling claim of sensitivity for HTLV-II,
23 that is, that the kit contained HTLV-II antigens.

24 Based on the availability of a suitable test

1 and on additional data establishing the association of
2 HTLV-II with disease, the committee recommended that donor
3 blood be routinely screened for antibodies to HTLV-II when
4 a licensed test becomes available for this purpose.

5 The committee also considered strategies to
6 implement this testing and revisited the issue of detection
7 of antibodies to HTLV-II based on cross-reactivity with
8 HTLV-I antigens. Data was presented which showed that due
9 to recent technical improvements, some currently licensed
10 test kits for detection of antibodies to HTLV-I exhibit a
11 level of sensitivity for detection of antibodies to HTLV-II
12 which is comparable to a test kit that contains both I and
13 II antigens based on performance with an FDA panel of anti-
14 HTLV-II positive sera.

15 The committee voted that a claim could be made
16 for detection of antibodies to HTLV-II for HTLV-I test kits
17 that could demonstrate equivalent sensitivity to a kit
18 containing HTLV-II antigens and that criteria for
19 equivalent sensitivity may include use of an FDA panel of
20 HTLV-II positive samples.

21 FDA recognizes the need to provide guidance on
22 implementation at the time that a new test is approved.
23 Therefore, we are developing an appropriate guidance
24 document. I would like to present today the concepts being

1 entertained by the FDA pertaining to implementation of
2 screening for HTLV-II.

3 FDA is proposing to develop a guidance
4 statement recommending that all donations of whole blood
5 and blood components for use in transfusion should be
6 screened for antibodies to HTLV-II by an FDA-licensed test
7 labeled specifically for use in donor screening for HTLV-
8 II.

9 In addition, FDA is intending to recommend that
10 screening for antibodies to HTLV-II should be implemented
11 within 90 days of the commercial availability of a licensed
12 test containing HTLV-II antigens.

13 FDA also proposes to recommend that licensed
14 HTLV-I screening tests may continue to be used on an
15 interim basis following the licensure of the first HTLV-II
16 test if the HTLV-I test is labeled for significant cross-
17 reactivity to HTLV-II based on documented equivalent
18 performance on an FDA HTLV-II panel in comparison with a
19 licensed HTLV-II test at 95 percent confidence.

20 At the end of this interim period, FDA intends
21 to require that labeling claims for sensitivity to HTLV-II
22 be validated by either a more rigorous demonstration of
23 equivalent sensitivity based on clinical studies of an
24 unselected group of individuals from an HTLV-II endemic

1 population, including a comparison to a licensed test which
2 contains HTLV-II antigens or modification of a test to
3 incorporate HTLV-II antigens.

4 In other words, for a permanent claim of
5 sensitivity for HTLV-II, FDA would provide a period of
6 time, an interim period, for manufacturers to either add
7 HTLV-II antigen to their kits or to perform rigorous
8 clinical trials to substantiate equivalent sensitivity
9 compared with the test containing HTLV-II antigens.

10 In the interim, HTLV-I kits, meeting an
11 equivalency criterion based on FDA's HTLV-II panel, could
12 remain in use as HTLV-II screens.

13 Now, I would like to emphasize that these are
14 proposed guidance statements and that there will be an
15 opportunity for public comment.

16 Comments based on this presentation or the
17 previous Blood Products Advisory Committee discussions may
18 be addressed to the Division of Transfusion Transmitted
19 Diseases, HFM-310, 1401 Rockville Pike, Rockville, Maryland
20 20852.

21 Thank you.

22 DR. SWISHER: Questions of Dr. Mied from the
23 committee? Susan?

24 DR. LEITMAN: Paul, is this panel already

1 prepared by the FDA, or is it still under preparation? The
2 HTLV-II panel.

3 DR. MIED: I'm sorry, Susan. I couldn't hear.

4 DR. LEITMAN: Is this panel already prepared by
5 the FDA, or is it still under development?

6 DR. MIED: We have a panel that we had prepared
7 previously with sera that was partly composed of sera that
8 had been preselected using an HTLV-I test. We're in the
9 process of preparing a new panel with sera that would be
10 entirely unscreened using an HTLV-I test. We hope to have
11 that panel ready for testing of these kits.

12 DR. SWISHER: Other questions?

13 DR. NELSON: Since you're preparing the panel
14 now, this may not be an appropriate question, but do you
15 intend to include in the panel individuals with early stage
16 infections, around the window period, or are these people
17 that predominantly may have been prevalent infections that
18 may have been infected for some time? How are you going to
19 characterize? Do you have an ideal standard for selecting
20 or preparing the panel?

21 DR. MIED: Yes. We will select the sera based
22 on reactivity with a 1/2 combination test and proceed to
23 type the virus as HTLV-I or II. Yes, we would welcome
24 early infections in our panel. That would be very helpful.

1 DR. KHABBAZ: Any ideas of what this interim
2 period might be?

3 DR. MIED: I'm sorry. I can't hear, Dr.
4 Khabbaz.

5 DR. KHABBAZ: The interim period that you are
6 talking about allowing, what are we talking about? Months,
7 years?

8 DR. MIED: Well, I think we're open to
9 suggestion on that. That's one of the reasons that we're
10 encouraging comment. We haven't really decided how long
11 that interim period should be.

12 DR. AUGUST: Could you give us an update on any
13 new information linking HTLV-II with disease? You referred
14 to the fact that the last time we visited this, the
15 evidence was accumulating but not conclusive. Is there
16 anything new in that regard?

17 DR. MIED: Yes. Some of that was prepared at
18 the December 1996 meeting of the advisory committee. I
19 haven't prepared a summation of their studies. If someone
20 would care to comment on the new associations that were
21 described.

22 DR. SWISHER: Other questions?

23 It strikes me that this proposal does, in fact,
24 take something of a middle ground between the actions of

1 this committee at the last meeting and the previous
2 proposal from the committee where the emphasis was on the
3 actual presence of HTLV-II antigens in the test and that
4 this is a good and practical blend of those two
5 perspectives and will be interesting to see what kind of
6 comments come from the field. I'm sure we will have
7 another update on that.

8 DR. KHABBAZ: I wasn't here in the December
9 meeting, but to respond to Dr. August, there has been
10 reports of neurologic disease associated with HTLV-II in
11 two different populations.

12 DR. SWISHER: Thank you very much.

13 We now will undertake a topic that has been, to
14 some extent, overhanging our agenda for some time and that
15 is the issue of nucleic acid testing of plasma pools for
16 infectious agents. There are three presentations, and I
17 think except for direct questions of the committee of each
18 presenter, we will sort of defer the general discussion
19 until after our break. Dr. Ed Tabor will lead this off by
20 giving us the FDA perspective on this topic.

21 DR. TABOR: I'm going to be talking this
22 morning about some current issues regarding the possibility
23 of applying nucleic acid testing to pools of plasma.

24 A fairly recent publication by Schreiber, et

1 al. showed that nucleic acid testing, if it were applied to
2 individual units, could significantly reduce the number of
3 window period donations in the blood supply. As shown
4 here, it's estimated that there are now about two donations
5 containing HIV per million donations, and if nucleic acid
6 tests were applied to individual units, this would be
7 reduced to one per million, potentially preventing 12
8 infectious donations per year. And for HCV, similar
9 testing is estimated to prevent 84 infectious donations per
10 year, and for HBV 81.

11 Clearly at this point in time, nucleic acid
12 testing is the most sensitive method for detecting if a
13 virus may be present during the window period. If it were
14 possible to do nucleic acid testing of individual units, it
15 appears certain that we would succeed in reducing the
16 number of infectious units for HIV, HBV, and HCV in the
17 blood supply. This would also result in earlier diagnosis
18 and treatment and the benefits that would result from those
19 for the individuals involved.

20 Unfortunately, the technology available at
21 present makes it only practical to test pools of plasma
22 rather than individual units.

23 We will be issuing a notice in the near future
24 in the Federal Register to request public comment on

1 proposed methods of regulating nucleic acid testing of
2 plasma pools, but in the meantime, I think it's worth
3 discussing some of the issues related to this testing. The
4 issues I would like to discuss with you this morning
5 include those related to the concept of minipool testing,
6 the concept of using a centralized testing service, donor
7 notification, the possibility of substituting nucleic acid
8 testing of pools for other existing tests of individual
9 units, and the issue of final container testing.

10 With minipool testing, by definition the
11 individual donors who are found to be infected are
12 identifiable, and this raises concerns that must be
13 addressed regarding the validation of tracking methods to
14 identify the individual unit and the issue of donor
15 notification.

16 In addition, the sensitivity and specificity of
17 the test itself and its reproducibility must be addressed.
18 There are also issues regarding manufacturing consistency,
19 GMPs of the test manufacturer, and also the logistics of
20 identifying and removing infectious material.

21 Some people have proposed using a central
22 testing service to do nucleic acid testing of plasma pools.
23 This has been proposed because nucleic acid testing is very
24 labor intensive, and in addition the technology and

1 procedures for preventing cross-contamination can be quite
2 complex.

3 From a regulatory point of view, there are two
4 aspects of the regulation of a test that's done at a
5 central testing service. This includes the regulation of
6 the test itself, ensuring that the test is manufactured in
7 a way that will provide a minimum level of sensitivity and
8 specificity that can be counted on by the user, and
9 regulating in a way that the central testing service can
10 provide the test for many customers without additional
11 paperwork for each customer and each product.

12 There is also the issue of the regulation of
13 the products involved, since the addition of the test
14 changes the process by which the product's purity and
15 potency are insured.

16 We view donor notification as a very important
17 issue in connection with nucleic acid testing of plasma
18 pools and something that must be discussed. Donor
19 notification has been a guiding principle of all FDA
20 recommendations for viral marker testing for many years.

21 First of all, there's the donor's right to know
22 if we know that the donor is infected.

23 Secondly, there is the public's right to the
24 public health benefits of donor notification. Donor

1 notification would prevent repeat donation by an infected
2 donor and would prevent secondary transmission to sexual
3 and other close contacts of the donor, and it would provide
4 the donor with the opportunity for early treatment.

5 It's possible that if nucleic acid testing of
6 plasma pools is put in place, that eventually someone will
7 propose substituting this testing for other existing test
8 recommendations. The prototype for this might be a
9 theoretical proposal to substitute nucleic acid testing of
10 pools for the recommended HIV p24 antigen testing on
11 individual units.

12 I'd like to point out that the recommendations
13 for p24 antigen testing that were issued by FDA last year
14 did include the offer to consider alternative strategies if
15 these were proposed.

16 One way to approach this issue might be to show
17 equivalence of the nucleic acid testing to the existing
18 test for p24 showing that nucleic acid testing could
19 capture all p24 antigen positives. In any case, it seems
20 fair to say that an IND and PLA supplement might be needed
21 for each blood product since substituting for a recommended
22 or required test is something that would require
23 modification of the license.

24 Final container testing presents a somewhat

1 different situation. Final container testing is generally
2 not linked to individual donors, and it might be possible
3 to regard final container testing as an in-process control.
4 In this case, a PLA supplement would be needed for each
5 product just as it would for any change in the
6 manufacturing procedures and control testing.

7 When an FR notice appears in the near future,
8 some of the regulatory concerns that we would like to see
9 addressed in the discussions and comments include the
10 rationale for selection of minipool size, the impact of the
11 size of the minipool on the sensitivity of the test, and
12 the impact of the degree of dilutions.

13 The sensitivity and specificity of the test
14 itself must be addressed and the ability of the test to
15 detect virus variants, for instance, the ability to detect
16 HIV group O variants.

17 There are issues relating to tracing the
18 positive results back to the donor and the logistics of
19 retrieving or removing the infected units.

20 Manufacturing consistency and GMPs must also be
21 addressed.

22 Because of the technology of nucleic acid
23 testing, controls for contamination by previously amplified
24 products must be in place. The stability of the nucleic

1 acid being amplified must be addressed in terms of the
2 temperature in which specimens and reagents have been
3 stored. The reproducibility of the assay and validation of
4 instrumentation software for identifying the infected unit,
5 that is, the software that is used to plan the pool and
6 matrix, and lot release requirements will have to be
7 addressed.

8 In summary, I'd like to say that it seems clear
9 that nucleic acid testing has merit, but that assay
10 validation is necessary to ensure that the test is
11 reliable.

12 There are issues regarding the regulation of
13 the test and regarding the regulation of the products that
14 are subjected to the test that must be addressed.

15 Donor notification is an important ethical and
16 public health issue that needs to be addressed.

17 And I would like to encourage any manufacturers
18 who have an interest in nucleic acid testing of plasma
19 pools to please schedule meetings directly with FDA. At
20 any time seems appropriate, including before the appearance
21 of any recommendations for regulatory policy.

22 Thank you.

23 DR. SWISHER: Are there questions from the
24 committee for Dr Tabor? Yes.

1 REV. LITTLE: Perhaps you've already said this,
2 but were the statistics given in the first slide based on
3 sensitivity of testing in the minipools or on individual --

4 DR. TABOR: Individual units.

5 REV. LITTLE: Individual units.

6 DR. TABOR: That's from a published study.
7 Some of that data has been discussed. I believe it was
8 discussed at the December advisory committee meeting, but
9 it certainly has been discussed in a number of fora during
10 the past four to six months.

11 REV. LITTLE: Also, how are you defining
12 minipool, or has that not been established yet?

13 DR. TABOR: Let me make one general comment
14 first before answering that.

15 This is a very unusual regulatory situation.
16 This is not a situation yet in which FDA is asking
17 manufacturers to do the testing. This is a situation in
18 which manufacturers are knocking on the door of FDA asking
19 to be allowed to do the testing or perhaps asking trying to
20 do the testing with a minimum amount of FDA control.

21 We're concerned that this be addressed by the
22 advisory committee because there are a number of regulatory
23 and health issues that could arise from whatever decisions
24 are made regarding regulation of this testing.

1 Now, minipool size is one of those issues.
2 Clearly, the larger the pool, the greater the dilution of
3 the material. This clearly would also affect your ability
4 to detect samples that have a lower concentration of virus
5 in them.

6 I think probably in the open public hearing
7 part of this session you'll hear comments by industry
8 representatives concerning the size of the pools they're
9 proposing, but clearly that's an important issue. Just to
10 give you an idea, some people are proposing pools involving
11 500 donors, for instance.

12 DR. SWISHER: Carol?

13 DR. KASPER: Would you help me with the
14 bureaucracy aspect of this? Are manufacturers allowed to
15 use nucleic acid testing before the FDA decides exactly how
16 and what size and how it would be regulated and so on, or
17 are they forbidden to use such testing?

18 I think we went through this once with HCV
19 testing of plasma where it was forbidden. You were not
20 allowed to do HCV testing for source plasma until the FDA
21 decided that they were allowed to do HCV testing.

22 Are manufacturers allowed to use nucleic acid
23 testing while all of these fine points are being worked out
24 since some of them have it ready I gather?

1 DR. TABOR: Dr. Epstein, would you like to
2 comment?

3 (Laughter.)

4 DR. EPSTEIN: Why do I always get the hard
5 questions?

6 I guess the paradox is they're allowed when
7 they validate. In other words, it's not that they're ready
8 and they're not allowed. It's that they're allowed when
9 they're ready. So, our role is to establish the conditions
10 for accepting approvals to implement. The key concept here
11 is that we want to know that the tests work as they should
12 work.

13 Now, much of the discussion that you're going
14 to hear is in regard to the strategy for linking
15 development of pooled PCR as a manufacturing control for
16 product -- and here we're talking really about plasma
17 derivatives -- to concurrent development of the PCR as a
18 donor screen linked to notification.

19 The posture that FDA is putting forth as a
20 proposed policy, which will be published for comment, is
21 that we will permit manufacturers to go forward and
22 implement PCR as a manufacturing control provided that they
23 have done the necessary preclinical studies to validate the
24 assay characteristics, the consistency of the reagents,

1 lot-wise monitoring, analytic sensitivity, reproducibility
2 of the assay, et cetera, and provided that they have
3 committed to some linkage to an IND to validate the
4 clinical performance and the accuracy of the information
5 for donor notification.

6 Now, the manufacturer will not necessarily have
7 to be also the IND sponsor, but the FDA wants that linkage
8 because otherwise what you will end up with is the
9 implementation of the PCR and lack of clarity whether the
10 public health implications of positive tests will ever be
11 addressed.

12 We feel that whereas it is certainly important
13 to allow PCR to be developed so that only PCR-negative
14 pools are fractionated into plasma derivatives, that it is
15 also important that when you have positive pool testing and
16 can identify the positive donor, that that donor be
17 notified so that the donor can have early intervention and
18 so that secondary prevention can be provided to exposed
19 partners and so that further donations, which might also
20 still be in the window period, could be interdicted.

21 So, what FDA is saying is that we care equally
22 about the implementation of the pooled PCR as a process
23 control and the development of the PCR test as an accurate
24 donor screen. That's why we're putting forth a policy that

1 links those developments.

2 Again, the short answer to your question is
3 that, yes, manufacturers must get a green light from the
4 FDA, but the condition for implementation is simply that
5 they have valid assays. They just have to demonstrate
6 valid assays and then they can go forward.

7 DR. SWISHER: It's clear that one of the
8 principal motivations for PCR testing is the European
9 market. Another way of putting Dr. Kasper's question would
10 be to say, well, if the manufacturer made no claims, vis-a-
11 vis the products that are made and distributed in the
12 United States, would it be possible for them to use their
13 own version of a PCR test and to exert those claims only in
14 their European market? Would that be within the legal
15 requirements?

16 DR. EPSTEIN: U.S. manufacturers cannot make
17 different claims for their products in the U.S. Since we
18 will be permitting manufacturers to implement
19 investigational assays -- in other words, we would allow
20 them to implement after preclinical validation provided
21 that they're linked to an IND. In essence then, we're
22 regarding the assays as investigational from the standpoint
23 of donor screening. However, we would be regarding the
24 implementation for product testing as approved under the

1 license. Certainly that fact can be made known to anyone,
2 whether domestic or Europe.

3 But we are seeking to avoid a situation in
4 which there is stratification either of product, screened
5 or unscreened, for the U.S. or for the European market or
6 stratification of claims. So, in fact, what could be
7 claimed up to the point of licensure of the pooled PCR as a
8 donor screen is that an investigational test is being used
9 to screen the collections. That would be a true statement.
10 It could be labeled. It could be stated in the U.S. or
11 Europe. And we believe that that would fully enable
12 manufacturers to comply with the European requirement.

13 So, that's the essence of the implication of
14 the policy. The policy that we'll publish will be a
15 statement of criteria for implementation and approval of
16 pooled PCR. The implications of that policy will be that
17 there can be interim implementation of an investigational
18 pooled PCR, and that should be timely to meet any European
19 requirement.

20 I believe that we do have representatives of
21 the European fractionation industry who are prepared to
22 comment about the developments in Europe at the appropriate
23 time on the agenda.

24 DR. SWISHER: I raised that question because

1 having heard the question in another context in another
2 discussion of this particular topic, it seems pretty clear
3 that the route that is being laid out now is the route that
4 we're going to have to take for United States manufacture
5 of these products.

6 DR. EPSTEIN: Well, we're talking about a
7 proposed route to take. I think the part that's clear is
8 that the manufacturers perceive urgency on account of
9 European requirements pending.

10 DR. SWISHER: Let's move along unless there are
11 other questions of Dr. Tabor and hear a little bit more
12 about the technological side of this issue from Dr. Indira
13 Hewlett who will talk about the overview of the nucleic
14 acid testing and validation procedures. Dr. Hewlett?

15 DR. HEWLETT: Good morning. What I'd like to
16 do this morning is to provide you with a very brief
17 overview of nucleic acid testing and then discuss some of
18 the issues in validating these assays, as well as some
19 procedures that might be helpful to achieve this
20 validation.

21 Nucleic acid technology has been under
22 development for almost a decade now, and these techniques
23 can be broadly classified as target amplification or probe
24 amplification based methods. The most commonly used target

1 amplification methods are PCR and NASBA, nucleic acid
2 sequence based amplification, although there are other
3 methods such as strand displacement amplification which is
4 also being used in limited settings, particularly in
5 research laboratories.

6 The target amplification involves the actual
7 amplification of the target sequence, whereas probe
8 amplification works by amplifying the probe sequence that
9 binds to the specific target.

10 Examples of probe amplification are branched
11 DNA and ligase chain reaction. The first method, branched
12 DNA, seems to have gained more popularity than other probe
13 amplification methods. What I'd like to do in the next
14 couple of slides is briefly outline the principles behind
15 the three most commonly used methods, PCR, NASBA, and
16 branched DNA.

17 This basically outlines the schematic of PCR
18 technology, and I think most people here are aware of
19 what's involved with PCR. PCR can be used to amplify both
20 RNA and DNA. In the case of RNA, one goes through the step
21 of converting the RNA template into cDNA using a reverse
22 transcriptase enzyme.

23 The rest of the reactions are common to both
24 RNA and DNA templates, and they involve denaturation of

1 your target sequence, followed by binding of specific
2 oligonucleotides, referred to as primers, that would anneal
3 to complementary sequences in the target sequence. This
4 annealing step is then followed by extension where the
5 strand is copied. Repeated cycles of this process then
6 result in the amplification of your target sequence several
7 million-fold.

8 With PCR techniques, I think there have been a
9 range of sensitivities. The sensitivity is often dictated
10 by the primer sequences and the probe sequences, as well as
11 the target that is identified for amplification. If one
12 wants to enhance the sensitivity of PCR, you can then go
13 back, of course, with probe sequences that are derived from
14 or complementary to the amplified DNA. Sensitivities range
15 anywhere from a single copy level up to several hundred
16 copies.

17 The second technique, NASBA, differs from PCR
18 in that it is carried out under isothermal conditions.
19 Generally this is 42 degrees, which is the optimal
20 temperature for activity of the enzymes that are involved
21 in this method. Again, the RNA template is converted to
22 DNA by reverse transcriptase. In this instance, however,
23 instead of using TAQ polymerase, you then prime synthesis
24 of a new RNA strand, that is, transcription off of the cDNA

1 using a T7RNA promoter sequence and T7RNA polymerase. So,
2 this is just a variation on the theme, but it allows the
3 amplification to proceed under isothermal conditions which
4 makes it more user friendly and easy to manipulate.

5 Again, the sensitivity of NASBA has been shown
6 to range anywhere from a few copies to several hundred
7 copies.

8 Finally, branched DNA amplification, which is
9 different from the previous two methods in that you
10 actually use a series of probes to detect and amplify a
11 target sequence, involves release of the nucleic acid,
12 followed by capture of the released nucleic acid by a
13 series of contiguous capture probes. These probes are then
14 further hybridized, and all of this is based on homologous
15 base pairing as opposed to enzymatic extensions. These
16 probes are then hybridized to a series of extender probes,
17 followed by hybridization to a branched DNA which is
18 referred to as an amplification multimer.

19 This entire complex is then hybridized to
20 probes that contain reporter molecules, usually an enzyme,
21 and the branched DNA is then detected using a
22 chemiluminescent reaction.

23 When this technology first came out, it was
24 less sensitive than the target amplification methods.

1 However, there have been more recent versions of this
2 assay, but apparently do go down to a detection limit of a
3 couple hundred copies.

4 So, that basically gives you a flavor of the
5 types of techniques we're talking about here with reference
6 to their application to pooled testing. As you can see,
7 although they are different in some ways, there are certain
8 common elements to them. Most of these techniques involve
9 the use of synthetic oligonucleotides and enzymes to
10 amplify a piece of DNA in your target.

11 So, there are a set of issues that are common
12 to all of these nucleic acid tests, and I'll briefly go
13 through the issues listed here.

14 The first is that nucleic acid testing is in a
15 state of constant evolution, and this is a very important
16 aspect. The reason this is happening is the technologists
17 are obviously trying to improve specificity and
18 sensitivity. So, assay modifications occur more frequently
19 than with some of the other analytes that we've been used
20 to detecting in the past such as antibodies.

21 It's important to bear in mind that these
22 different methods, such as PCR, NASBA, et cetera, have
23 different sensitivities. They often range anywhere from
24 the single copy range to several thousands of copies, and

1 this again varies. It can also vary among various PCR
2 techniques. So, there is no specific, defined limit of
3 detection for a PCR assay. It's often dictated by the way
4 the assay is configured.

5 Problems with PCR and related techniques.
6 Because of the intrinsic sensitivity of these methods,
7 there tends to be a possibility or there tend to be some
8 false positive reactions, and this happens because of
9 either sample or amplicon contamination. There may be some
10 false negative reactions due to the presence of inhibitory
11 substances in clinical specimens that might even copurify
12 with the extracted nucleic acid.

13 Another issue to be borne in mind with regard
14 to nucleic acid testing is that amplification, in general,
15 to detect a target, involves a small fragment of the
16 genome, and often these fragments are as small as 200 to
17 300 base pairs. This is pretty small when you think of the
18 size of a viral genome such as HIV which is almost 9.7
19 kilobases.

20 So, this of course generates a concern about
21 potential false negatives if one uses just a single primer
22 set that defines a very small fragment because there could
23 be some misses due to mismatches which can occur
24 particularly in relation to genetic variance. This is an

1 issue that I'll address later on in the design of primers.

2 We also run into the desirability, the issue of
3 having automation of the integrated test method. There are
4 several different aspects or different steps in PCR
5 technology. Starting from the actual specimen processing
6 to the amplification and detection, one could have as many
7 as a half a dozen steps in the assay. Ideally it would be
8 highly desirable to automate the integrated test method,
9 and I think this is also an issue. Of course, it's an
10 issue for most assays in general, but in particular for
11 nucleic acid technology, so that this may now become more
12 widely applicable in a variety of settings.

13 A point in favor of development in nucleic acid
14 testing is that there have been rapid technical advances
15 made in specific areas such as sample processing, enhanced
16 test performance, novel ways of quantitating viral nucleic
17 acid, and ways of improving the throughput of the assay.

18 So, as I've said previously, nucleic acid
19 testing offers us certainly a very attractive way of
20 achieving greater sensitivity for viral detection and for
21 quantitation, and it has been used in both research
22 laboratories and in clinical laboratories.

23 In regard to blood and plasma-derived products,
24 there have also been situations where there is demonstrated

1 utility for these nucleic acid tests. Of particular note
2 is the early detection of virus in the seronegative window
3 phase. This, of course, greatly helps in reducing the
4 transmissions that might arise from contamination of pools
5 by window donations.

6 So, the use of these assays, of course, would
7 then be to screen individual donors. They could be
8 screened by donor pools, testing of donor pools. This type
9 of an approach would also work to reduce or eliminate any
10 contamination of plasma pools prior to manufacture.
11 Finally, it may also be applied to final container testing,
12 and some of this has already been in effect due to
13 recommendations from the FDA for testing of certain
14 products for HCV RNA.

15 I'd now like to move on to the actual
16 validation issues and discuss some of the techniques that
17 might be useful to validate these methods. Validation, of
18 course, has two different parts to it: first the
19 validation of the manufacture of the test kit and, second,
20 the clinical validation which does in fact establish
21 performance characteristics for the assay.

22 Since this discussion is focused more on pool
23 testing, what I've done here is to enumerate a few issues
24 that are unique or specific for pool specimens. I'd like

1 to very quickly go through these and then address some of
2 the manufacturing issues in the subsequent slides.

3 The issues that are specific for pool specimens
4 obviously is the demonstration of enhanced sensitivity of
5 the pool test or equivalence of testing pools to currently
6 licensed methods, the establishment of the absence of
7 matrix effects due to pooling that might have a negative
8 impact on the test performance.

9 There will be a need to establish validated
10 procedures for logging and tracking of inventory of
11 specimens in a given pool so that specimen retrieval
12 procedures would identify the true positive specimen in a
13 positive pool. This, of course, would require good quality
14 control and quality assurance in computing of the entire
15 procedure and a reporting of results so that tracing can be
16 performed accurately. Obviously, instrumentation and
17 software which almost definitely will be involved
18 performing these procedures will need to be validated.

19 I'm going to now focus on some of the
20 manufacturing issues with assay validation. Before getting
21 into the actual manufacture of the test kit and its
22 components, I think it's very important to think carefully
23 when designing the assay and to establish a very good
24 rationale for the specific assay format and the actual

1 components that I used in the assay.

2 Most important I think are the selection of
3 target sequence. That is, you want to figure out which
4 target you would like to amplify for detection in the test.
5 Some of the criteria could be, for example, assessing the
6 degree of conservation of the sequences among different
7 variants. This, of course, is a big issue in detection of
8 viruses where there are several different strains that are
9 genetically diverse.

10 The issue of single versus multiple target
11 sequence also should be addressed. This is important,
12 particularly in light of what I had mentioned previously,
13 in that amplification often involves a very small fragment
14 of the target DNA, and there may be a possibility to
15 generate false negatives because of mismatches or other
16 reasons, but primarily mutational effects and mismatch
17 effects.

18 So, we want to think carefully about whether
19 it's adequate to use just a single primer pair to detect a
20 specific virus or would it be better to use multiple target
21 sequences. At this moment I believe our preference at the
22 FDA is to see multiple target sequences in the assay so
23 that this would minimize the potential for false negatives.
24 Of course, this can be demonstrated or can be established

1 through clinical validation.

2 We then should also consider the selection of
3 the primary probe sequences which has the same impact, in
4 fact, a greater impact than the actual selection of the
5 target sequence, but both of these aspects bear very
6 heavily on the sensitivity and specificity of the assay and
7 therefore should be designed very carefully.

8 Again, a rationale for the specific type of
9 controls, both internal and external, as well as any
10 quantitation standards if you're talking about a
11 quantitative assay, should also be very strongly
12 considered.

13 Having established a rationale for the assay,
14 then moving to the optimization phase -- and this is also
15 very critical and does have impact, of course, on the
16 actual performance characteristics in the end.
17 Optimization can involve optimizing, for instance, the
18 length, the specificity, the efficiency of the primers and
19 the probes, establishing optimal conditions for extraction,
20 amplification, detection, optimizing the limits on internal
21 and external controls, calibrators, procedures to control
22 contamination. This is also a very critical aspect of
23 amplification because of course you can get contamination
24 from both specimen carryover and ideally it would be useful

1 to have some chemical way of inactivating amplicons. If
2 not, then there have to be very good validated procedures
3 that would enable one to track these contamination events.

4 At this point it's also important to determine
5 an estimated lower limit of detection and establish the
6 linear range of the assay for quantitative technique. Of
7 course, these two aspects will need to be addressed by
8 statistical methods.

9 The manufacturing issues. Then having
10 optimized the assay, you then move into actually a
11 manufacturing test, test kit and the components. Of
12 course, this is just a very small list of points that I
13 hope to address in the next couple of minutes. Of course,
14 there are a lot of different issues when one gets into
15 manufacturing of the kit components, controls, et cetera,
16 but what I'd like to focus on are sample processing, some
17 issues to do with the components, primers and probes,
18 controls, capture probes, detectors, et cetera, and the
19 solid phase that's used for capture, detection.

20 An important issue is the stability of the
21 specimen as well as the kit and its components. Specimen
22 stability obviously can be linked to studies on sample
23 processing, and it's a good stage whereby you can work up
24 conditions for storage.

1 Finally, there is the issue of instrumentation
2 of software, but I'm not going to discuss that in today's
3 presentation.

4 Sample processing involves, of course,
5 collection, and in most instances, as I think we're
6 beginning to see, the sample is collected and is shipped to
7 a different site for testing. So, it is very critical to
8 establish validated conditions for collection of the
9 sample. This should include evaluation of anticoagulants
10 that are used to prepare plasma, conditions for shipping as
11 well as for storage of these specimens both at the
12 collection site as well at the testing site.

13 It would be important to specify what types of
14 reagents are being used to collect and extract. That is,
15 you have to define the reagents that are actually critical
16 to extracting the nucleic acid. Of course, at the sample
17 preparation stage, you want to consider, in fact very
18 strongly consider, the use of controls that would monitor
19 the extraction efficiency. Ideally these should be similar
20 to the specimen type that is being tested. Other controls
21 that you want to assess at this point is actually reverse
22 transcription and amplification which really comes into
23 play only once the nucleic acid is extracted.

24 Another issue with regard to sample preparation

1 is determining the reproducibility of the extraction method
2 and defining a percent recovery for the extraction method
3 so that you can monitor whether there is reproducibility
4 during the extraction process. Of course, as we know, the
5 percent recovery does have an impact on the overall test
6 performance.

7 This slide just lists some of the issues to do
8 with primers and probes. What I'd like to focus on here,
9 since I've already discussed the rationale for design of
10 primers, as well as the types of information that you would
11 be looking for when optimizing the assay -- I'd like to
12 just discuss these two points, and that is the use of in-
13 process controls and good quality control testing to
14 establish the purity of the oligonucleotides that are being
15 used and the nucleotide sequencing, some way of
16 establishing the identity of the synthetic
17 oligonucleotides.

18 This, of course, may be considered as a one-
19 time validation, but at this point I think what we'd like
20 to see is established specifications for these parameters
21 on a lot-by-lot basis.

22 The generation of specifications for the
23 components, of course, will also apply to components such
24 as the enzymes. Obviously with techniques like PCR and

1 NASBA, there are several different enzymes that actually
2 perform the amplification and are critical to the overall
3 assay performance. So, here the issues would be similar to
4 what I discussed for primers and probes in that you would
5 want to perform some type of testing to demonstrate
6 identity, purity, potency, and specific activity,
7 particularly if these enzymes are produced in-house. In
8 some instances, one may purchase these enzymes from vendors
9 where, of course, a certificate of analysis is very
10 helpful, but in addition, the sponsor should perform some
11 type of acceptance testing to qualify the component and
12 establish acceptance criteria.

13 Controls are critical to ensure that a test kit
14 is performing optimally. Controls are part of any given
15 test kit. In the case of nucleic acid testing, there is an
16 even greater need to run additional controls, as I had
17 discussed in my previous slides. So, you end up having
18 more than two different controls, that is, a negative and a
19 positive. You actually have multiple controls. These
20 would include controls for the various steps, extraction,
21 amplification, et cetera. There are usually internal
22 controls that are added to the specimen and are used to
23 monitor the actual extraction and amplification methods.

24 This, of course, would then mean that there is

1 a need and a rationale to ask for more than one positive
2 control. Ideally we'd like to see two positive controls,
3 one close to the lower limit of detection of the assay.
4 There may be multiple negative controls in the kit, such as
5 reactions that do not contain the enzymes or the primers
6 and probes. There may be controls for cross-contamination,
7 and in all cases and for all types of controls, we would
8 want to see validation data and acceptance criteria
9 established for each of these components.

10 Finally, I'd like to discuss very briefly what
11 is generally involved in clinical evaluation.

12 Clinical evaluation has several different
13 components, but the most critical ones are establishing the
14 reproducibility of the assay which includes precision and
15 proficiency testing. Precision is done on multiple days
16 using different operators and kit lots. Proficiency
17 testing assesses the proficiency of the operator. The
18 value of both these types of testing is greatly enhanced by
19 using operator training programs to generate proficient
20 operators, as well as the use of well-characterized
21 reference materials.

22 Some reference materials have already been
23 generated by the AIDS Clinical Trials Group, ACTG, of the
24 NIAID. However, more recently there has been a lot of

1 effort both within CBER and at the international level,
2 that is, the WHO and the NIBSC, to generate standards that
3 can be used to optimize these various amplification
4 methods.

5 Reproducibility, of course, establishes whether
6 the assay generates the same result within a certain range
7 from run to run. The analytical sensitivity defines the
8 dilutional endpoint, that is the lowest limit of detection
9 of the assay. It can be assessed using dilutional panels
10 or plasma and sera that have been spiked with the analyte.
11 In all of the testing that's involved, I think it's optimal
12 to include some comparator assays. Ideally these should be
13 antibody, antigen, and other RNA tests wherever possible.

14 RNA tests, like other types of tests, do have
15 some nonspecific reactivity that might arise from a
16 different set of conditions. However, the effect of
17 interfering substances and other conditions on the possible
18 false positivity or in some instances false negativity,
19 which is a sensitivity issue, has to be addressed by
20 looking at a variety of conditions.

21 Most common I think and most pertinent are
22 other infections that might result in false positivity, the
23 use of anticoagulants which might interfere with the assay,
24 cause false negative results, certain conditions of the

1 sample, that is, hemolysis, contamination, and as well as a
2 series of conditions that may be specific and unique to
3 nucleic acid testing where specimens that involve or might
4 contain nucleic acid binding substances or nucleic acid
5 based drugs, metabolites, et cetera may also need to be
6 evaluated to rule out any nonspecific reactivity.

7 Finally, of course, autoimmune diseases also
8 might contribute to certain false positive reactions.

9 Finally, the use of clinical trials and field
10 testing is obviously the ultimate proof that the test does
11 in fact work as it's expected to in a given patient
12 population. These are just very general points here, and
13 the numbers you're seeing are generally numbers that we
14 require for HIV 1 testing.

15 But in general, specificity is established by
16 testing clinical specimens from a seronegative population
17 where the reactive specimens should be resolved by follow-
18 up testing. Sensitivity is established by testing known
19 positives, and these positives for viral detection, of
20 course, should include various genetic variants, subtypes,
21 and groups, and should also be derived from various risk
22 groups, disease stages, and possibly address gender
23 effects.

24 So, with those brief points that I've again

1 very briefly discussed, I'd like to conclude by summarizing
2 the key points that are relevant for testing of plasma
3 pools and basically reiterate what I've already said.

4 There need to be established and validated
5 procedures for tracking plasma pools and retrieval of
6 specimens, if one runs into reactive specimens.

7 The sensitivity of pool testing should be
8 established and its equivalence to currently licensed
9 methods should also be evaluated, as also should matrix
10 effects that might have an impact on the performance
11 characteristics of the pool test.

12 There should be adequate, in fact, good use of
13 quality control methods to assure that manufacturing
14 consistency of the test kit components does in fact occur
15 on a lot-by-lot basis.

16 Nucleic acid testing, being obviously a very
17 complicated protocol relative to some other types of
18 testing, is going to be greatly benefitted by the use of
19 operator training programs that are designed to make the
20 staff proficient at running these tests. And this type of
21 testing program, of course, would also be greatly aided by
22 the use of well-characterized reference materials.

23 Finally, the performance characteristics of the
24 assay, which define whether the assay is useful or

1 acceptable for that particular purpose, which in this case
2 is testing of plasma pools, is established by clinical
3 validation.

4 So with that, I think I'd like to conclude and
5 thank you for your attention.

6 DR. SWISHER: Are there questions from the
7 committee? Dr. Verter?

8 DR. VERTER: Yes. It's not a question. It's
9 more of a request. I was wondering if Dr. Hewlett could
10 give Dr. Smallwood a copy of her overheads to distribute to
11 the committee for future use. I know it would help me a
12 great deal in thinking about the issues before I come to
13 the committee in helping formulate questions.

14 DR. AUGUST: This is a very small point but it
15 has come up twice so far this morning. What is a matrix
16 effect?

17 DR. HEWLETT: I think we're talking about -- a
18 matrix effect is just a term that has been coined to define
19 any effects that might occur within the pooling matrix or
20 the matrix that is being tested, which in this instance is
21 a plasma pool. The matrix effects we're referring to are
22 effects that might be generated when you pool 11,000
23 donors, for example, or donations from several different
24 donors that might have in them substances that in a single

1 donation may not cause any problems in an assay, but when
2 it is mixed in with other components, the substances that
3 may be present in other specimens can in fact cause certain
4 types of reactions that might interfere with the assay.

5 So, we're looking usually at inhibition when
6 you talk about these matrix effects. I don't believe there
7 have been any reports of false positivity.

8 DR. HOLLINGER: Charles, we saw that many years
9 ago when samples were often pooled for testing and you'd
10 have a group of samples that were all negative, for
11 example. Then you'd pool them, and then all of a sudden,
12 the pool would sometimes appear to be positive either from
13 a false positive standpoint or perhaps even from a positive
14 standpoint. I think this sort of points out some of the
15 matrix effects that one sees with pools.

16 DR. VERTER: So, are you saying that if you
17 were to test the 11,000 individuals, you would not have
18 that effect. It's just a function of the fact that there
19 are 11,000 donors and there's some interaction between some
20 of them that create a falseness.

21 DR. HEWLETT: Right. That's essentially what
22 -- and yes, I think Dr. Hollinger is right. There can be
23 both false positive and false negative reactions.

24 DR. NELSON: You referred only briefly to how

1 you determine pool size. To me it's a rather complex issue
2 because the pool will be tested for several different
3 infectious agents, and the sensitivity and the specificity
4 of each PCR assay or each nucleic acid assay might be
5 different. Then you throw in the matrix issue and it
6 becomes very complex because it may not be a single agent
7 that will be tested.

8 Do you want to comment on that? Or how are we
9 going to go about making that decision?

10 DR. HEWLETT: I think that's a very good
11 question and that's the question that we're all wrestling
12 with actually even within the FDA as to what is the optimal
13 pool size. We're going to be seeing data as we go along as
14 to the impact of pool size. It very clearly will have an
15 impact on the actual sensitivity of the test.

16 But with regard to the different viral markers,
17 there's a combination of things going on there. There's
18 the impact of the pool size, the matrix effects, and then
19 you have the varied sensitivities of the PCR or the NASBA
20 test that has been used to detect the hepatitis C versus
21 HIV. As we know, with HIV there seems -- it sounds like
22 you can go into the single copy range detection, not taking
23 into account the matrix effects or the pool size. Now you
24 add those to the algorithm.

1 So, I don't know where we're going to end up in
2 the end, but I think obviously there may be ways to modify
3 the assays so that the impact is minimal.

4 DR. NELSON: In testing this, will the
5 manufacturers have various combinations of infections or
6 numbers of positive specimens with different viruses,
7 combinations of that in the standard -- for the performance
8 standard? Would that be required?

9 DR. HEWLETT: I'm sorry. I didn't understand
10 the question. Are we talking about a standard that has
11 multiple viruses like the ACTG is thinking of?

12 DR. NELSON: Yes.

13 DR. HEWLETT: For pool testing, if it's a
14 multiplex assay where two different tests are going to be
15 run on the same specimen in the same tube, obviously that's
16 the type of standard we would need. At this point I think
17 most agencies are looking at single standards where you're
18 looking at an HIV 1 clade B virus, for example, an HCV
19 genotype 1a.

20 I think eventually, though, we are going to get
21 to a point where we'll have to put in different viruses or
22 strains. For example, with HIV 1 there has been some
23 discussion of generating a standard that it includes all of
24 the known clades in one specimen. That's the direction in

1 which I think we'll be going in the future.

2 But whether there are going to be two different
3 viruses in the same standard I think will be dictated by
4 the application of that particular test. If it's going to
5 be used as a multiplex test on pools in a single tube,
6 obviously the best standard there is one that has both
7 viruses in the same preparation.

8 DR. KHABBAZ: Another question. You raised the
9 issue of validation vis-a-vis currently licensed tests,
10 current sensitivity, and Ed in his presentation alluded to
11 substitution of nucleic acid tests for other tests. Are we
12 talking about nucleic acid testing replacing other required
13 tests at this point or an additional test for plasma pools?

14 DR. HEWLETT: I think we're probably looking at
15 two different scenarios, as Dr. Tabor mentioned. There is
16 a scenario where one could possibly consider substituting
17 an RNA test for perhaps a p24 antigen test or do it in
18 addition to p24 antigen. I think that's probably the only
19 scenario where we at this point may be considering
20 substitution of tests. But in general this is going to be
21 a test that is performed in addition to all the other viral
22 marker tests.

23 DR. TABOR: The issue of substitution is a
24 theoretical one at present, but it's certainly going to be

1 raised by somebody before long. I think it's a potential
2 issue that may be raised for more than one of the viruses.

3 DR. SWISHER: It seems to me we're quite a
4 distance from making that decision at the present time.

5 I think we'll move on and ask Dr. Paul Mied --

6 DR. KHABBAZ: I hope so. I think my concern is
7 that we may not be that much away from substitution and
8 that raises concern relating to validation and making sure
9 that when it happens, it happens in due time and not be
10 rushed.

11 DR. SWISHER: We'll ask Dr. Paul Mied to
12 conclude the staff presentations on this topic, donor
13 deferral, notification, reentry, and lookback issues.

14 DR. MIED: Thank you, Dr. Swisher.

15 These are considerations for the committee
16 concerning nucleic acid testing of plasma pools on the
17 issues of donor deferral, notification, reentry, and
18 lookback following the obtaining of a positive nucleic acid
19 test result on the minipool and then a positive test result
20 on an individual donation in that minipool.

21 In the near future, FDA will be publishing a
22 Federal Register notice containing draft guidance for
23 public comment regarding the testing of plasma pools for
24 viral nucleic acid. That draft guidance likely will state

1 in part that if a positive result is obtained for a plasma
2 pool, subsequent testing to identify the individual unit
3 that is positive, as the basis for the positive result on
4 the pool, may be appropriate.

5 FDA considers a positive result obtained on an
6 individual plasma donation for nucleic acid of HIV, HBV, or
7 HCV, using an investigational testing method performed
8 under IND, to represent presumptive evidence of infection
9 with the virus. If a blood or plasma donation is positive
10 on an investigational testing method for viral nucleic
11 acid, a concern for recipient safety emerges due to the
12 possibility of disease transmission if the unit is used and
13 if a donor continues to donate. This possibility should be
14 taken into consideration particularly in the case of tests,
15 such as viral nucleic acid test methods, because of their
16 potential for identifying units from donors in the
17 infectious window period which would not be interdicted by
18 currently available EIA tests for markers of viral
19 infection. A positive nucleic acid test result, even
20 though the assay is investigational and not FDA-approved at
21 the time, might indicate ongoing donor infection and thus
22 pose a risk to recipients.

23 In December 1993, FDA sent letters to the
24 American Association of Blood Banks, the Council of

1 Community Blood Centers, and the American Red Cross
2 expressing concerns relative to donor suitability, informed
3 consent, and recipient safety during the testing of viral
4 marker assays under IND.

5 In accordance with FDA's stated concerns, we
6 feel that as part of informed consent, it is desirable to
7 notify donors that should they test positive by nucleic
8 acid assay under investigation, that their donations will
9 not be used. It is also desirable that the information
10 state that the accuracy of the investigational test results
11 has not yet been determined but should be defined by the
12 completion of the clinical trial.

13 We would also like to set forth the following
14 considerations for the committee which may represent the
15 most appropriate course of action pertaining to the donor
16 and the donation in the face of a positive test result on
17 an individual plasma donation using an investigational test
18 method for viral nucleic acid. I'd like to emphasize that
19 these are not recommendations by the agency, but they're
20 considerations for the committee in advance of future
21 publication of these issues in the Federal Register for
22 public comment.

23 First of all, unit exclusion. Exclusion of the
24 donation from transfusion for further manufacture into

1 injectable products may be warranted as a means of
2 safeguarding the recipients of transfusable products to be
3 made from this donation from possible infection with the
4 virus.

5 Donor deferral. In general, FDA has previously
6 recommended that, as a result of a repeatedly reactive
7 result on a licensed viral marker test and for some markers
8 repeatedly reactive on more than one occasion, the donor
9 should be deferred indefinitely or for a minimum period of
10 time, for example, six months.

11 We would like to suggest for the committee's
12 consideration that a donor whose donation tests positive,
13 using the nucleic acid testing method, when it becomes a
14 licensed testing method, be deferred from further donating
15 until it can be conclusively determined whether or not the
16 donor is infected.

17 In addition, in accordance with our letters to
18 the blood organizations in December 1993, we feel that if
19 the nucleic acid testing method is an investigational
20 method under IND, holding the donor in abeyance and
21 classifying them as investigational results pending and not
22 accepting subsequent donations from that donor until their
23 suitability can be resolved in the context of the clinical
24 trial may be the appropriate course of action.

1 Donor notification and counseling. Now, Dr.
2 Tabor listed some of the benefits of donor notification,
3 and we would also like the committee to consider this
4 ethical and public health issue of notification and
5 counseling of the donor regarding the meaning of a test
6 result and the need for medical referral so that follow-up
7 testing may be performed to conclusively determine whether
8 or not the donor is infected.

9 Donor reentry. In general, for purposes of
10 reentry of donors who have been deferred, it appears most
11 appropriate to obtain a fresh sample from the donor
12 following the deferral period and to perform testing for
13 viral markers in accordance with current FDA
14 recommendations for the use of licensed tests and reentry
15 algorithms that are currently in use. These considerations
16 may also be applied to donors deferred following a positive
17 nucleic acid test result.

18 Product retrieval. We would also ask the
19 committee to consider that if a positive result obtained on
20 an individual plasma donation for nucleic acid of HIV, HBV,
21 or HCV represents presumptive evidence of infection with
22 the virus, as outlined in FDA's existing recommendations
23 regarding product retrieval and the published rule on
24 lookback, it is appropriate to quarantine previously

1 collected units of whole blood and blood components for
2 transfusion dating back three months or units of plasma for
3 further manufacture which have been previously collected
4 from the donor dating back three months.

5 If so, it may also be appropriate to notify
6 consignees so that units they hold in inventory which have
7 not been pooled or further processed may be quarantined.
8 As outlined in previous FDA recommendations, consignees
9 would then be notified concerning the results of
10 supplemental testing on the donor's current sample so that
11 prior collections held in quarantine may be released or
12 destroyed, and recipient notification may be performed at
13 the discretion of the attending physician.

14 FDA welcomes comments on these considerations
15 and on other issues pertaining to donor deferral and
16 notification, reentry, and lookback. FDA's proposed
17 guidance to blood and plasma establishments concerning
18 these issues will be published in the Federal Register for
19 public comment.

20 Thank you.

21 DR. SWISHER: Questions from the committee for
22 Dr. Mied? Charles?

23 DR. AUGUST: When this discussion started, the
24 reference was made to the testing of minipools. What's the

1 definition of a minipool?

2 DR. MIED: A minipool is not the real pool of
3 plasma. It's a pooling of samples from the individual
4 donations.

5 DR. AUGUST: My question really is, how many
6 individual samples comprise a minipool? The issue of pool
7 sizes has come up before in the committee and it gets to
8 the issue also of expense and so forth. My feeling is that
9 this is critical for us to know how many samples are going
10 to be in the minipools that are going to undergo testing.

11 DR. MIED: I think we'll hear some of those
12 proposals during the open public hearing, and maybe it's
13 best to defer discussion so that we can --

14 DR. AUGUST: Any ball park figures, ball park
15 estimates?

16 DR. MIED: We've heard estimates of 500 and
17 upwards.

18 DR. SWISHER: Carol?

19 DR. KASPER: As I understand it, minipools
20 would be tested before they become large pools --

21 (Laughter.)

22 DR. KASPER: -- therefore, before they are
23 pooled together to become maxipools.

24 (Laughter.)

1 DR. KASPER: -- and are then fractionated. So,
2 this step of nucleic acid testing is not very far removed
3 from the steps that are done on the individual donors such
4 as HIV antibody, HBV antigen, and so on. And those donors
5 who prove positive are notified I presume by the blood bank
6 or the plasma pheresis establishment.

7 It makes sense that the mechanism for
8 notification of someone who is positive by nucleic acid
9 testing should be through the same route. Why is this an
10 issue? Would it be any different?

11 DR. MIED: What we're doing is we're looking
12 ahead how we're going to handle these issues, keeping in
13 mind that there is not the capability for mass screening of
14 donors at the time that antibody testing and testing for
15 other markers is performed on those donations. So, we're
16 going back and testing individual units when a positive
17 result is obtained on the minipool. So, we're anticipating
18 that these issues will need to be dealt with when an
19 individual unit is identified as positive from that
20 positive minipool.

21 DR. KASPER: I don't understand because I do
22 know how this is working at one laboratory, and there isn't
23 this big interval of time. The idea is that the minipool,
24 on one pilot project, is tested within a short time of

1 donation and the results are back within a short time,
2 which is not much longer, that is a few days more, than the
3 HIV antibody and so on. So, what is the difference between
4 the mechanisms for this kind of testing versus the standard
5 serologic which may also be sent to a reference lab?

6 DR. SWISHER: Jay, do you want to respond at
7 this point?

8 As I understand, the minipool proposition is to
9 reduce the total number of PCR or nucleic acid tests that
10 have to be done, and this becomes an issue of the
11 availability of the resource and the cost and so forth, as
12 contrasted with testing each individual donation within a
13 pool.

14 DR. KASPER: Yes, I understand that, but if you
15 find a positive minipool, then you go back and test the
16 individuals in the minipool.

17 DR. SWISHER: Well, there may be strategies for
18 shortening that too.

19 DR. EPSTEIN: If I could comment, Dr. Kasper,
20 there are three issues that have been put in front of the
21 agency. Let me say that I'm pleased that you find the
22 agency's point of view self-evident, but others have not.

23 (Laughter.)

24 DR. EPSTEIN: And the issues that have been put

1 in front of us are these.

2 Some sponsors of minipool testing have argued
3 that this is a manufacturing process control which affects
4 the quality of the pool for fractionation and there should
5 be no linkage back to the donor. The argument there is
6 that the purpose of the test is to enable you to pitch
7 positive units and protect the pool and that it's simply a
8 separate thing from screening the donor. The FDA does not
9 take that point of view.

10 A second argument that has been made is that it
11 is not practical to go back to testing the individual units
12 based on the size of the pool. Now, although it has been
13 correctly stated that the primary testing of the minipool,
14 which as Paul explained, is a virtual pool -- it's not a
15 sample from the fractionation pool; it's a pretend pool
16 made from samples -- that although the screening of that
17 primary minipool may be constituted of 500 or so units, the
18 fact is -- and you will hear this -- that essentially all
19 of the sponsors of such protocols intend to backtrack and
20 test ever smaller pools. Those smaller pools range in size
21 anywhere from about 25 to about 50.

22 Now, the issue with going back and retesting
23 smaller and smaller pools and ultimately individual units
24 is cost, as well as logistics and time, because PCR is

1 labor intensive. It's not highly automated and it's very
2 costly, and so there is a disincentive for tracking all the
3 way back.

4 Now, FDA is simply saying you have to. We're
5 saying that if you're testing a pool of 50, you have a
6 choice. You could either inform 50 donors and let them get
7 follow-up medical testing or you can test 50 samples and
8 figure out which one it is. We're saying you cannot walk
9 away from the fact that this is medical information
10 pertinent to individual and public health.

11 Then the third argument which has been made is
12 that it's impractical on the grounds of the delay in
13 testing making this not comparable to the up-front
14 screening of the donor.

15 Now, you are correct that there are scenarios
16 in which we expect rapid turnaround time of PCR within a
17 few days of antibody testing. However, that is not
18 everybody's projected scenario and there are other
19 scenarios in which it is conjectured that testing could be
20 delayed by weeks or even months. At that point, clearly
21 you are in a situation more analogous to lookback than up-
22 front screening because you don't really have the ability
23 to quarantine, say, the transfusable products that may have
24 accompanied a plasma collection. So, we have to sort out

1 what is our posture on the use of the PCR as an up-front
2 screen in scenarios where the quarantine is possible or the
3 use in lookback notification where the quarantine is not.

4 So, for example, it may not be possible to hold
5 the platelets in quarantine because they only have a 5-day
6 shelf life and there isn't anybody's scenario in which
7 there's going to be a turnaround time that would permit you
8 to quarantine the platelets. So, at least for platelets,
9 you're talking about lookback.

10 So, there have been these three arguments that
11 would suggest that the FDA should not take the point of
12 view of looking at pool PCR or minipool PCR testing in the
13 same way as up-front donor screening by other markers.
14 What you are hearing the FDA say is, no, the system has to
15 be engineered so that all of those same principles of
16 screening, deferral, notification, and lookback can be put
17 in place with the PCR result. And there will be some
18 limited circumstances in which that won't work such as
19 platelet testing if PCR takes a week or two, but short of
20 that, we want all these same safeguards in place.

21 Again, I'm very pleased that that seems self-
22 evident and I hope I've illuminated the counter-arguments
23 which FDA does not accept.

24 DR. KASPER: I think I understand where you're

1 coming from and I think that's why there are so many
2 questions about what do you mean by the size of the pool by
3 a minipool.

4 Would FDA regulations on PCR testing and
5 lookback then -- one of the pools that I'm aware of as
6 proposed for testing is a European product but licensed in
7 the United States where the minipool is not so very mini.
8 It's more modi, moderate size pool, in which it would be
9 more difficult to look back at the individuals.

10 But how do FDA regulations affect? Do FDA
11 regulations affect products sold in the United States or
12 manufactured in the United States?

13 DR. EPSTEIN: Well, they affect products
14 distributed in the United States. In other words, if they
15 are made here, if they're distributed abroad, we regard
16 that as part of interstate commerce. If they are brought
17 in, though not manufactured here, they're subject to the
18 same license requirements because the law is focused on
19 distribution.

20 DR. KASPER: If I could clarify. I'm sorry.
21 If the product is made in Europe, we would be concerned
22 that the European donor, if it's a European donor, is
23 looked back at. It's hard for us to validate that.

24 DR. EPSTEIN: Well, to be sold in the United

1 States, the product has to possess a U.S. license. If we
2 require lookback provisions, they would apply to the
3 licensee operating in Europe. So, the same would apply.

4 DR. SWISHER: Susan?

5 DR. LEITMAN: I think Jay may have answered
6 this. In reading the material before the committee met
7 today, the constant referral to plasma pools made me think
8 the committee was going to be asked to consider use of this
9 test for products intended for plasma fractionation. I
10 didn't think of it in terms of every single whole blood
11 unit, every single donor of a whole blood unit being tested
12 in this manner, and that changes the considerations
13 enormously.

14 As you just said, it almost can't be done.
15 There are many centers, mine included, that don't send
16 plasma for fractionation which would change the method of
17 operation completely.

18 So, could you clarify what we're being asked to
19 consider?

20 DR. EPSTEIN: We are talking about proposals
21 related to plasma pools for fractionation. However, as you
22 well know, about 15 or 20 percent of plasma for
23 fractionation is recovered plasma from whole blood
24 collection. So, the schemes that are being put in place

1 are also being developed to be applicable to recovered
2 plasma and therefore, if we regard it as donor screening,
3 that is screening of whole blood donors. So, we do expect
4 to see this system more generalized.

5 Now, we are not, as I think Ed explained, at
6 this time mandating this. So, there may be sectors that
7 opt out because they're not selling recovered plasma for
8 fractionation.

9 At some future date we will, I guess, need to
10 discuss whether we should have FDA recommendations or
11 requirements for use of pooled PCR for all screening, but
12 that is not in fact what is on the table for consideration
13 today. We are, indeed, talking about schemes applicable to
14 qualifying plasma for product fractionation.

15 DR. NELSON: I wholeheartedly support the FDA's
16 public health approach. I think it's critical.

17 But given the issues you raised about the time
18 that it might take to identify an individual unit, is the
19 FDA considering making some reference to what a reasonable
20 time would be to identify and notify a donor, or will that
21 be solved in the courts? How would you deal with that?
22 Because obviously once someone could be identified and you
23 could do it, from that time on you are culpable for
24 transmission that might occur of the agent from that time

1 forward. How will you deal with that? Is that going to be
2 dealt with at all or just leave it as reasonable or
3 something?

4 DR. EPSTEIN: Well, I think that we haven't
5 come up with a time frame. In the past where there has
6 been lack of clarity, we have simply advocated as soon as
7 possible or as early as feasible and put that kind of
8 language into our recommendations.

9 I think the situation that we're in right now
10 is that this is evolving technology, that the logistics are
11 highly complex, that we have not yet seen the systems that
12 are being brought forward and we are not in a position to
13 mandate any particular time frame to accomplish testing.
14 On the other hand, we certainly can take a proactive
15 position on how long it takes you to notify once you have a
16 result. So, I think there is some lack of clarity, but
17 that is a point that we understand and will not ignore.

18 DR. NESS: I think it's important that we urge
19 that the donors who may be infected are notified as quickly
20 as possible for public health concerns, but what I'm really
21 concerned about and I haven't heard a lot about except for
22 the discussion of lookback is the numbers of recipients who
23 may get products that are tested in the process of the
24 recovered plasma business and getting blood that is

1 infectious or may be infectious for PCR and hearing about a
2 variable period of time until we're going to notify the
3 donor when what our real concern ought to be is a recipient
4 who already got infused with red cells or platelets from
5 one of these donations who may be able to be treated by
6 some sort of early intervention. It seems to me that that
7 really is probably a more important public health concern
8 than the fact that some donor has been identified by sort
9 of an early diagnostic procedure.

10 DR. SWISHER: Corey?

11 MR. DUBIN: I think that's an important point,
12 but I think actually both sides of the equation are
13 important, both the donor and the recipient.

14 What I want to remind the committee is I do not
15 want to approach this with a sense that I'm hearing that
16 lookback and notification is something that has been
17 functioning smoothly, is well done, and does not have
18 problems. We spent a number of hours with FDA staff this
19 week in a meeting pointing out some major problems that
20 have happened with lookback and some lookback vis-a-vis
21 recipients of tainted products that were never looked back
22 and identify and still remain out there.

23 So, I think we've come down to a real core
24 issue that's a public health issue both on the side of the

1 donor and on the side of the recipient, and we're looking
2 at a system that in some basic ways has fundamentally
3 broken down at times.

4 I think if this is the issue and now we're
5 really going to start to address it as a body, we really
6 need to look at that and begin to consider very strongly
7 the things that we can put on the table and do to create a
8 functional system. No system is perfect but I think
9 certainly we do have to do some very strong consideration
10 about where to take this to really tighten it down so we
11 don't find the kinds of failures that we've seen in the
12 last 10 years and some that have repeated themselves.

13 DR. SWISHER: This issue, of course, appears on
14 our agenda at another point, and I think it's appropriate
15 to tie these two together.

16 I'd like to move along unless there are
17 critical questions because we're a little behind our
18 schedule right now and declare that we will have our break.
19 I'm going to try to have that shortened up to about 20
20 minutes and ask you to resume your positions here at 20
21 minutes before the hour. Thank you.

22 (Recess.)

23 DR. SMALLWOOD: We're ready for the open public
24 session at this time. We are running approximately a half

1 an hour late.

2 I have been notified that there are nine
3 speakers during the open public hearing. The first two
4 speakers will be making scientific presentations that have
5 significant relevance to the previous discussion.
6 Therefore, they have been allotted more time to
7 appropriately make the scientific presentations. However,
8 I will try to accommodate reasonable time for all of the
9 remaining speakers.

10 The first two speakers are allotted 10 minutes
11 each. The following speakers will be allotted
12 approximately 6 minutes each. We would ask that you try to
13 stay within those time frames, and I will be glad to help
14 you.

15 (Laughter.)

16 DR. SMALLWOOD: Also, in the interest of
17 fairness, we will invite individuals that did not contact
18 me to speak during the open public hearing if, by the
19 discretion of the Chair, there is reasonable time to do so.
20 May I emphasize that it is better if you do notify me in
21 advance so that we can make preparations to have you speak
22 during the open public hearing. Thank you.

23 Dr. Swisher.

24 DR. SWISHER: The open public hearing is now

1 open, and let the record so indicate. The first speaker is
2 Dr. Susan Stramer from the American Red Cross who will
3 present some data.

4 DR. STRAMER: Thank you, Dr. Swisher.

5 It was inevitable that one day my slides
6 wouldn't get here on time and today is the day I actually
7 validated that.

8 (Laughter.)

9 So, I'm going to use some overheads.

10 Firstly, I'd like to discuss data on
11 collaboration that the American Red Cross has had with the
12 National Genetics Institute, one of the central testing
13 labs for pooled PCR. What I'm going to try to attempt in
14 my 10 minutes is to define sensitivity, specificity, and
15 some of the stability issues associated with pooled PCR
16 testing.

17 The overall goal of this is to evaluate the
18 feasibility, logistics, and yield of PCR testing of pooled
19 donor samples for HIV, HBV, and HCV.

20 You've heard the goal for the plasma industry
21 is to decrease the viral load, but also for whole blood, we
22 have the issue of closing or reducing the remaining window
23 period.

24 There's a relationship, especially with HIV,

1 that we know now that we have closed the window
2 substantially between copy number and viral load. So, as
3 we reduce the copy numbers, we reduce the viral load. The
4 viremic window period will also be reduced.

5 Firstly, I will discuss an unlinked study
6 focused on specificity. Its purpose was to determine the
7 frequency of unexpected findings to really test
8 specificity, defined as a PCR positive, in a diluted pool,
9 since we were using pools that are diluted from donations
10 that may not be supported following retesting of pools
11 having a higher sample concentration than a smaller pool or
12 the associated unpooled sample.

13 Studies are being done unlinked previous to
14 linked studies because the donor/recipient notification
15 issues need to be resolved. We will be tracing back to
16 single donations even in this unlinked study to be able to
17 look at those issues for the future.

18 Other goals of the study include determining
19 the ability to reproduce, reproducibly detect a finding,
20 and these unlinked studies use spiked samples of hepatitis
21 B and hepatitis C in a blinded fashion to test
22 reproducibility.

23 Also, we looked at tracing, the ability to
24 trace a positive result. So, having these linked spiked

1 samples will also allow us to examine the issue of
2 reproducibility.

3 The protocol involved seronegative only, such
4 that all seropositives tested were removed. We looked in
5 the unlinked study at hepatitis B, hepatitis C, HAV,
6 Parvovirus B19. As I mentioned, it included spikes in all
7 pipetting schemes as positional controls. The pipetting
8 was performed in duplicate. One set of plates was pipetted
9 without a spike so that we wouldn't have any issues of
10 cross-contamination, and a pair of sister plates, if you
11 will, was pipetted containing a spike. Each sister plate
12 contained one spike of hepatitis B and one spike of
13 hepatitis C. Each pool included 2,500 samples, but each
14 individual pool that was tested is really just a pool of
15 500.

16 The study was blinded. One centralized NTL was
17 sent unlabeled seronegative tubes from the entire system.
18 The study was IRB approved and also reviewed by FDA. The
19 study duration was 8 weeks, 2,500 samples per week, for a
20 total of 20,000 donations.

21 The matrix involved two steps. First of all,
22 there was a primary matrix in which all 2,500 samples were
23 pipetted into 100 primary pools, pipetted in two
24 directions. First of all, there were 50 pools that are

1 created in an X direction and 50 pools that are then
2 created in a Y direction, so that you would have 100 total
3 pools representing each sample in two pools, an X pool and
4 a Y pool, such that an intersection points to a single
5 donation.

6 Following the primary pooling, there was a
7 secondary matrix from the 100 primary pools that created a
8 secondary pool. The secondary pool had a total of 20
9 samples, again 10 pipetted in the X direction and 10
10 pipetted in the Y direction. Each secondary pool was a 1
11 to 10 dilution and each primary pool was a 1 to 50
12 dilution. So, the final dilution factor for each donation
13 was 1 to 500.

14 The pooling was all performed in one
15 centralized national testing laboratory and then the 10A
16 and 10B pools, or the 20 total 1 to 500 diluted pools were
17 shipped frozen to NGI.

18 Again, just to show you the outline, 2,500
19 samples at the bottom were pipetted twice, once in an
20 unspiked direction and once then removing two donations and
21 substituting those two each with an HBV and an HCV spike.
22 After the primary pool at a 1 to 50 dilution, the secondary
23 pools at a 1 to 500 dilution were prepared. So, 20 tubes
24 went on to PCR testing.

1 Part of the study had to define what a positive
2 result would be. What would be an expected finding? We
3 could positives if there was a random positive result that
4 could not be supported at a higher sample concentration.
5 If we got a positive at a 1 to 500 dilution, could it be
6 reproduced at a 1 to 50 dilution which is a tenfold
7 concentrate of what we were initially testing?

8 We would call something that could not be
9 reproduced at a higher sample concentration an aberrant
10 finding.

11 Also we could have a source of positivity
12 resulting from contamination, for example, from an EIA
13 positive, but since those were removed, our sources of
14 contamination in this study could have been from a spiked
15 sample, but knowing our spiked sample either by genotype or
16 knowing that it was antibody positive, there's an easy way
17 to trace back perhaps to the spiked sample.

18 Lastly we could have had a true viremic
19 positive. Even though our study only included 20,000
20 donations, there was still the possibility of finding a
21 positive.

22 I don't expect you to know this. I just want
23 to be able to show you what a matrix looks like. This is
24 the 100 primary pools in a secondary pool configuration.

1 So, you pipette in the X direction and the Y direction,
2 creating the lines of A and B. Once those 20 A's and B's,
3 A 1 through 10 and B 1 through 10, are tested by PCR, a
4 correct result in spiked plate would be 4 positives
5 because, again, we're governing by an intersection rule,
6 and since this is a double matrix, you need 1 X and 1 Y for
7 1 donation. Since this is now in a secondary plate, the X
8 and Y, which are defined by yellow, again require two
9 intersections to define a positive. So, a normal result
10 would be 4 positives in a secondary pool.

11 So then the two yellow boxes eventually will
12 point back to the single donation within the primary pool
13 containing 2,500 samples. This is when the system works.

14 (Laughter.)

15 DR. STRAMER: Frequently systems don't work.
16 That's why we do validation and that's why we do unlinked
17 studies. So, in this case you can imagine the situation --
18 and we did, as you can see from the label, Batch 8: HBV.
19 In this case we had an unexpected finding, where only 1
20 pool of the 20 was positive. That one pool relates back to
21 the three that are starred and the X axis that includes X21
22 through X30. I told you each of those pools contains 50
23 donations. We have 10 of those pools. If something
24 doesn't work, you hold up release of 500 products if this

1 were done in real-time, linked fashion. So, one has to be
2 wary in a matrix design study that you can sort through the
3 issues of product release.

4 I mentioned, as far as unexpected findings,
5 what happens when the system doesn't work. Well, the
6 system doesn't work in many ways in that we can also detect
7 a true positive. I said that each sample was represented
8 in pools, in two different pools, in an X direction and a Y
9 direction. So, you're really testing each sample in one
10 matrix twice. Because we were pipetting these matrices
11 twice in addition, one with a spike and one without a
12 spike, each unknown sample in actuality is tested four
13 times.

14 So, what happened with donation from week 2
15 sample 1495 was we detected a positive in one of four
16 secondary pools. It was implicated by a single row just
17 like I just showed you but it was in a pool that also
18 contained a spiked sample. So, the issues became quite
19 complex in that plate.

20 What we found was a true positive hepatitis C
21 sample that was masked by a intersection. As I showed you
22 in the very first plate, when systems do work properly,
23 we're believing that only the intersections are where a
24 positive could occur. But also you could envision that an

1 intersection may mask a true positive contained within a
2 row or a column, and that's exactly the reaction that we
3 saw or the reactivity that we saw.

4 The associated primary pools and donations were
5 identified, each at an increasing signal strength, and the
6 sample was linked to genotype 3a whereas our HCV spiked
7 sample was genotype 1a. And genotype 3a is relatively
8 uncommon in the United States.

9 The sample was antibody negative. So, I just
10 wanted to mention that. There are other issues containing
11 the dilutional strength and if RNA can dilute out further
12 than antibody, if this truly was a contamination, but
13 because of the unique genotype and antibody negativity, we
14 believe this was a true positive finding.

15 So, of the total donations tested in the study,
16 which were 20,000, all HBV and HCV spikes in all 8 weeks of
17 plates were correctly identified. There was one HCV
18 viremic seronegative sample that was detected. There was a
19 different genotype in the HCV spike, but no follow-up
20 sample is available since this is an unlinked study.

21 We found two HCV aberrant results that could
22 not be reproduced through the donation; two hepatitis B PCR
23 positive pools that were also aberrant; one, perhaps up to
24 three, true Parvovirus results that probably were real; and

1 additional Parvovirus false positives. There were no HAV
2 viremic samples identified in the study, but if this were a
3 linked study, up to 9 percent of our blood supply would
4 have been on hold awaiting results of secondary testing.

5 I just want to mention a few things on
6 sensitivity and then I'll conclude. This is the slide that
7 Ed Tabor showed earlier. We know from HIV p24 antigen
8 experience that, relative to RNA, we could close the window
9 potentially 5 more days, but if we look at the yield with
10 HIV antigen, we know after implementation, we've only
11 gotten one positive. So, these are basically estimates.

12 I offer the same suggestion for hepatitis C.
13 The rest predicted 84 HCV annually viremic samples if we
14 were to include PCR. If the 1 in 20,000 number I showed
15 you was real, that would be up to 600 products annually in
16 the U.S.

17 If you model data, depending on what your
18 sensitivity is, this is a box plot showing different
19 periods or different window periods during seroconversion.
20 The first plot represents RNA positive/antigen negative,
21 and you can see if you have 100 copy sensitivity, adding a
22 dilution factor of 500 would dilute all the window samples
23 down to below the level of detection.

24 DR. SWISHER: Dr. Stramer, can you conclude?

1 DR. STRAMER: Yes. If you can go to the box
2 and whisker plot for HIV.

3 This may be difficult to see, but we did the
4 same thing modeling this using the NGI procedure and
5 pooling at pools of 500. Initially we looked at single
6 quantitation of individual samples in seroconversion and
7 extrapolated this at the level of sensitivity of NGI to a
8 500-fold dilution. Doing this, we could close the window
9 potentially 3 days on HIV.

10 Now, we need to validate this looking at
11 multiple dilution factors to see if in fact the claims that
12 NGI makes on their copy sensitivity can be validated. But
13 at least for HIV, using the data that's supplied, we know
14 that using quantitative assays at the cutoff that NGI
15 claims, potentially 3 days could be removed from the HIV
16 window.

17 Looking at HCV, the situation is a little bit
18 different because viremic levels are very high, frequently
19 exceeding 5 million copies per ml. At the baseline
20 sensitivity, using the NGI procedure of 6,000 copy
21 sensitivity, including a 500-fold dilution, in this case
22 the HCV window would be closed 20 days even using a pool of
23 500.

24 If you look at the four series of those we

1 tested, which I won't show you, each of the overall mean
2 window reduction, when we had the entire PCR positive
3 period covered, was up to 42 days. So, there is
4 significant viral load in hepatitis C, and even at pools of
5 500, significant window closure could be obtained.

6 Thank you.

7 DR. SWISHER: I think we'll have our presenters
8 available for later questioning and we'll continue with Dr.
9 Andrew Conrad of the National Genetics Institute.

10 DR. CONRAD: That was a whirlwind tour through
11 the project and I know it's quite confusing. So, I thought
12 I would just take a little time to look at the matrix and
13 pooling designs -- I know that this has been a paramount
14 question that you've all had -- and try to maybe clarify
15 exactly what we did.

16 When designing the pooled designs, we had to
17 consider a few different factors. We had to consider the
18 sensitivity of the assay, and that directly impacted on how
19 large a pool we could make. We had to be able to maintain
20 positive identification of the sample and donor
21 identification. Then you had to look at the economics and
22 the ethics of it, the economics in the smaller the pool,
23 the more expensive the cost. The ethics is if you made the
24 pool too big, how many patients would you miss, how many

1 donors would you miss, and also if the pooling regime would
2 take too long to adequately obtain the data, would that
3 mean that too much product was released prior to analysis.

4 So, basically there are three different schema
5 that you can use to design a matrix. There's a three-
6 dimensional, a two-dimensional, and a pyramid matrix.
7 These are all the matrices that we were able to use. We've
8 used them both, and you'll see from other presenters that
9 we've done all these matrices and you can see the effects
10 of each.

11 Briefly you need an automated pipetting device
12 of some kind. You need a robot to do this. It's way too
13 complicated to have a technician do it because you're
14 pipetting things in multiple clades. You need computers
15 and that obligates you to have very careful data
16 management. These matrices are quite complex.

17 What I'm going to show you is cartoons of how
18 these matrices work. In real life the computer keeps track
19 of it much better than our simple heads can.

20 Basically a two-dimensional matrix is what we
21 used for the ARC, which Dr. Stramer just demonstrated.
22 It's simply the group of samples are put on a plate and
23 they're pipetted in this direction and then subsequently
24 pipetted in this direction. So, every sample will be

1 represented uniquely in two of the pools that are analyzed.
2 You can make secondary pools from that and jump back and
3 find the original donor, which Dr. Stramer demonstrated.

4 In a three-dimensional pool, it gets one
5 dimension more complicated. Here what you do is you take a
6 group of samples and you put them into a row, column, and a
7 layer, combine them into a cube. It's like the Rubic's
8 cube of PCR. What you have to do is see that where a row,
9 column, and a layer intersect would be the unique sample.

10 So, what's done is you first test the entire
11 cube. If it's negative all the 512 samples within the cube
12 are negative. If it's positive, you then go test each row,
13 layer, and column, and the intersection of positivity
14 between those rows, layers, and columns will implicate a
15 single sample. This obligates two rounds of testing to
16 identify a donor.

17 The pyramid scheme is not the one to make money
18 with, but a pyramid scheme is where you take a whole bunch
19 of samples and you fractionate them into smaller and
20 smaller groups. You'll first test the big group. Then
21 you'll test a subgroup and then an even smaller subgroup
22 and finally down to the individual samples.

23 This is the most economic of the regimes of the
24 pyramid of pooling schemes. The problem is it obligates

1 you to take several rounds of testing, so that temporally
2 it's the slowest. You have to wait for a previous result
3 to come back, find the next one, then the next one, then
4 the next one. So, it's a step-wise approach but it's the
5 most economical.

6 Briefly the automatic device that we chose to
7 do this is called the Tecan. It's the Mega 2M. It's a
8 big, giant automatic pipetting device that uses individual,
9 exchangeable ART aerosol-resistant tips with carbon fiber
10 to make sure that they have fluid analysis, that they dip
11 into the tube and won't say something was there that didn't
12 have any liquid in it.

13 Contamination control. Dr. Hewlett
14 demonstrated the need for contamination control in PCR.
15 This is really, really an important consideration when
16 making a matrix because false positivities can cause
17 tremendous trouble. In National Genetics, we use multiple
18 locations. We have pre and post PCR facilities, separate
19 personnel dedicated to each facility. These aren't
20 different rooms. These are totally different buildings
21 miles apart. So, each laboratory has its own set of
22 supplies and reagents and they're never interchanged.
23 That's an important consideration.

24 The clinical components of this test. National

1 Genetics has filed now two INDs, or we're sponsors of an
2 IND, two of them, one for HIV, one for HCV, in which Alpha
3 Therapeutic Corporation and the American Red Cross are
4 investigators. Those INDs have been filed. February 18
5 and February 20 was the filing date. In those INDs we hope
6 to analyze 300,000 donors from the source plasma and
7 300,000 from the whole blood of the American Red Cross.
8 Those are the IND numbers, if anyone cares.

9 In order to support the preclinical components
10 of these INDs, we did some studies based on ICH 3
11 guidelines for reproducibility, precision, and those other
12 factors Dr. Hewlett discussed earlier.

13 The precision. We took 100 copies per ml of
14 HIV and added it to three independent pools, and then we
15 tested it with both intermediate precision, having
16 different people test it on different days, as well as
17 testing the three pools multiple times. We found that they
18 were 100 percent positive. We didn't miss them at all.

19 The problem is that there's no accepted
20 international standard for the HIV genome, so we had to
21 develop our own standards.

22 Specificity was tested by taking 1,000 copies
23 of HAV, HBV, and HCV, and spiking pools with high copy
24 numbers or relatively high copy numbers of those other

1 viruses and seeing if they were detected with the HIV
2 primers, and they were not.

3 The other things that we did is we've looked at
4 window period donations and that's some of the data that
5 Dr. Stramer showed you, so I won't go over it.

6 Sensitivity was the final component of the ICH
7 3 guideline dependent study. What we found is using ultra
8 centrifugation high volume analysis, we were able to take
9 150, 25, 12 and a half, 6.25, or in other words, dilutions,
10 one-fold dilutions, of these materials and used statistical
11 analysis to determine that our estimated 95 percent
12 confidence interval of detection is 9 copies per ml. With
13 that 9 copies per ml number, you can times that by the pool
14 size and see the likelihood of any single inoculum being
15 detected.

16 This was just to let you see the same thing in
17 HCV where we were able to detect, again doing the same
18 analysis, doing multiple replicates of the exact, same
19 thing for hepatitis C. We had a 95 percent confidence
20 interval, depending on which pool of 18 copies, or about 50
21 percent, twice as much as the HIV. Those were the numbers
22 that were submitted in the two INDs.

23 It's important that Dr. Hewlett again said that
24 you have to maintain the genome peak environment. Now

1 we've constructed new facilities at National Genetics and
2 we maintain proper records and all sorts of other things on
3 materials and stuff like that, and the results are stored
4 in computer generated databases and that follow GMP
5 regulations.

6 The last thing is the current capacity at
7 National Genetics now exists with the personnel and
8 automated equipment that we now have to perform a million
9 reverse transcription PCR reactions on HCV or HIV per year.

10 That's all.

11 DR. SWISHER: Thank you very much.

12 Do you have any preliminary figures on
13 turnaround time?

14 DR. CONRAD: Yes. The current turnaround time,
15 what we're shooting for now, is 72 hours.

16 DR. SWISHER: Our next request for time on the
17 agenda is Dr. Margaret Savage with Bayer Corporation and
18 she will also make the presentation of the material Dr.
19 Thomas Wytes of Immuno Corporation who was unable to be
20 here today. Dr. Savage?

21 DR. SAVAGE: My name is Margaret Savage. I am
22 employed by Bayer Corporation. I'm speaking to you today
23 representing the member companies of the International
24 Plasma Products Industry Association. Since Alpha

1 Therapeutic has their own presentation, this presentation
2 will be representative of the views of the other four
3 companies.

4 One thing to remember is that plasma products
5 are important because they are very important to
6 recipients. Approximately 3 million people per year in the
7 U.S. receive plasma derivatives.

8 The other thing that we would like for everyone
9 to remember is that safety is the sum of all of the
10 measures, not just limited to only one issue. It certainly
11 isn't just a national issue. It's really a global issue
12 because people receive plasma derivatives all over the
13 world.

14 The next four slides are going to address a
15 questionnaire that was sent out to the member companies of
16 the IPPIA and also the sister affiliate in Europe, the
17 European Association of Plasma Products Industry, and the
18 member companies of that organization.

19 The first question that was asked is, what are
20 the currently employed nucleic acid testing methodologies?
21 The most popular answer that came back was PCR, polymerase
22 chain reaction. Other methods are in-house, commercial,
23 modified commercial methods. Branched chain DNA has also
24 been used.

1 The currently investigated viruses. All of the
2 companies were developing and are developing methods for
3 detection of hepatitis C. Most of the companies are also
4 evaluating methods for HIV 1. Hepatitis B and hepatitis A
5 are also being worked on.

6 Obviously, there are a number of different
7 stages where this methodology could be employed. Certainly
8 combined samples, minipools, as we have heard, or pigtail
9 pools as I like to call them -- that did cause some
10 consternation in Europe until we figured out what a pigtail
11 actually was. The subpools and manufacturing pools can be
12 tested, intermediate/final product or some combination of
13 the above, which is what most of the companies are looking
14 at.

15 The possible reference preparations that have
16 been used by the companies as they were questioned. Most
17 had used for HCV the material from the National Institute
18 of Biological Standards and Control in the UK. Others have
19 used materials from the central lab of the Netherlands
20 Transfusion Service, the Pelispy material, and some
21 companies that also use the final container material from
22 CBER.

23 For HIV the material that was most often quoted
24 was material from NIBSC again as a part of the

1 standardization on gene amplification testing that has been
2 in meetings that are in process that are in Europe.

3 For HBV, the Eurohep standard.

4 Next I'd like to show you some data from the
5 various companies, and this actually addresses using
6 different standard preparations that are available, what
7 percentage of the assays are positive at different levels
8 of genome concentration. This is using the NIBSC material
9 for hepatitis B and there will be four examples of
10 hepatitis C data and then I'll show you one example for HIV
11 1.

12 You can see here that at approximately 4,000
13 genome equivalents per ml, as this is diluted, the percent
14 of positive assays is decreased. This was an in-house
15 nested PCR assay.

16 The next, a different company uses an in-house
17 nested PCR assay again. This is an internal, in-house
18 working run control that has been run in each of the
19 assays, and as you can see, as the copy number is
20 decreased, the percent of assays that are positive is also
21 reduced.

22 A different member company has used the 96-586
23 material from them that is currently available, and in this
24 situation that also has approximately 4,000 genome

1 equivalent per ml. Here again, as the copy number is
2 reduced, having been diluted into negative plasma pools,
3 the percent of assays that are positive also is decreased.

4 Then the last company is using modified PCR
5 assays with scaled-down FDA protocol coupled with the
6 Amplicor test kit for amplification and detection. Again,
7 this is using a different standard material, this time the
8 Pelispy from CLB. As the material is diluted, the copy
9 number is reduced and the percent of assays that are
10 positive also decrease.

11 The next example that I'll show you is from HIV
12 1. This is from a different member company. This is an
13 in-house PCR method using an in-house HIV 1 calibration
14 material. Again, as the copy number is decreased, the
15 percent of assays is also reduced.

16 The next two slides -- there have been a lot of
17 questions about what is a minipool. I'd like to show you a
18 couple of examples of some testing strategies that have
19 been considered by the member companies of IPPIA and EAPPI.

20 This particular example, there were 6,000
21 donation samples that were blinded using two different
22 extraction protocols. Samples were combined in sets of 100
23 or in sets of 400 for these two different sets of
24 experiments. There was a spike of approximately 7,000

1 genome equivalents per ml spiked into one of the tubing
2 segments. This spike was detected 100 percent of the time
3 and identified in each case.

4 Another one of the companies in Europe was
5 looking at the option to contract out, as are companies in
6 the U.S. The variables that they had considered were the
7 method used, the capacity certainly, detection limits,
8 whether the assay is qualitative or quantitative, and what
9 external laboratories are available. The laboratories in
10 Europe are TexCell, Inveresk, Q-One Biotech, and Corning
11 Hazleton, and of course, NGI in the U.S., as you know.

12 The places that they considered for testing
13 were the final plasma pools or smaller pools, subpools,
14 prior to the manufacturing pool, and then going further
15 down if the pool was positive.

16 So, the variables that have to be considered
17 are -- and this is very important. In a global issue like
18 this, standardization is certainly critical. So, the
19 standards used for validation, the matrix and matrix
20 effects, as we have already heard, stage of testing, sample
21 size, and the algorithm.

22 The IPPIA companies feel like this is the
23 responsibility of the manufacturer to determine and
24 validate the mechanism that would best suit their system.

1 Obviously, the immediate goal is to achieve
2 non-reactive manufacturing pools.

3 Just a couple of slides to talk about the
4 European position, because this is important in Europe
5 today, the European regulators want to achieve non-reactive
6 manufacturing pools. Their first priority is HCV. They
7 want to see progress reports on the progress the companies
8 have made with the implementation of gene amplification
9 technology, and the strategy is in development in Europe
10 and will be expected sometime later this year.

11 They are being very cautious with any mandatory
12 requirements at the moment. They initially thought that
13 they wanted to have mandatory requirements, but after
14 meeting with the industry and looking at the logistics of
15 the numbers of samples and the complicated tests that would
16 be implemented, they have decided to hold off on this for
17 the moment.

18 They think that it's very important to have
19 work on standardization.

20 In the U.S., the FDA position is, as of a
21 meeting on February 19th, a filing of analytical supportive
22 data, category II PLA supplements for products, and then
23 filing of an IND by a manufacturer or contractor.

24 So, the conclusion at this point is right now

1 there isn't a harmonized regulatory approval, and different
2 testing strategies are available to achieve non-reactive
3 manufacturing pools. The IPPIA members plan to implement
4 nucleic acid testing for HCV and HIV 1 in 1997, but that of
5 course is subject to appropriate regulatory approval.

6 The issues to consider: standardization,
7 validation, harmonization, donor notification. This is one
8 of many options that can be used to increase the margin of
9 safety.

10 I want just briefly to tell you a little bit
11 about the voluntary standards program of the IPPIA members.

12 This is proposed to look at overall safety,
13 safety at the donor, which could include prescreening,
14 testing, manufacturing, GMP, and quality assurance,
15 certainly very important, viral inactivation and removal
16 techniques which are in place in the manufacturing
17 processes, and then most importantly again, the recipients
18 looking at post-marketing surveillance.

19 In fact, there is a document and everyone
20 should always have at least one of these slides that no one
21 can read.

22 (Laughter.)

23 DR. SAVAGE: If your eyes are like mine, you
24 won't be able to read it.

1 So, we have broken this down into some points
2 that I'd like to tell you just a little bit about.

3 The first is donor management. If you look at
4 all of the donors for plasma derivatives, the entire
5 population, there is a small percentage of that population
6 that are first-time donors. If you look at the testing
7 that is done for all plasma derivatives, that percentage
8 that contains the highest number of reactivities is from that
9 small population.

10 So, the donor management program includes the
11 questionnaire and physical exam, but also has a different
12 aspect in that there is a pretest, a second test. So, the
13 donor must have two sequential negative tests in order to
14 be qualified. Therefore, one-time-only donors are
15 rejected.

16 The second part of the program is unit
17 management. This is a 60-day inventory hold. If a donor
18 donates and then seroconverts in the 60 days, this allows
19 the removal of previously negative tested units to be
20 removed and not enter the manufacturing pool.

21 The third component is the subpool management
22 which is the adoption of nucleic acid testing. This
23 component allows for closing the gap of window donations
24 and covers the issue of non-returning donors within the

1 inventory hold. This would result in rejection of reactive
2 subpools. I want to show you some real data on how this
3 actually can work.

4 This is from a lookback study. So, here is the
5 antibody positive donation and here are 6 previously
6 negative, by all licensed assays, donations which are PCR
7 positive or reactive for HCV which did not get included in
8 the manufacturing pool because of the inventory hold. They
9 were able to be removed. So, this is a combination of
10 those two steps showing its potential efficiency.

11 The fourth component is center management. The
12 center management is to be done to assure that the
13 manufacturers actually collect from low risk populations.
14 There will be a maximum allowable viral marker rate limit
15 imposed for the centers for antibodies to HCV, HIV, and
16 hepatitis B. This implementation of this part of the
17 program will assure that the collections will be from low
18 risk populations.

19 So, in conclusion, the implementation of the
20 voluntary standards, which also includes nucleic acid
21 testing, will further increase the margin of safety for the
22 plasma derivatives which are received by 3 million people
23 in the U.S. today.

24 DR. SWISHER: Thank you, Dr. Savage.

1 Particularly useful are the observations about the European
2 position which were a little murky.

3 The next request for time is Dr. Celso Bianco
4 who will present on behalf of the Blood Centers of America.
5 Celso, I'm sorry. I made a jump here.

6 Alpha Therapeutic Corporation has substituted
7 Dr. Chuck Hildebrandt for Sue Preston.

8 DR. HILDEBRANDT: I'd like to present some of
9 the data which we have already submitted to the agency in
10 both May and August 1996 about our pooling.

11 Again, Alpha uses a three-dimensional matrix.
12 We have our samples arranged in 8 rows, 8 layers, and 8
13 columns. It comprises 512 samples.

14 We do automatic pipetting, as Dr. Conrad
15 indicated, where we make 8 column pools, 8 row pools, and 8
16 layer pools. When we have a positive pool, we test the 24
17 row, column, and layer pools, and as you can see by the
18 intersection, which Dr. Conrad showed you the final version
19 of, you can indicate the hot unit, or what we call Red
20 October is over here at the intersection.

21 We've also worked with NGI to determine the
22 analytic sensitivity of the test. The first table here
23 just again shows you a tabulation. This is for HIV. Again
24 known amounts of HIV from a well-characterized standard are

1 put into three separate plasma pools, and this total
2 positive column here represents the total positives for all
3 of the samples.

4 You can represent this graphically again. Here
5 are the percent positivity, the log of the HIV copies per
6 ml and percent positivity. The estimated mean sensitivity
7 is down here in this range. These brackets are the upper
8 and lower 95 percent confidence limits for the estimate of
9 mean sensitivity. The arrow is approximately where 95
10 percent of the samples are found positive all the time.
11 The arrow and the 95 percent confidence upper and lower
12 estimates are very different.

13 This is the tabulation which again shows -- and
14 these numbers, of course, are rounded of whole copies of
15 genome per ml, a mean of 7, a lower confidence interval of
16 4, an upper of 8 for this estimate of the mean.

17 Similar data for HCV, again graphically here
18 for HCV ranging from 100 down to approximately 6 copies per
19 ml. The blank doesn't show because a log of 0 doesn't
20 work. Here is the actual sensitivity line. Again, the
21 estimate for mean sensitivity for the plasma pools is 13
22 with confidence limit estimates of approximately 8 to 18.
23 Again, this is the point at which 95 percent of the samples
24 are positive.

1 Again, in tabular form, the mean sensitivity,
2 13 copies per ml with confidence limits of 8 and 18.

3 We also performed studies to assess the ability
4 of the NGI HIV PCR test to detect pre-seroconversion HIV
5 antibody positive samples, in other words, the so-called
6 window period units. These were made either both by PCR or
7 by p24.

8 It's important to note that in these studies we
9 utilized not only naturally occurring window period units,
10 but we also measured their p24 antigen signal-to-cutoff
11 ratios and tried to dilute these down so that they would be
12 at, equal to, or below the cutoff for p24 detection, so
13 that while the initial sample in each series is a naturally
14 occurring unit, all of the others are artificially
15 constructed to work around the signal-to-cutoff ratio for
16 the p24.

17 In this study PCR and p24 found 71 of these
18 samples positive by both tests. PCR was negative on 10 of
19 them, p24 was negative on 24 the PCR found positive, and
20 there were 9 samples that neither test was able to detect.

21 This is also shown in a little bit busier
22 graphical plot here where we plot HIV copies per ml against
23 the p24 signal-to-cutoff ratio for the Coulter kit. Here
24 is the positive cutoff of 1. Anything below this is

1 negative. Above it is positive. This is approximately the
2 upper confidence limit for the HIV test.

3 What we find here in the blue circles here are
4 positive with the procedure. The red ones are negative.
5 You can see that the negative samples here by PCR, with one
6 or two exceptions, all clustered below our detectability
7 limits. And again, the same thing here for the p24
8 samples.

9 This is a different plot showing again the p24
10 signal-to-cutoff. Here's positivity at 1.0. These are the
11 HIV copy numbers per ml, and these are for the 8 individual
12 naturally occurring window period units and their dilution
13 constructs. In each case, the initially occurring unit was
14 found positive by PCR each and every time after it had been
15 diluted 1 to 512 in pooled plasma. Virtually all of these
16 are detected as positive by PCR with the exception of these
17 units here which had been diluted to levels that, at a 1 to
18 512 dilution, were below 1 copy per ml.

19 This particular sample had an extremely high
20 p24 antigen-to-HIV ratio which was substantially outside
21 what we found for all of the other units.

22 In summary, we'd like to indicate that we
23 believe, using this algorithm at a dilution factor of 512,
24 the number of genome copies per milliliter in an original

1 sample that we could detect 95 percent of the time is
2 estimated to be approximately 2,500.

3 For HCV, again using a dilution factor of 1 to
4 512, the number of HCV genome copies in the original sample
5 we expect to be able to detect 95 percent of the time is
6 estimated currently to be between 20,000 and 50,000 copies
7 per ml. We believe this method of testing pools of source
8 plasma donations for HCV and HIV RNA by PCR gives us a
9 sensitive method to detect and eliminate these units from
10 manufacturing pools.

11 Thank you.

12 DR. SWISHER: Thank you very much, Dr.
13 Hildebrandt.

14 Next Dr. Celso Bianco will speak on behalf of
15 the America's Blood Centers.

16 DR. BIANCO: I feel that I was placed on
17 quarantine and then released.

18 (Laughter.)

19 DR. SWISHER: Dr. Bianco has a set of slides on
20 the bureaucratic process that if you ever have an
21 opportunity to see them, don't miss it.

22 DR. BIANCO: I'm going to speak on behalf of
23 America's Blood Centers, the organization that was formerly
24 known as CCBC, the Council of Community Blood Centers.

1 It congregates 73 community blood centers in
2 the country. The members collect approximately 45 percent
3 -- the number of units is higher -- of units of blood a
4 year from volunteer community donors, and a substantial
5 amount of the blood separated from these units is used for
6 further manufacture of derivatives, that is, what's called
7 recovered plasma.

8 I think my attempt here is to make clear for
9 all members of the committee that there are different types
10 of plasma according to their source and their intended use.

11 Fresh frozen plasma is the plasma that we
12 recover when we separate red cells from plasma and
13 platelets, and we freeze within 8 hours of collection, and
14 this is used for transfusion into recipients.

15 There is a product that is called, according to
16 regulations, recovered plasma. It is the same thing as the
17 fresh frozen plasma. However, that plasma is destined for
18 further manufacture.

19 We also produce platelets that expire in 5
20 days, and we also prepare red cells that in current
21 anticoagulants expire in 42 days.

22 Source plasma, on the other hand, is the plasma
23 obtained by the plasma industry using source plasma donors
24 by plasma pheresis. There are no recipients of other

1 products in this case. And as we heard some of the
2 pervious speakers, this plasma can be maintained frozen for
3 a long time before it's pooled.

4 We also heard that pool testing is a strategy
5 that is being approached in order to deal with the
6 difficult and sophisticated but difficult technology and
7 deal with the cross of that technology, the lack of
8 automation and the lack of some of the basic requirements.
9 But those pools, if we have a test when we are discussing,
10 is about going in rounds of testing of minipools of about a
11 day per round to identify the culprit, the sample that is
12 positive.

13 However, there are two regulatory approaches
14 that could be taken here. One is that it's manufacturing
15 qualification, in-process quality control, as Dr. Epstein
16 actually mentioned a few minutes before, and a donor
17 screening test.

18 They have very different concepts for the
19 volunteer whole blood collection system in this country.
20 If we qualify it as in-process control, a positive result
21 in a large pool would not require timely testing to
22 identify the sample, would not require notification follow-
23 up for donors, would not require notification of recipients
24 of platelets and red blood cells that were transfused

1 before the results became available, and the decision to
2 break down the pools into minipools for more rounds of
3 testing is essentially financial. It is a decision of how
4 many units of plasma we would like to discard.

5 On the other side, if we classify it as donor
6 screening, then there are requirements for IND, there are
7 requirements for licensure, there are requirements
8 approval. Positive results require timely testing to
9 identify the sample, notification and follow-up of donors,
10 notification of recipients of platelets and red blood cells
11 that were transfused before the results became available.

12 The consequences of the classification -- and I
13 do not intend to make a comparison here of safety of paid
14 donors or volunteer blood donors. I'm making these as the
15 two different sources of plasma that we have in the
16 country. I don't think that there is a documented
17 difference in safety.

18 But the covered plasma obtained from the
19 volunteer blood donors, because of the complexity and all
20 the liability that is attached to it, essentially becomes a
21 less desirable product than the source plasma. It's much
22 easier to deal with a source plasma donor where there are
23 no other products than to deal with recovered plasma.

24 So, maybe there is a possible approach that FDA

1 could use and it's an approach based on time, on phases. I
2 believe that we are getting into phase I now. We are
3 discussing more manufacture qualification. In a certain
4 way, the people who are doing it have stopped at the
5 minipool level. There is no labeling that is allowed in
6 the United States, and also there hasn't been donor
7 notification or recipient notification.

8 Obviously, there are many issues here: ethical
9 issues of notification, legal issues because somebody could
10 actually demand access to the PCR results, and issues of
11 regulatory flexibility, how flexible could the agency be in
12 this case.

13 However, we could migrate then after all these
14 validations and all those things and after the system has
15 adapted to a phase of FDA approval of testing laboratory
16 and procedure, allow the labeling, resolve the positive
17 pools, notify donors and recipients.

18 Our major issue here before technologies such
19 as the ones that are being supported by the National
20 Institutes of Health for development of the automated
21 individual tests that will have no issues of sensitivity of
22 pools, no issues of sample identification, and all that,
23 that until they become available, we are ready to do that.
24 But until they become available, the logistics are not yet

1 compatible with the volunteer community-based donor system.

2 In phase III, obviously that's our hope. The
3 NIH contract says 3 years or 32 months from last October,
4 the company should be ready to present everything in a PLA
5 package to FDA. The FDA licenses the individual kit.

6 But then comes the question that I think is a
7 very serious question. For those companies that are
8 providing PCR testing for the industry, should pooled
9 testing remain as an acceptable option for screening at
10 that time in 3 years or 4 years? Should the approved
11 testing laboratory be disapproved? Because, undoubtedly,
12 the individual test will be more sensitive unless we again
13 go back to the issue of manufacture qualification
14 diminishing the viral load, or making sure that all donors
15 are negative in the issue.

16 There is a precedent for not rushing to
17 classify it as a donor screening test. Currently FDA
18 requires that derivatives, particularly immunoglobulins
19 that have not been virally inactivated for HCV, be tested
20 by PCR for each HCV product released. This is currently
21 classified as manufacturing qualification for product
22 release. If the product is positive, the final container,
23 the product is discarded. There is no notification of
24 donors and recipients.

1 However, I'm sure that under current good
2 manufacturing practices, every manufacturer has a list of
3 all the donors that went into that pool that gave origin to
4 that vial that was tested and tested positive or negative.

5 So, I think that the difference there is simply
6 historically there was no requirement for that manufacturer
7 to retain samples from all the donors that went into the
8 pool that could be subdivided into minipools and all that.
9 So, there is a precedent and I'd like this precedent to be
10 considered.

11 In summary, ABC supports the efforts to add
12 another layer of safety to the manufacture of plasma
13 derivatives. ABC requests that FDA consider the
14 consequences of different regulatory approaches to donor
15 screening based on still unlicensed molecular technologies.

16 Finally, we believe that the volunteer blood
17 donor is the mainstay of the safe whole blood supply. That
18 is, our hospitals, our patients depend on those products,
19 the platelets and the red cells. We are committed to
20 support volunteer blood donations to the community. We
21 believe that the FDA and the Blood Products Advisory
22 Committee are strong supporters of the volunteer blood
23 donor system. So, we hope that FDA will take a cautious
24 regulatory approach.

1 Thank you.

2 DR. SWISHER: Thank you very much, Dr. Bianco.

3 The next presentation is Dr. Kathleen Sazama of
4 the American Association of Blood Banks.

5 DR. SAZAMA: Thank you, Mr. Chairman.

6 The American Association of Blood Banks
7 appreciates the opportunity to comment on nucleic acid
8 testing of plasma pools.

9 The AABB is the professional society for almost
10 8,500 individuals involved in blood banking and transfusion
11 medicine. It represents more than 2,200 institutional
12 members, including community and Red Cross blood collection
13 centers, hospital based blood banks, and transfusion
14 services, as they collect, process, distribute, and
15 transfuse blood and blood components. Our members are
16 responsible for virtually all of the blood collected and
17 more than 80 percent of the blood transfused in the United
18 States. The AABB's highest priority is to maintain and
19 enhance the safety of the nation's blood supply.

20 The AABB supports appropriate consideration of
21 rational measures to improve the safety of the blood
22 supply. The AABB recognizes that the manufacturers of
23 pooled plasma products for distribution in Europe are
24 facing regulatory pressure to implement PCR testing of

1 incoming plasma. This testing is designed to ensure that
2 the levels of viral load of pools are minimized and that
3 the capacities of existing inactivation processes are not
4 exceeded. The AABB acknowledges and supports the need for
5 U.S. manufacturers to deal with these pressures by
6 investigating implementation of PCR testing in pools of
7 plasma samples.

8 It is apparent that PCR testing will be
9 performed, at least initially, on pools of several hundred
10 samples, that such testing will be performed in centralized
11 sites, and that the results of the testing will not be
12 available until a number of days have elapsed.

13 The AABB supports the need to assure
14 standardization and appropriate quality control of the
15 testing process and therefore supports regulatory oversight
16 of PCR tests and testing services for blood plasma.

17 The AABB is concerned that PCR testing of pools
18 of plasma samples will have significant implications for
19 blood establishments, since it is anticipated that the
20 testing will be applied to both source and recovered
21 plasma. And we thank Dr. Bianco for clarifying what those
22 materials are. Each unit of recovered plasma, which comes
23 from a whole blood donation, will necessarily be associated
24 with one or more labile components prepared from the same

1 collection. Some source plasma will also be associated
2 with platelets pheresis that were collected concurrently.

3 Consequently, the results of PCR testing of the
4 plasma will relate also to individual components. The
5 rationale for plasma testing is to minimize viral load in
6 pooled plasma, whereas benefits for single donor products
7 will accrue only if pooled PCR testing can reduce the
8 infectious window period. Therefore, until the results of
9 extensive evaluations of the sensitivity of pooled testing
10 are available, the safety benefits of pooled PCR testing
11 are unknown. Indeed, experience with HIV antigen testing
12 has shown that predictions of the efficacy of new tests may
13 overestimate their benefits.

14 The nature of testing of pooled plasma samples
15 suggests it may not be possible -- it may not be possible
16 -- to use the results to control and quarantine the
17 issuance of platelets and it may not be feasible to control
18 the issuance of all red cell products. Additionally, PCR
19 data may be available only for those units from which
20 recovered plasma is prepared which raises concerns about a
21 blood supply with two different perceived levels of safety,
22 that is, inventories which will contain units that are both
23 PCR tested and PCR untested in hospitals. Alternatively,
24 the complexity of the issues may force plasma manufacturers

1 or blood centers to even reevaluate the use or provision of
2 recovered blood.

3 The AABB recognizes the need for responsible
4 reporting to assure public health and agrees that licensed
5 PCR testing should be performed in a fashion which permits
6 responsible notification and deferral of infected donors,
7 along with appropriate lookback procedures for recipients
8 of products subsequently found to be PCR positive.

9 However, the association is concerned that such
10 actions should not be taken solely on the basis of PCR data
11 and recommends careful consideration of ways in which the
12 presence of infection associated with a reactive PCR result
13 could be confirmed by additional testing or subsequent
14 evaluation of a donor.

15 The AABB is particularly concerned that the
16 implications of pooled testing by PCR have not been fully
17 evaluated in the context of single donor components. There
18 are major technical, operational, and ethical issues which
19 cannot be solved purely by regulatory activities.

20 Therefore, the AABB urges that FDA exercise
21 restraint and caution in the development of regulatory
22 guidance. In particular, issues of donor and recipient
23 notification, lookback, and deferral should not be strictly
24 regulated until sufficient experience has been gained. The

1 premature development and regulation of inappropriate
2 messages to donors, as was the case for HIV antigen
3 testing, was an unfortunate example of this approach.

4 The AABB urges the FDA to consider the need to
5 maintain an adequate and uniform voluntary supply of both
6 single donor components and plasma for further manufacture.

7 The AABB calls on its membership and other
8 organizations to work together in developing and
9 recommending policies and procedures for the management of
10 PCR testing of pooled donor samples.

11 Further, the AABB encourages the FDA, in its
12 process of developing a regulatory position, to include a
13 public forum for the FDA to obtain input on critical issues
14 related to donor and recipient notification and donor
15 deferral.

16 Finally, the AABB asks that the Office of Blood
17 Safety immediately review and provide recommendations
18 covering the broader implications of PCR testing.

19 Thank you very much.

20 DR. SWISHER: Thank you, Dr. Sazama.

21 The next speaker is Dr. Bruce Ewenstein of the
22 National Hemophilia Foundation.

23 DR. EWENSTEIN: I'd like to present on behalf
24 of the National Hemophilia Foundation our position that's

1 being considered now by the Blood Products Advisory
2 Committee. These positions, I should say, reflect careful
3 discussion and input from members of the Blood Safety
4 Working Group of the NHF.

5 My name is Bruce Ewenstein. I'm a member of
6 the NHF's Medical and Scientific Advisory Council, and I'm
7 also an assistant professor of medicine at Harvard Medical
8 School and a physician and Director of the Boston
9 Hemophilia Center. But I'm here to present the NHF's
10 position on nucleic acid testing of plasma in plasma pools.

11 We believe in principal genome amplification
12 techniques such as PCR are more sensitive and specific than
13 antigen or antibody detection methods that are currently
14 employed to screen viruses out of collected plasma. These
15 techniques are capable of identifying donors during the
16 window period of infection, a time at which neither viral
17 antigens nor host antibodies are detectable.

18 For example, we've heard data presented today
19 to indicate that PCR can identify plasma units containing
20 hepatitis C and hepatitis B that were not detected using
21 currently approved serologic screening tests. Since these
22 viruses have long window periods, this is not unexpected.

23 Thus, genome amplification can prevent
24 inclusion in the plasma pool of potentially infectious

1 units containing these hepatitis viruses. If this
2 technique were also applied to screen for viruses that are
3 poorly inactivated by current viral elimination methods,
4 such as hepatitis A and Parvovirus B19, the safety of
5 plasma pools would be further enhanced.

6 For these reasons, the NHF strongly supports
7 the implementation of genome amplification to improve
8 detection of pathogens in plasma used to produce
9 therapeutic products. We recognize that this area is
10 clearly scientifically complex and rapidly evolving.

11 Whether these tests are used to screen
12 individual donors or elsewhere in the production process
13 for the screening of small minipools, appropriate quality
14 control procedures are essential to assure consistent
15 sensitivity, specificity, and reproducibility of the test
16 results.

17 We also recognize the importance of donor
18 notification if a positive donation is identified and
19 strongly encourage the manufacturers and FDA to design the
20 testing strategies that allow for the identification of the
21 infected donor. We recognize that implementation of PCR
22 testing, such as in-process QC checks, may not permit
23 identification of the donor, and while these may be
24 appropriate initially as such tests are being brought on

1 line, the goal must be donor notification of positive test
2 results long term.

3 To maximize the sensitivity and utility of the
4 assay, standardization and consistent QC are essential.
5 We've heard many of these details and that consideration
6 needs to be given to such variable as time of testing,
7 preparation and storage procedures, amplification
8 conditions, primer selections, the size of the pools to be
9 tested and the effect of pool size on the cost, safety, and
10 supply of the final product.

11 It appears at this time that genome
12 amplification testing should occur early in the production
13 process. Testing of the final vial content is likely to be
14 an insensitive strategy, at least for now, which may offer
15 minimal incremental benefit to the recipient of the
16 product. Testing of plasma aliquots, on the other hand,
17 combined in small test pools, may increase sensitivity
18 while minimizing the waste of plasma.

19 So, it is our position that the FDA and
20 industry should work together to identify the most
21 expeditious regulatory pathway that would allow for the
22 implementation of these tests at the earliest possible
23 time. Viruses which should receive the highest priority
24 for screening by genome amplification include hepatitis C,

1 hepatitis B, hepatitis A, HIV 1 and 2, and Parvovirus B19

2 But for each of these viruses suitable
3 standards and sensitivity need to be developed. Product
4 claims based on PCR testing need to reflect results
5 obtained with standardized methodologies.

6 In conclusion, we believe there's now a
7 convergence of FDA and NHF viewpoints and that nucleic acid
8 testing, coupled with other pharmaceutical industry
9 initiatives, such as quarantining all donations for 30 to
10 60 days, deferral of first-time and other selective donors,
11 and improved viral inactivation and elimination techniques,
12 will serve to further enhance blood product safety for all
13 recipients.

14 I thank you for your attention.

15 DR. SWISHER: Thank you very much.

16 The last speaker who has asked for reserved
17 time is Dr. Richard Davey of the American Red Cross.

18 DR. DAVEY: Thank you, Dr. Swisher.

19 I'd like to present a statement from the
20 American Red Cross on nucleic acid testing of blood donors.

21 The American Red Cross is committed to
22 exploring the use of new technologies designed to improve
23 the safety of the blood supply. We've supported such
24 initiatives in the past. For example, we encouraged the

1 FDA to license the HIV 1 p24 antigen test, and we're now
2 conducting research on other potential threats to the blood
3 supply, such as Chagas disease and bacterial contamination
4 of blood components. Accordingly, as you have heard, we
5 are evaluating the use of PCR technology to detect early
6 evidence of viral infections that may be transmitted by
7 transfusion.

8 You have heard the results of our preliminary
9 sensitivity and specificity studies from Dr. Stramer. She
10 didn't have time to present also some very interesting
11 sample stability studies looking especially at HCV.

12 These preliminary studies, that have been
13 discussed at length with the FDA, suggest that testing
14 pooled donor samples in a dilution of 1 to 500 may prevent
15 the transfusion of several hundred components each year
16 that may be infectious for hepatitis C. Reductions in the
17 window period for hepatitis B and for HIV are also
18 possible, as you've heard, using PCR technology.

19 Now, many technical and operational challenges
20 remain to be addressed before PCR testing of the volunteer
21 blood supply can be implemented. For example, again as
22 you've heard, the current turnaround time for PCR testing
23 makes it likely that short-dated products, such as
24 platelets, will be transfused before PCR tests results will

1 be available. As a result, it is possible that recipients
2 would be notified of positive PCR test results after the
3 implicated unit has been transfused.

4 I think this is far from ideal but it's worth
5 keeping in mind that those recipients would be receiving
6 information about their health under this system that they
7 are currently not receiving under the present testing
8 system. Therefore, they might be able to initiate
9 interventions that would positively affect their health or
10 perhaps adjust some of their lifestyle to prevent secondary
11 transmission of disease.

12 Another problem with the turnaround time, again
13 as you have heard, is that quarantining red cells, while
14 PCR test results are pending, may indeed be difficult in
15 times of national blood shortages.

16 We at the Red Cross are exploring testing and
17 transportation alternatives to address turnaround time and
18 other technical and operational challenges. Our goal is to
19 implement PCR testing in such a manner as to improve the
20 safety of the blood supply in a way that is operationally
21 feasible.

22 We intend to continue our studies of PCR
23 testing of samples from volunteer donors under an
24 investigational new drug application which has been filed

1 with the FDA. This linked donor study, which has been
2 approved by our institutional review board, is essential to
3 determine the optimal approaches to donor and recipient
4 management. The study will allow the Red Cross to evaluate
5 new pooling designs and operational issues in an orderly
6 fashion under IND guidelines. We're excited about this
7 opportunity and we look forward to generating information
8 that will add to the safety of the nation's blood supply.

9 We intend to communicate the results of our
10 investigations as data become available. We look forward
11 to productive interactions with the FDA, with private
12 industry, and with others in the blood banking community
13 that are interested in evaluating PCR technology as a
14 useful tool in improving blood safety.

15 Thank you, Mr. Chairman, for the opportunity to
16 speak on this issue.

17 DR. SWISHER: Thank you, Dr. Davey.

18 This is obviously a topic of great interest and
19 great import in many respects with regard to the nation's
20 blood supply both of its standard donor products as well as
21 those that are manufactured.

22 We're running late, obviously, and we will
23 obviously have to extend this part of our agenda, but I
24 would like to invite anyone who has not requested time --

1 and I hope the whole house doesn't stand up -- who would
2 like to make a contribution in two or three minutes to do
3 so.

4 (No response.)

5 DR. SWISHER: If not, you obviously have been
6 well represented by the people who have spoken in the open
7 meeting. With that, I think we will officially close the
8 open public hearing and consider the matter at the level of
9 the committee.

10 To get things started, I'd like to tell you
11 about a little change in procedure that we have developed
12 since the last meeting. Many of the committees of the FDA,
13 such as ours, have a designated discussant, particularly
14 for problems that have some relatively high level of
15 technical expertise and/or scientific knowledge. This
16 discussant, who was chosen from the committee, is asked to
17 make a brief summary and a brief presentation of an overall
18 perspective of the problem and to use this to guide and
19 focus the discussion, particularly on those issues that
20 seem to be highly relevant. We have decided to give this a
21 try at this meeting. So, Dr. Blaine Hollinger will fill
22 this role for this particular topic.

23 But before we hear from him, I think it would
24 be also useful to focus the committee's attention if we

1 could have a presentation of the specific questions that
2 we're going to be asked to respond to. Paul, are you the
3 official -- or Ed?

4 DR. TABOR: The questions for the committee
5 are, number one, does the committee endorse the FDA
6 position that nucleic acid tests used to screen plasma
7 pools should be regulated as licensed biologics, that is,
8 should require an IND and a PLA?

9 Number two, does the committee endorse the
10 position that donor notification must follow the finding of
11 a positive test result?

12 And number three, what does the committee
13 recommend concerning donor deferral, reentry, and lookback
14 procedures following detection of a positive donor in the
15 course of nucleic acid screening of plasma pools? Are
16 current algorithms adequate?

17 DR. SWISHER: Do we have that on a slide or an
18 overhead?

19 DR. TABOR: It's possible that we don't.
20 (Laughter.)

21 DR. SWISHER: We may ask you to refresh us from
22 time to time.

23 DR. TABOR: Let me ask Dr. Smallwood. That's
24 all right. I think oral is as good as handwritten.

1 DR. SWISHER: Are there questions on the charge
2 to the committee?

3 (No response.)

4 DR. SWISHER: If not, I'll ask Dr. Hollinger to
5 undertake the task of trying to tell us where we are and
6 where we may be going.

7 DR. HOLLINGER: Dr. Swisher, this may be the
8 last time that we do this.

9 (Laughter.)

10 DR. HOLLINGER: It's very difficult because one
11 of the reasons you come here to this committee is to hear
12 the thoughts from the blood banking community and so on,
13 and so none of this information really was available to us
14 in many ways prior to our coming here. So, it's difficult
15 to formulate some thoughts about this, although we clearly
16 are at another era when we have some very sophisticated
17 tests now which are very sensitive.

18 I obviously must remind everyone that what is
19 being detected, of course, is nucleic acid. That doesn't
20 necessarily mean it's infectious, but nucleic acid is being
21 detected, and for the most part, the presence of this
22 nucleic acid does indicate a virus that potentially could
23 be transmitted. Nothing has been shown necessarily that
24 these individuals who are being detected at certain levels

1 may or do transmit the infection to others, but we assume
2 that this would take place.

3 I think there were some excellent evaluations
4 by the staff this morning to help us focus a little bit on
5 all the very complex issues that are faced here: stability
6 of products, sensitization of assays. When one talks about
7 sensitization of assays down to certain copies per ml,
8 there are all sorts of nuances there of what exactly this
9 means.

10 I think what we've seen today is that probably
11 these tests, in many cases with viral inactivation
12 procedures available, are not necessarily going to modify
13 the safety of these plasma products very greatly.
14 Certainly viral burden will be reduced, but in many cases
15 they won't modify that.

16 One of the things that Dr. Epstein reminded me,
17 when we were discussing this a little earlier, was the fact
18 that donors from source plasma are donating blood and can
19 donate blood as frequently as every 48 hours or so. So,
20 it's not like you're going to have someone who comes in to
21 donate a unit of blood and may not donate it again for 8
22 weeks or 3 months or 6 months where you might be able to
23 interdict that individual from another donation in that
24 regard.

1 On the other hand, also by the time they come
2 in to donate again, they will probably have seroconverted
3 if this is truly in the window period. So, they would be
4 detected with the current tests which are available.

5 For the source plasma, it's a little bit
6 different in that these individuals would be donating very
7 frequently and therefore many units of blood would have
8 been collected.

9 What I didn't hear from plasma industry -- and
10 I might just ask someone here now because it would be
11 helpful to me as I'm discussing this, but I didn't hear how
12 long blood is usually collected. If blood is collected
13 from an individual and is stored, how frequently is that
14 put into a pool? How soon? Are these stored for perhaps
15 2, 3, 4 months before they're put into a pool or are they
16 pooled perhaps within a week to 10 days? The storage
17 aspects of this, the logistics of it are mammoth, but could
18 somebody just quickly answer that for me please, routinely
19 what is done?

20 MR. REILLY: One of the slides that you saw in
21 Margaret Savage's presentation.

22 DR. SMALLWOOD: Excuse me. Could you please
23 state your name? Thank you.

24 MR. REILLY: Jim Reilly, American Blood

1 Resources Association.

2 One of the slides that was in Margaret Savage's
3 presentation is a commitment on behalf of the industry to
4 store plasma for a minimum of 60 days before it would be
5 pooled.

6 DR. HOLLINGER: Okay, thank you. So, that
7 capacity seems to be there.

8 Anyway, Dr. Swisher, I think it's important for
9 many of these things to be discussed. I'd like to hear
10 more from the committee members about some of the thoughts
11 that they have about the questions that have been brought
12 for the committee here before perhaps I make any further
13 conclusions.

14 DR. SWISHER: We can open the discussion up now
15 to the rest of the committee. Kenrad?

16 DR. NELSON: I remember a discussion we had
17 from a previous meeting where there was a single case
18 presented and then an investigation of somebody that
19 received intramuscular gammaglobulin and a question about
20 hepatitis A. There were studies of pooled treated globulin
21 and a high proportion had nucleic acid, were positive by
22 nucleic acid amplification methods. That sort of rang a
23 bell about the positive tests not being equated with
24 infectivity necessarily. Clearly this is an important

1 issue with this product.

2 But I just wonder how much of that problem is
3 there in either treated or untreated products with either
4 hepatitis A or other viruses? In other words, by looking
5 at amplification, would we detect problems that aren't
6 really there? How often would we be detecting non-
7 infectious units that were really fragments -- that would
8 contain some nucleic acid but weren't infectious? Is there
9 any good data on any of these issues?

10 DR. HOLLINGER: No, but I think these are
11 really the critical issues. We talked about pools a little
12 while ago, and of course, as was mentioned today, the pools
13 depend upon the median concentration of virus in the
14 communities.

15 Now, we know, for example, for hepatitis C, by
16 and large the median concentration for hepatitis C, if you
17 take a whole large population to look at, runs somewhere
18 around 2 million to 3 million per ml. So, you could sort
19 of backtrack a little bit.

20 In fact, about 85 percent of the patients with
21 chronic hepatitis C -- but these, of course, now will also
22 have antibody positivity, so the issues might be a little
23 bit different when you're looking at the window period.
24 But at least in those individuals, about 85 percent of them

1 will have over a million copies per ml. So, you can sort
2 of backtrack a little bit to see what kind of pool size you
3 might get with the sensitivity of the tests that were
4 discussed a little earlier. So, those are clearly issues
5 that need to be taken into account.

6 On the other hand, if you take other viruses
7 like hepatitis A, which has a very low level of viremia, or
8 the newer virus like hepatitis G virus which has about 10
9 to the 4th to 10 to the 6th copies per ml and with which 1
10 to 2 percent of the population may be infected, you can see
11 that you'd have to test very small numbers of pools because
12 every pool would be positive. If you took a pool of 100
13 for hepatitis G, every pool potentially would be positive.
14 Therefore, you'd have to test all of the individual samples
15 in the first place.

16 Fortunately for C the level is high. Generally
17 for HIV the level is generally high. For HAV it's fairly
18 low but the prevalence is very low in that population also.

19 So, the answer to the question about the
20 fragments are important. We know that conventional immune
21 globulin as you mentioned, probably as far as I know,
22 rarely if ever caused transmission of hepatitis A. Yet,
23 many of the lots contained HAV RNA when looked for.

24 DR. SWISHER: Does anyone have a useful number

1 for what might be called the minimum infective dose of
2 specifically HIV? All sorts of speculations seem to be
3 rampant, but are there any data that anyone really has any
4 confidence in about minimum infective dose?

5 It seems to me this is a critical number and if
6 there was some way to get at it, it might --

7 DR. BUSCH: My name is Mike Busch.

8 I agree completely that the critical issue here
9 is the relationship between nucleic acid detectability and
10 infectivity, particularly as we look at implementing these
11 expensive assays and the cost effectiveness will clearly be
12 low, but on the other hand, if we believe that these assays
13 could eliminate infectivity, then I think that it's
14 probably well worth implementing.

15 We're beginning to try to study that question.
16 Obviously people have taken in the chimp model HBV, HCV
17 positive material and diluted it out to endpoint and done
18 correlations. There actually the sensitivity of PCR
19 correlates within a log or so of the chimp infectious doses
20 for those two agents, but that's based on dilutional
21 studies of chronically infected seropositive specimens, and
22 whether that's applicable to the infectivity-to-
23 detectability relationship in window phase is another
24 question that needs to be studied.

1 This is a study actually that Harvey Alter
2 initiated a few years ago and then I've gotten involved
3 with and is actually under review at Nature Medicine where
4 it addressed that question specifically for HIV in the
5 chimp model. Chimps are susceptible to HIV transmission.

6 In this study what was done was an inoculum of
7 HIV 3b, which is the widely used lab strain of HIV, was
8 introduced into a first chimpanzee and that chimpanzee was
9 then monitored with weekly collections of fairly large
10 volumes of plasma in PBMC. You see there the serial weekly
11 collections across the top.

12 That chimpanzee seroconverted to second
13 generation antibody tests on week 8 and actually was
14 positive on the current third generation antigen sandwich
15 assays that are used in most blood banks on week 6. So,
16 that last line of anti-HIV could be pushed back to week 6
17 in terms of the current mass blood screening assays.

18 But the chimp was, interestingly, found to be
19 PCR positive and isolation positive on week 5, but
20 importantly it was negative for a longer period prior to
21 that. This is true in humans as well where you can
22 demonstrate that post-exposure there appears to be a period
23 of weeks to sometimes months before an individual becomes
24 viremic and then viremia proceeds in a rapid ramp-up in

1 seroconversion.

2 But there's this long period of pre-viremic
3 predetectable window phase, and the question that this
4 study attempted to address is whether individuals are
5 infectious during that phase and the correlation between
6 infectivity and PCR.

7 What you see at the bottom is what was done
8 then is that 10 milliliters of plasma and approximately 5
9 million PBMCs from each of these weekly samplings prior to
10 seroconversion, beginning with the third week, were
11 transfused into another chimpanzee, and then that
12 chimpanzee was monitored for a period of 3 months to
13 determine whether there was any evidence of viral
14 replication or seroconversion.

15 What you can see is that the first two
16 infusions into that secondary chimpanzee from week 3 and
17 week 4 caused no evidence of infection, no seroconversion,
18 no virus detectable by any direct virus methods, whereas
19 the PCR positive antibody negative unit did cause
20 seroconversion in a typical time course of 4 weeks with
21 positive virus, positive RNA, and then subsequent
22 seroconversion. So, this indicates, in a limited study,
23 weekly intervals, that there does seem to be a direct
24 correlation between PCR detectability and infectivity.

1 There's a plan now -- and Harvey has requested
2 from NIH funding -- to look at three additional chimpanzees
3 actually using plasma donor panel source material where we
4 have real human starting material and we're selecting
5 panels that are chimp infectious, first of all, and that
6 have very frequent bleeds with sub-detectable RNA to
7 extraordinarily low level RNA to increased ramp-up of RNA
8 to further define this relationship between seroconversion
9 window phase detectability and infectivity. And I think
10 these same studies need to be followed suit on HBV and HCV.

11 DR. SWISHER: But the paradox here is that at a
12 time when you can't detect anything by PCR, you also can't
13 detect infectivity by this technique, but that doesn't
14 really tell us how many copies are necessary in the
15 inoculum to infect the chimpanzee when in fact it does
16 become infectious.

17 DR. BUSCH: Right. If you look at the plasma
18 donor panels, a large number of these panels, many of which
19 have very frequent bleeds literally starting with 10 copies
20 per ml and then 300 copies, and then you finally get to
21 antigen positive -- and the plan is to start back two
22 bleeds prior to any detectable RNA and move through those
23 very low titered copy number transfusions and try to get at
24 that.

1 DR. SWISHER: Insofar as the chimpanzee
2 reflects human infectivity, that will certainly be
3 information --

4 DR. BUSCH: I agree with the caution there.
5 That's a very --

6 DR. SWISHER: Thank you very much.

7 DR. NELSON: I see in the 4 week, PBMCs were
8 included, as well as plasma but not in the 3 week?

9 DR. BUSCH: Yes, right.

10 DR. NELSON: So, the PBMCs were also negative
11 at 4 weeks prior to PCR positivity.

12 DR. BUSCH: That's correct.

13 DR. NELSON: Because obviously there could be
14 earlier replication in cells that are circulating.

15 DR. BUSCH: Right. In this setting, they were
16 able to pull PBMCs and plasma off of these serial donations
17 during the window phase. As we move on to these next level
18 studies using the plasma human panels, the intent is
19 actually to infuse allogeneic PBMCs along with the human
20 plasma just to give it the allogeneic stimulation that
21 could result in increased susceptibility, but we don't
22 obviously have PBMCs --

23 DR. SWISHER: Dr. Tabor?

24 DR. TABOR: I think with regard to the issue of

1 fragments, I think even though fragments of nucleic acid
2 can be detected in some products, as Dr. Hollinger was
3 saying, I believe the issue with small pools of recently
4 collected plasma donations that fragments should not be
5 considered too important an issue.

6 I think finding a nucleic acid should be
7 presumptive evidence of intact virus. In a recently
8 collected donation, were there small fragments of nucleic
9 acid in the donor's blood, they would be destroyed, I
10 believe, by endogenous nucleases and would not survive for
11 any length of time. So, I think the finding of nucleic
12 acid, until there's additional information, has to be
13 considered the finding of virus.

14 DR. NELSON: So, you would conclude that the
15 fragments that are in intramuscular immunoglobulin is due
16 to the preparation, not due to --

17 DR. TABOR: I would assume that in most cases,
18 they resulted during the course of preparation, yes.

19 I'm sorry. Dr. Finlayson says it's not true.

20 DR. FINLAYSON: Dr. Yu should be here to
21 present her own work, but I believe the committee has it in
22 their packets.

23 The material that was found in the non-
24 infectious intramuscular immune globulins seems by buoyant

1 density measurements to have been complexes between antigen
2 and antibody rather than fragments.

3 DR. TABOR: In which case what I said still
4 holds. It results from the process of creating the
5 globulin and the pool. I think in individual donations
6 that are pooled, any nucleic acid that's there probably
7 represents virus in the donor.

8 DR. FINLAYSON: I agree with that. I think
9 that it is virus and I think, at least presumptively, that
10 the reason for non-infectivity was several-fold, but all of
11 which involved complexing. So, yes, I agree with you.

12 DR. CONRAD: Actually the best piece of
13 evidence of all this is when we do the pooling, you use
14 ultra centrifugation, and viral fragments don't have
15 different buoyant densities than whole virus. So, the fact
16 that by obligation to concentrate the virus, we do ultra
17 centrifugation, means what we detect in these pooling
18 regimes is protein encapsulated nucleic acids that have
19 buoyant densities similar to whole viruses, and if you take
20 that into account, it means detection is probably much more
21 likely to equal infection because the fact that it had to
22 be encapsulated in a protein. I would be very afraid to
23 inject a protein encapsulated nucleic acid that has a
24 specific buoyant density of a virus and in the homologies

1 to that virus. That to me wreaks of a whole real virus.

2 DR. KASPER: I think one of the people who
3 presented characterized the PCR procedure as very
4 expensive, and although that's not our first consideration,
5 I wonder if we could get an order of magnitude, even though
6 that doesn't affect our decisions. Is there someone who
7 represents the people who actually do this who could
8 estimate what are we talking about on a per donor basis
9 that this will add to the cost of -- so that we kind of
10 have a feeling of the magnitude of the expense? That was
11 raised. The question was raised.

12 DR. CONRAD: Remember, the primary analyte that
13 we're looking at is the 500-fold dilution in a pool. So,
14 whatever the cost is -- say, it's \$150, which is roughly
15 the cost -- divided by 500. So, it's actually cheaper than
16 any of the other tests that are used now. We figure even
17 with the retesting to identify the individual donor, it
18 turns out to be about 33 cents per donor per virus. PCR in
19 individual donors is very expensive. It's \$150 a donor,
20 but in the pooling construct, it reduces that exponentially
21 by the size of the pool.

22 DR. SWISHER: One of the things that has
23 concerned me about this particular topic is that I think we
24 all carry the HIV concern in the front of our minds. We

1 want to remember that we really have a lot of morbidity and
2 mortality in this country that is related to the hepatitis
3 viruses. Under these circumstances, I think we really need
4 to keep both of those kinds of perspectives. Yes, HIV is
5 clearly the number one target, but a significant reduction
6 in the transmission of hepatitis B and C would certainly be
7 in the interest of the patient recipient as well as
8 ultimately the donor.

9 DR. McCURDY: I wonder if I could ask Mike
10 Busch a question. I seem to recall some data from the
11 Transfusion Safety Study about the units that did transmit
12 versus those that did not transmit. Does that bear on the
13 infectious dose issue?

14 DR. BUSCH: It does in the sense that we
15 published a paper where we looked at the viral load in
16 seropositive units. In TSS -- of course, this is the 6
17 months prior to the availability of the HIV antibody test
18 -- 200,000 donations were saved, subsequently tested. The
19 seropositive donor units, the recipients were traced, and
20 90 percent of the antibody positive donor units
21 transmitted.

22 The question we asked was why didn't 10 percent
23 transmit, and the answer was that it related to viral load,
24 that the donor units that did not transmit were all in the

1 lower 20 percent of the viral load distribution, compounded
2 by the fact that those units averaged to be stored greater
3 than 2 weeks in the refrigerator. So, the relationship
4 between viral load and infectivity by parenteral and sexual
5 transmission for HIV and all agents is pretty well
6 established.

7 One other piece of data I think that's
8 important. In the TTVS study with respect to HCV, there
9 were 140 seropositive donations detected by second
10 generation HCV tests. Only 110 of those approximately
11 transmitted, caused seroconversion in the recipients
12 detectable by second generation tests. We're now looking
13 at the relationship between the viral load in those
14 donations and transmission.

15 But there were also 7 recipients who
16 seroconverted who did not get any seropositive units, and
17 work in Jim Mosley's lab has found that 3 of those cases,
18 there was a PCR positive donation that was associated with
19 the recipient seroconverting.

20 Linkage sequence work needs to be done, but it
21 does suggest that there may be more of this occult HCV
22 infection than the incidence data would predict.

23 DR. SWISHER: The other thing is we're talking
24 about another element of biological variability, namely,

1 the variability of the recipient, the potential victim of
2 the virus. So, that may be a significant variable too, and
3 the idea of a "single minimum infective dose" may even be a
4 will-o'-the-wisp that can't ever be caught.

5 Rev. Little?

6 REV. LITTLE: As someone who's not medically
7 trained, I've been sitting here trying to figure out from
8 what we've read and from what I've heard whether or not the
9 PCR testing is significant or not. I believe it is and
10 that it's a good thing.

11 However, if we are saying that this is
12 significant enough to make a difference, I'm really
13 confused by the question of donor notification. I think
14 the question isn't whether or not to notify donors, but the
15 question is how do we do this. I think that's just a given
16 fact that if this makes a difference in detecting
17 something, there's no issue about whether or not to do
18 this, but to spend the energy on what is the process, how
19 do we do this.

20 The other thing is the question of pool size
21 keeps coming up. We've had a discussion about pool size
22 for fractionated products in previous meetings. I'd like
23 to just again keep that in mind. I would like to see some
24 kind of standard pool size established, and I would like to

1 see some involvement of FDA in determining pool size with
2 the industry.

3 The final thing is it sounds like this
4 individualized testing seems to be the ideal way to do it,
5 and I would hope that at the same time there would still be
6 ways that maybe there would be a better way to do
7 individualized testing so that the question of pool size
8 then becomes a different kind of question.

9 DR. PILLIAVIN: I'm rather curious about why the
10 Europeans seem to be ahead of us on this. How did it arise
11 that they're starting to be concerned about this?

12 In this connection, I really would like to have
13 somebody tell me about viral inactivation one more time. I
14 had gotten perhaps lulled into some sort of state of
15 complacency with regard to the source plasma products and
16 so on, thinking that essentially all of the viruses we knew
17 about were being deactivated. I thought the concern that
18 we had were for the ones that we didn't know about. So, I
19 guess I would like a discussion of that.

20 MR. DUBIN: I'm going to try to answer some
21 part of your question, Jane, but I want to say something
22 else first because I feel like sometimes we seem to have
23 some discussions of some of these issues in a vacuum.
24 We've talked about pool size in the past and now we're

1 talking about PCR testing of pools.

2 There's a report out that I think the committee
3 should be reading that should be informing this decision.
4 It was released in February of this year and it's the GAO
5 report on Blood Supply, FDA Oversight and Remaining Issues
6 of Safety, and Part 2 Transfusion-Associated Risks. I
7 think it's interesting. I think it's informative, and I
8 think it's the kind of tools we should be having as part of
9 these discussions because I think there's a context.

10 The other thing that I think needs to be part
11 of these discussions is that every member of the committee
12 ought to sit down one evening, instead of with a good book,
13 with the 1978 FDA recall regs that are still in force and
14 really learn them because I think when we start talking
15 about lookback, lookback has a context that relates to
16 recall. It does not live in a vacuum. It's something
17 we've been looking at very extensively with our regulatory
18 team at the Committee of Ten Thousand.

19 So, I think sometimes we really feel like some
20 of these discussions get done out of context and not
21 looking at the larger global picture which they all live
22 in.

23 That said, in terms of our perspective, Jane,
24 on viral inactivation, certainly a lot of the really

1 important lipid envelope viruses are being inactivated.

2 DR. PILIAVIN: The ones that they're testing
3 with this PCR.

4 MR. DUBIN: Right, but there are non-lipid
5 envelope viruses like Parvo B19, for instance, which we
6 don't really know the impact. We're certainly going to see
7 some of it and we've seen some impact in people with
8 hemophilia who are immune-compromised from Parvo.

9 DR. PILIAVIN: But that doesn't speak to the
10 ones that the PCRs are being done on. If those are the
11 ones that are being inactivated, then I don't understand
12 the problem.

13 MR. DUBIN: Let me go a step farther. I was
14 just trying to answer a general question.

15 We've just come through -- and I can't count
16 them because my fax machine has been going so much, but
17 we've just come through a two-week period where I believe
18 there were six -- a market withdrawal, and four or five
19 recalls being contemplated and problems with Centeon and
20 problems with Alpha. Before we had a transferrin problem
21 late last year and early this year.

22 So, I think there are some issues to be
23 discussed or we wouldn't be having this rash of problems
24 the way we are. We've been pretty close to this and it has

1 been a pretty head-spinning three weeks from our
2 perspective trying to take a look at these things. So, I
3 think obviously, given that, there are things to be
4 discussed. We're not in a position, it seems to me, where
5 the inactivation structure or system being brought to bear
6 makes it a moot issue, so why are we bothering to discuss
7 this.

8 Then the last thing I want to say is a couple
9 of things I heard that I just want to point out to people
10 that I think are interesting because you mentioned the
11 Europeans.

12 I think the Europeans are head of us in a few
13 areas. One of them is paid versus unpaid donors.

14 Hepatitis genome on HCV came up. Somebody
15 mentioned that 3a was unusual in the United States. It is.
16 The only two communities that significantly show 3a are
17 people with hemophilia and IV drug users, and I think you
18 can draw your own conclusions from that. We've been saying
19 certain things about that for a number of years, and now
20 the data is starting to come through that shows it.

21 The last thing I would say is in Italy there
22 was a study of genotypes in HCV, and the hemophilia
23 population was statistically no different than the
24 mainstream population with HCV. And in the United States,

1 that's not true. I think the conclusion there is about the
2 donor population.

3 So, again, I think we have these discussions a
4 little out of context and we make some assumptions that
5 maybe we ought to step back from and take a longer look at
6 this because they are really important public policy
7 issues.

8 DR. SWISHER: I want to terminate -- well, not
9 terminate -- I want to suspend this discussion.

10 DR. PILIAVIN: There's somebody at a mike who
11 may have answers.

12 DR. SWISHER: I still want to suspend, and we
13 will break for lunch.

14 DR. PILIAVIN: I think he may have had an
15 answer to my question about Europe.

16 DR. SWISHER: Do you have a specific --

17 MR. BULT: I can do this very briefly. My name
18 is Jan Bult. I'm the Executive Director of the European
19 Association of the Plasma Products Industry.

20 I thought it was a specific question about the
21 situation in Europe or why the Europeans were ahead of
22 this.

23 I think I would be a little bit hesitant in
24 using that expression. It's not a competition. It is a

1 safety issue. It's a global issue.

2 What I could do just very briefly, the
3 chronology of what happened.

4 At a meeting in September 1995, the total
5 industry was invited to have a meeting with the European
6 regulators. At that moment priorities were set. One of
7 the first issues where industry had to come together was on
8 PCR.

9 There was a meeting in May 1996 and industry
10 was requested to show the progress, the experience with the
11 implementation of PCR. The issue that drove the discussion
12 was the intramuscular immunoglobulins without viral
13 inactivation in the manufacturing procedure.

14 Now, the goal was to have PCR implemented as
15 soon as possible. Because of all the complex issues that
16 we all heard about today, we had a subsequent meeting three
17 weeks ago. You heard the details in the presentation of
18 Dr. Margaret Savage. And if I would analyze, the problems
19 at this moment are this.

20 First of all, the regulators in Europe are
21 fully aware of the complex issue. We told them about the
22 position here in the United States about donor
23 notification. We told them about the differences that we
24 have as an industry if you have two different requirements

1 at two sides of the Atlantic. That puts the industry in a
2 difficult position. Just think about liability issues.

3 Another issue was you cannot impose a mandatory
4 implementation for PCR if you have not the possibility to
5 have that done for source material and for whole blood
6 material because that would create two different standards.
7 That was considered to be unacceptable.

8 However, the Biotech Working Party said, you,
9 industry, have to show us the further progress that you
10 make with the implementation of this technology because we
11 have millions of people, patients, waiting for these
12 products, and we should exercise every option to further
13 improve the margin of safety of these products.

14 They are fully aware of the consequence of
15 donor notification. However, the technology in development
16 is not that far at this moment.

17 I had a meeting last week in London and spoke
18 with the regulators to have a good understanding about
19 timing because that is an important issue. As far as I'm
20 informed at this moment, this week there is a meeting in
21 London with the Biotech Working Party in which the first
22 internal strategy will be developed which has to be
23 approved by the official regulatory body, the CPMP, in
24 Europe.

1 The expectation is that by mid-year this
2 strategy will be discussed with the involved parties for a
3 first consultation followed by a public consultation.

4 On my specific request, could you give me an
5 indication for timing, they said, no, we cannot. We have
6 to be extremely cautious because of the arguments given and
7 every time that we would mention that, it would indicate
8 that we are further than we are. We will allow industry to
9 further progress and develop the technology, but we have to
10 listen to the comments and arguments given and avoid two
11 different standards.

12 I think hopefully that is an answer to your
13 question.

14 DR. PILIAVIN: Thank you.

15 DR. SWISHER: We will now break and we will be
16 back at 1:30.

17 MS. PIERCE: Dr. Swisher, I have a specific
18 question for him that might just be quicker to ask now.

19 In terms of the European PCR testing, is that a
20 quality control test or is that more of a screening test
21 similar to the p24 antigen?

22 MR. BULT: No. It's no screening test at all.
23 It is a political opinion that if PCR is involved, it
24 should be a part of the IVDD Directive, which is a

1 diagnostic directive. It is considered as a manufacturing
2 tool at this moment.

3 (Whereupon, at 12:41 p.m., the committee was
4 recessed, to reconvene at 1:30 p.m., this same day.)

1 AFTERNOON SESSION

2 (1:38 p.m.)

3 DR. SMALLWOOD: We're going to continue the
4 discussion on nucleic acid testing of plasma pools.

5 Dr. Swisher?

6 DR. SWISHER: First I'd like to indicate that
7 we really regret, on behalf of our guests and observers,
8 the problems that you had in getting a reasonable lunch.
9 This came up as a bit of a surprise to everybody just a few
10 days ago. It was not for lack of consideration. It was
11 for lack of information that it came out this way. We'll
12 certainly try to have better accommodations in our
13 subsequent meetings.

14 Our discussion of the nucleic acid testing set
15 of issues is now reopened. I'd like to just point out
16 that, as Dr. Tabor stated in his initial presentation, this
17 is a very complex issue and it extends out into essentially
18 all of blood services. But the issue that we specifically
19 have before us is the issue of the testing of plasma pools
20 that are designated for further manufacture. Obviously,
21 there's going to be an evolution of this topic until we
22 find some way of applying it to a broader base specifically
23 of donors.

24 So, I'd like to make sure we focus our

1 discussion for the remainder of this session on the
2 question, that is, the impact of nucleic acid testing on
3 plasma that is designated for further manufacture.

4 Susan?

5 DR. LEITMAN: I want to make some comments on
6 statements that were made by Dr. Bianco and by Dr. Ness
7 earlier and that's to distinguish PCR testing on paid or
8 source plasma donors and PCR testing of pools of recovered
9 plasma from whole blood donors. It would seem that those
10 two donor populations are worlds apart ethically and
11 operationally.

12 I think that we are ready for PCR testing of
13 source plasma donors because we can operationally and in a
14 very cost acceptable manner interdict the product before it
15 is used and inform the donor, as appropriate, and interdict
16 further donations by that donor, et cetera.

17 But I have great difficulty saying that we're
18 ready, again ethically and operationally, for linked PCR
19 testing in the case of recovered plasma from volunteer
20 whole blood donors and for tracing results back not only to
21 the donor, which I don't really have a problem with, but to
22 the recipient of that unit. We can't interdict those units
23 now, the red cells or the platelets.

24 It's a nightmare to even begin to think of

1 notifying a recipient that only 1 week ago, 4 weeks ago, 8
2 weeks ago, 12 weeks ago, they received a viral positive
3 product. As someone said to me at lunch, the next phone
4 call would be to their lawyer. Testing was available but
5 not performed. Units weren't held.

6 Then another speaker earlier raised an issue I
7 hadn't even thought of. If units are held, then there will
8 be two classes of units, a PCR-tested whole blood donation
9 inventory and a non-PCR-tested.

10 So, holding onto the link is something I don't
11 think we're ready for yet, but I don't think that should
12 necessarily hold up the ability to have source plasma
13 donors tested with a link.

14 DR. SWISHER: You've obviously put your finger
15 right square on the interface between what might be called
16 the general blood donor population and the problem of
17 plasma for further manufacture. That obviously is a
18 critical question.

19 Does anyone care to discuss and develop that
20 further?

21 DR. HOLLINGER: Susan, what if I were to tell
22 you that treatment of an acute HCV infection would result
23 in a 60 percent response rate and a cure compared to the 5
24 to 15 or 20 percent that we get now? That's a considerable

1 piece of information that I think we have to deal with
2 there, and we can't ignore someone who has been infected.
3 If they've been infected, you can't do anything about it if
4 they've gotten the blood. The bigger issue is whether one
5 can get a turnaround time short enough.

6 The platelets are a real problem. So, we
7 obviously should push more for platelet pheresis with
8 donors who are tested perhaps initially or repeat donors.
9 But in terms of red cells, certainly I could see that a
10 delay in the distribution of the red cells for 7 days or a
11 period of time is not one that could not be put into place.

12 But I am concerned about leaving the recipient
13 out without knowing if there is an issue that you might be
14 able to effect a cure if you had to treat that individual
15 compared to what would happen once they become chronically
16 infected.

17 DR. SWISHER: Carol?

18 DR. KASPER: I'm strongly in favor of notifying
19 both the donor and the recipient trying to envision myself
20 in either position. As a donor I would expect a blood bank
21 to tell me if they found something the matter. I think
22 that's part of the donor gift. You should get back
23 whatever information might be useful. And as a recipient,
24 even if there's nothing you can do about it that you can

1 see, you might be able to do something about it later or
2 not transmit it to somebody else.

3 It was so difficult with the HIV lookback and
4 there was no money for it. The job was pushed onto people
5 who were already extremely heavily burdened. We shudder at
6 the thought.

7 I think the answer has to be not to not do it,
8 but how can we do it. How can we fund the doing of it?
9 How can it not be a hideous job for somebody who is already
10 terribly overburdened? That's one of the reasons I think
11 we hesitate.

12 MR. DUBIN: Unfortunately, we are a rather
13 litigious society, but I don't think we should make
14 decisions based on concern for litigation even though I
15 think it's a problem and I think there's too much
16 litigation out there.

17 As someone who was never looked back at
18 personally, so to speak, and who never got notification
19 that factor VIII units that I was infusing regularly that
20 were later admittedly in documents cited as tainted units,
21 it's 13 years later and I've still never received that
22 lookback notice.

23 As someone that's happened to, there's real
24 frustration around that. There's a real sense that somehow

1 the system broke down and the lookback that should have
2 occurred once the structure had knowledge and had lists of
3 tainted lot numbers from factor VIII units from different
4 manufacturers, someone who believes that lookback should
5 have occurred, it makes me rather uncomfortable to think
6 someone could get HCV and not be told when we're moving
7 into a period where there's some potential treatments for
8 HCV and certainly there are lifestyle impacts on HCV,
9 whether or not you consume alcohol or other stress-related
10 things in your life that really can impact hepatitis C.

11 I think the ethics of the issue is that we have
12 to struggle to find ways to do it, and I think Dr. Kasper
13 said something important. We have to look at creating the
14 conditions where it can be done in a non-destructive, non-
15 burn-out way.

16 But I think both on the donor's side and the
17 recipient's side, the confidence in the system is what's at
18 stake. The confidence of people at the street level in the
19 blood supply and the people that operate it is what you
20 give up when people aren't notified.

21 I have a lot of discomfort with structuring
22 decisions on other factors besides some basic ethical
23 questions. If a recipient gets a bag of red cells or a
24 plasma derivative and we know that that has come from a

1 donor who has HCV or any of the other long list, do we have
2 an ethical responsibility to inform the recipient.
3 Obviously, we think we do, and as you all know, that comes
4 from our experience, obviously.

5 So, I think the question is how can we do it.
6 Can we create conditions? Because obviously it's much
7 easier to do it with source plasma and we can do it.

8 On the other side of the equation, there's the
9 72-hour delay and there are some instances where it's going
10 to be more difficult. But I think we have to do it.

11 DR. SWISHER: Other comments?

12 I think our task is relatively -- I'm sorry.

13 DR. HOLMBERG: I guess I just would like a
14 clarification here. I think one of the better
15 presentations this morning was Dr. Bianco's with the
16 different phase approach, and I agree with the comments
17 that we may not be ready for this yet in the unit testing.

18 However, has the agency looked at a phased-in
19 approach?

20 DR. TABOR: The answer is, no, we haven't but
21 the whole issue is still under discussion, so it can become
22 part of the equation if it looks desirable.

23 DR. SWISHER: Recalling then again that there
24 is this nexus between the issues that we're being asked to

1 respond to today and the broader issues within the whole
2 area of blood supply, are we ready for a show of hands?

3 For those of you who don't have the questions
4 before you, the first question, does the committee endorse
5 the FDA's position that nucleic acid tests used to screen
6 plasma pools should be regulated as a licensed biologics
7 and thus require IND and PLA?

8 What this question basically says is do we feel
9 that test systems that are going to be used in this
10 connection should be licensed tests that have gone through
11 the standard process of testing and approval.

12 All those in favor, so signify.

13 (A show of hands.)

14 DR. SWISHER: All those opposed?

15 (No response.)

16 DR. SWISHER: Abstaining?

17 (A show of hands.)

18 DR. SWISHER: One abstention.

19 And our non-voting members?

20 REV. LITTLE: I vote yes.

21 DR. NESS: Yes.

22 DR. SWISHER: Let's go to the well again and
23 try. Does the committee endorse the position that donor
24 notification must follow the finding of a positive test

1 result?

2 All those in favor, so signify.

3 (A show of hands.)

4 DR. SWISHER: Opposed?

5 (No response.)

6 DR. SWISHER: Abstaining?

7 (No response.)

8 DR. SWISHER: No opposition and no abstentions.

9 Third proposition. What does the committee
10 recommend concerning donor deferral, reentry, and lookback
11 procedures following detection of a positive donor in the
12 course of nucleic acid screening of plasma pools? And as a
13 corollary of that question, are the current algorithms
14 adequate, as Dr. Mied has explained and extended?

15 All those in favor?

16 DR. LEITMAN: I'm sorry. Before we vote on
17 that --

18 DR. PILIAVIN: It's not a yes/no question.

19 DR. LEITMAN: Yes, I'm not sure it's a yes or
20 no question.

21 If there were some way to accelerate the
22 reporting of results so that units in active inventory,
23 whole blood units from which the plasma was derived, could
24 be interdicted, that would make such a huge difference in

1 my ability to vote on that question.

2 If this means right now, the red cell and the
3 platelet units could not be interdicted and it would be
4 retrospective notification, a lookback notification, but a
5 very rapid lookback notification, again it's such a
6 problematic thing. So, the ability for rapid turnaround
7 seems to be approaching quickly, very rapid turnaround, a
8 week turnaround, two weeks turnaround

9 Actually that's not correct. If you hold
10 plasma pools for 60 days, it would be several weeks from
11 the 60 days. So, you'd never be able to interdict the
12 units.

13 I'm just thinking out loud.

14 DR. HOLLINGER: Yes. For me I think this is
15 awful early to answer this question. I think it's too
16 early really to come to some conclusion. There are so many
17 unanswered questions here. I think Susan has brought up a
18 few of them, but it seems to me kind of early.

19 DR. SWISHER: I'm sorry. There was a protocol
20 violation with the last question. I forgot to ask our two
21 -- but the body language suggested.

22 (Laughter.)

23 DR. SWISHER: To put it on the record.

24 REV. LITTLE: I agree with the committee.

1 DR. NESS: I'm not sure I agree with the
2 committee on issue number 2, although I wanted to speak on
3 issue number 3.

4 My concerns with issue number 2 is that I have
5 concerns that we are placing donor notification issues as
6 equally as important as recipient safety issues, and I am
7 concerned that in this process that if there is something
8 that we can do to protect a recipient, we may be delaying
9 it because we don't know yet what to do about the donors.
10 I think that to delay something that could make a blood
11 product or a blood transfusion for the recipient because of
12 the donor dilemma may be wrong.

13 DR. SWISHER: I think maybe to sharpen the
14 question up just a little bit, it certainly doesn't say
15 anything about not notifying the recipient. Clearly that
16 is a linked question but not specifically posed here. I
17 don't believe that anyone would disagree with the position
18 that Paul has taken on this.

19 Well, to return to item 3, what is your
20 pleasure?

21 DR. NESS: I just wanted to make a comment on
22 item 3. We haven't heard much about these issues in terms
23 of the lookback, reentry, donor deferral issues, and we
24 haven't really as a committee at this point relooked at the

1 current algorithms to even make any kind of an informed
2 decision as to whether they're adequate.

3 But it would seem to be since we're talking
4 about perhaps getting information from a blood center, for
5 instance one that deals with recovered plasma, that may
6 lead a physician to want to treat a patient in a different
7 way, perhaps giving him or her a medication which may be
8 toxic, that the types of information that the donor centers
9 would need to get, the types of testing algorithms that one
10 would need to reassure the clinician that it's the right
11 thing to give something to try to intervene in the
12 infection at that point, we haven't really even begun to
13 discuss.

14 I would assume that all of these issues, if we
15 really want to deal not with lookback, which is sort of a
16 situation where the patient has already been transfused and
17 we're going to try to deal with the ramifications now, but
18 actually trying to intervene are entirely different and
19 need to be carefully considered.

20 DR. SWISHER: Carol?

21 DR. KASPER: We don't have a yes or no question
22 before us, but let me suggest that we just take those last
23 four words. Are current algorithms adequate for the time
24 being?

1 DR. SWISHER: For the time being?

2 DR. KASPER: Yes. If we find there is some
3 other problem with this, if somebody needs an algorithm now
4 and these tests are going to be done now or soon, would
5 that be a yes or no question that we could answer?

6 MS. PIERCE: I also have concerns about this
7 with these algorithms because, especially in light of Dr.
8 McCurdy's comments the last time we looked at the
9 algorithms, I looked at this pretty carefully. A donor
10 would be able to go back and donate again, go through all
11 the tests. If a majority of the tests that they went
12 through in the first series, the steps in this process, if
13 more than a majority of them were either positive or
14 indeterminate and then six months later they would be able
15 to go back and go through all these tests again. This
16 would be a number of different tests giving you results. A
17 majority of them can be positive or indeterminate. Looking
18 at it in that aspect I do have concerns.

19 DR. SWISHER: Other comments?

20 It seemed to me that the sense of Dr. Mied's
21 proposal was that in a sense we would use the same
22 algorithm, but if the inquiry was triggered by a nucleic
23 acid test, that would in a sense overlay all of the other
24 procedures until that particular issue had been resolved.

1 In other words, if all other criteria of suitability were
2 met by a donor but there was a positive nucleic acid test,
3 that donor is suspended from both future donations for the
4 use of the product.

5 I don't think that was actually part of the
6 handout. Was it, Paul? I didn't see that as part of our
7 handout. Would you like to clarify that again?

8 DR. MIED: Yes. Dr. Swisher, what we're saying
9 is that in the face of a positive nucleic acid test result
10 on an individual unit, the donor would be deferred or, if
11 it's still an investigational test, held in abeyance until
12 their status can be conclusively determined whether or not
13 they're infected.

14 With regard to product retrieval, we're saying
15 that there is reason to believe that what we're currently
16 following in terms of product retrieval for both whole
17 blood and plasma units that have not been pooled that were
18 previously collected from the donor, it seems reasonable to
19 quarantine them until additional testing is done on the
20 donor, again to determine whether or not that individual is
21 infected. So, we're talking about following the same types
22 of algorithms that are currently in place.

23 DR. SWISHER: Additional questions?

24 It seems to me that if the word "reentry" were

1 taken out of that, a lot of us would feel maybe a little
2 safer because in a sense we are not certain that our
3 current reentry protocol will cover the occasional patient
4 who for some reason is nucleic acid positive and does not
5 become classically antibody positive.

6 DR. MIED: Reentry is a little more difficult
7 to address in a general sense because there are virus-
8 specific considerations that come into play naturally. We
9 have reentry in place for HIV but not for hepatitis B
10 surface antigen or hepatitis B core or HTLV in fact. We
11 know that we have discussed modifying the reentry algorithm
12 for HIV, but as you know, that proposed algorithm is
13 currently on hold until the group O kits can come into
14 availability.

15 DR. NELSON: I have a question about the
16 lookback issue. Given the fact that it may be pools that
17 are tested and that some of the donors might donate with a
18 short interval, therefore might have been included in
19 another pool, that it might have been used in a very large
20 number of people, it seems like the lookback from an
21 administrative position -- I can foresee circumstances
22 where that might be kind of dicey. You might have 10,000
23 people that you might have to -- am I misinterpreting that?
24 Is that part of the question? Is it easier than it sounds?

1 DR. MIED: No. I think that's accurate. There
2 may be circumstances that we cannot foresee at this present
3 time with regard to that donor being in other pools.

4 DR. NELSON: Right. In other words, you'd
5 identify a person who was found to be positive. You'd find
6 that that person made a previous donation, and lookback
7 would mean you'd look back at the people who received the
8 products from that previous donation. But if it was in a
9 pool that went to very large numbers of people, I can see
10 where it might be rather difficult to handle. I can see
11 potential problems with it, but maybe my imagination is
12 just carrying me away. I'm not sure.

13 DR. SWISHER: Jay?

14 DR. EPSTEIN: Kenrad, you're correct that as
15 one looks back, one may discover prior collections that
16 have already been pooled to process into finished product.
17 I think that the FDA looks at that as a separable problem.

18 What we're talking about here is the retrieval,
19 quarantine, and destruction of units that have not yet been
20 transfused or manufactured and the notification of
21 recipients of units that may have been from prior
22 collections, in other words, the transfused units.

23 With respect to prior collections already
24 pooled and processed into finished products that are

1 virally inactivated, the agency is developing policies to
2 deal with that. We call that problem, generally speaking,
3 inadvertent contamination. The whole question is what
4 should one do when one discovers inadvertent contamination,
5 given that there is adequate viral inactivation and that we
6 believe that there is not a threat to product safety when
7 there is properly performed manufacturing.

8 It has to be understood that the introduction
9 of pooled PCR cannot prevent all contamination of pools.
10 It was mentioned this morning that it translates into a 3-
11 day shortening of a window period. That was not
12 elimination of a window period. So, what we see the pooled
13 PCR test as doing, it's a further safeguard that places a
14 limit on potential contamination of pools for
15 fractionation, but it may not eliminate contamination of
16 pools for fractionation.

17 So, for that reason, the issue of a previously
18 pooled unit in a finished product I think needs to be
19 separated and that we will be developing policies to deal
20 with that situation, but we shouldn't prejudge the outcome.
21 I think your speculation is correct. That could affect a
22 great deal of finished product and we have reason to
23 believe that those finished products are indeed safe.

24 So, what we are talking about is interdicting

1 the use of units that have not been processed or
2 transfused. That's what's on the table.

3 DR. NELSON: It's a little bit of a new
4 definition of lookback then from the traditional one.

5 DR. EPSTEIN: Yes and no. Unfortunately,
6 there's one word and we're bundling three different
7 concepts under that word. The lookback activity has to do
8 with retrieval of extant units from prior collections. It
9 has to do with tracing recipients of the products, and it
10 has to do in some circumstances with recall of products.
11 Those three activities are not the same thing. The
12 triggers are not necessarily all the same. It depends upon
13 the risk considerations attached.

14 At least the FDA is trying to separate those
15 issues and we aren't bringing all three of them to the
16 table here today. We're really just talking about the
17 retrieval of extant unprocessed or untransfused units and
18 what to do about recipients of prior components. What
19 we're saying is that we should look at a pooled PCR result
20 the same way we look today at an antigen or an antibody
21 result.

22 Now, there will be many details of refinement
23 because we're going to have to talk about how far back do
24 you go and what does it take to confirm a result. All of

1 that is not worked out yet. We're just asking in concept
2 or in principle does the committee believe that these kinds
3 of procedures are applicable.

4 DR. KASPER: I think one of the encouraging
5 things we heard this morning was the 60-day quarantine that
6 manufacturers are imposing. I don't know yet whether 60
7 days will be enough to get most of the testing and
8 notification, but the longer your quarantine, the more time
9 you have to do it.

10 DR. SWISHER: Other questions? Susan?

11 DR. LEITMAN: I don't have any difficulty
12 really with the donor algorithms defined by CBER. They
13 could be worked on further. I still come back to the
14 recipient of the active inventory unit from which the
15 plasma was recovered.

16 It would seem almost as if there would have to
17 be a different kind of informed consent for recipients,
18 that there will be testing that could impact them greatly
19 but won't be known until after they receive a red cell or a
20 platelet unit. But I have difficulty with that kind of
21 phrasing in a routine transfusion recipient.

22 DR. EPSTEIN: Well, I understand the point you
23 make but it's true now. If a donor comes back to donate
24 and is found to be seropositive, we will do a lookback.

1 DR. LEITMAN: It's qualitatively different if
2 it's on a different donation as opposed to on the same
3 donation. I think it would make a difference to the
4 recipient.

5 DR. EPSTEIN: Yes, that's true.

6 DR. SWISHER: Further questions or discussion?
7 Charles?

8 DR. AUGUST: It seems to me that a lot of what
9 has just been said is a form of dancing around an issue or
10 dancing around the question really that relates to should
11 everyone who donates blood products, no matter what they
12 are or what they're used for, be screened in some way prior
13 to that donation in order to make sure the product is
14 maximally safe. This raises, I'm sure, questions of
15 logistics and expense which may make it totally
16 impractical, but shouldn't it be that that's the goal
17 towards which we should strive?

18 So, if that in fact were the case, a lot of
19 what we've talked about and what we've thought becomes
20 moot. It may mean that even for donating an ordinary unit
21 of blood from which the red cells would be extracted and
22 transfused within 24 hours and the platelets would be the
23 same, you might have to call the donor in two or three days
24 in advance in order to get them tested. That's what I mean

1 by logistics and expense, but nonetheless, we would have
2 achieved a new level of safety with respect to blood
3 products and maybe we should put that on the table to
4 consider not for today or even next year but for -- in the
5 foreseeable future, but the goal towards which we should be
6 striving.

7 DR. SWISHER: I think questions like that have
8 been raised with the advent of every conceivable infectious
9 disease test, that we have ultimately incorporated the so-
10 called pretest donor. Very clearly there are great
11 advantages to that and there have been places that have
12 tried to implement that I know and it may well be a goal
13 that should be put up there.

14 But I don't think in a sense it's really
15 relevant to the limited application that we're talking
16 about here, which is plasma for further processing.

17 Let's try a vote on proposition 3 in the
18 absence of the last line, "are current algorithms
19 adequate." We will try to separate that out.

20 All those in favor --

21 DR. PILIAVIN: The first one cannot be answered
22 yes/no. The front part is not a yes/no.

23 DR. SWISHER: I'm proposing to divide it into
24 two yes/no questions.

1 DR. PILIAVIN: It says what do we recommend.
2 It doesn't say, do you agree.

3 DR. SWISHER: You're right. You're quite
4 right. The yes/no comes out of the second line.

5 Well, let's try it that way.

6 DR. AUGUST: I think the FDA has provided us
7 with the answer that we could formulate in yes or no terms.
8 What I think, if I remember correctly, Jay has said is that
9 the positive nucleic acid test would be treated in the same
10 was as a positive serologic test or antigen test, and then
11 everything else follows. I think that's how to phrase the
12 question so that we could answer yes or no to it.

13 DR. PILIAVIN: I think we don't have the
14 ability to know whether it's adequate. I think that's the
15 part that's sticking in my throat. There's no way that we
16 know whether it's adequate or not.

17 I think what they really want to know from us
18 is whether we should just for the time being go ahead and
19 deal with it the same way we do with other kinds of tests.

20 DR. SWISHER: I think that's the way I had
21 conceptualized the first part of that question.

22 DR. PILIAVIN: But that's not what the first
23 question says.

24 MS. PIERCE: And I think that gets back to what

1 I was saying. Looking at a system that regardless of what
2 the specific tests are, if more than half are positive or
3 indeterminate and they get thrown back in, you know.

4 DR. SWISHER: Charles, would you like to
5 rephrase the stem on that first question?

6 DR. AUGUST: I suppose I would phrase it as
7 should a positive nucleic acid test for the detection of a
8 microorganism be treated in the same way as a positive
9 serological or antigen test for the particular
10 microorganism. Actually Jay said it much better than I
11 could or did. Maybe he could address that or phrase the
12 question for us a little bit more eloquently.

13 DR. SWISHER: I think that's a clear
14 proposition. Let's not forget that the FDA is here and
15 listening.

16 (Laughter.)

17 DR. SWISHER: They will, I'm sure, pick up the
18 thrust of what it is that we're trying to get at.

19 All those in favor of this conceptual revision
20 of question 3, please indicate by the usual sign.

21 (A show of hands.)

22 DR. SWISHER: Opposed?

23 (No response.)

24 DR. SWISHER: Abstaining?

1 (A show of hands.)

2 DR. SWISHER: Consumer and industry?

3 REV. LITTLE: This is voting on the rephrasing
4 of the question? Are you voting on the rephrasing of the
5 question or are you voting on the question as it's
6 rephrased?

7 DR. SWISHER: We're talking about the question
8 as rephrased.

9 REV. LITTLE: As rephrased, I'd have to
10 abstain. I don't have enough information.

11 DR. EPSTEIN: I would like to read the
12 rephrased question following Dr. August's suggestion.
13 Should positive pooled PCR test results be treated
14 similarly to other serological tests with respect to donor
15 deferral, reentry, and lookback?

16 DR. KASPER: That's what we voted on.

17 DR. EPSTEIN: Yes. I'm just trying to clarify
18 for Rev. Little the question on which you've just voted.

19 DR. SWISHER: Paul?

20 DR. NESS: I would say no. I'm very much
21 concerned that the committee continues to look at this in
22 the framework of the recipient of plasma derivatives or the
23 donor of plasma derivatives, the source plasma donor and
24 isn't really looking at the issues that may affect the

1 recovered plasma donor or the issues that may affect the
2 recipient of blood products from which recovered plasma was
3 made. I am very much concerned that the time lines and the
4 kinds of information we use for one may be very much
5 different than we have to use for another. I think that's
6 a big concern to anybody who thinks about these things in
7 the transfusion service.

8 DR. SWISHER: I do not believe we will bring
9 the last question up because I detect a consensus here that
10 we can't really answer that question adequately because we
11 in a sense don't have any of the data of what this kind of
12 a policy might infer in practical terms. So, with your
13 agreement we will not respond to the last question.

14 Now, as part of our official record to close
15 this section, we need to recap the voting.

16 DR. SMALLWOOD: The results of voting on
17 question 1. There were 14 yes votes, no no votes, 1
18 abstention.

19 Question number 2. 15 yes votes, no no votes,
20 no abstentions.

21 Voting on the rephrasing of question 3, there
22 were 14 yes votes, no no votes, 1 abstention.

23 DR. SWISHER: Does that agree with everybody's
24 personal tally? Okay, I think we've crossed the Rubicon on

1 this particular problem.

2 DR. SMALLWOOD: Excuse me, Rev. Little. For
3 the record did you make a comment regarding the rephrased
4 question 3?

5 REV. LITTLE: I'm confused because I thought
6 according to protocol, first you had to vote on rephrasing
7 the question and then take a vote on the question as
8 rephrased.

9 The question as rephrased I would still abstain
10 from that based on not enough information.

11 DR. LEITMAN: Dr. Swisher, can I ask Dr. Ness
12 if he has an alternative proposal?

13 DR. NESS: Not at this time.

14 DR. SWISHER: We'll move along and call for the
15 next topic on our agenda. This was deferred from our last
16 meeting. We seriously ran out of time. It's in effect an
17 informational item for the committee on the redeveloped
18 biologics license application for blood products. Mary
19 Gustafson, the Director of the Division of Blood
20 Applications, will make the presentation.

21 DR. GUSTAFSON: Thank you, Dr. Swisher,
22 committee, this will be an easy presentation. There are no
23 questions for the committee. There are no three-
24 dimensional matrices or intersections or algorithms. Just

1 stay awake please.

2 (Laughter.)

3 DR. GUSTAFSON: For the next 30 minutes or so,
4 I will provide an overview of the Center for Biologics
5 transition from our traditional way of licensing biologics
6 to a new model.

7 Traditionally biologics licensing involved
8 issuing licenses for both the biological product and the
9 establishment manufacturing the product. This licensure
10 was based on review and approval of separate application
11 filings, one for the product, the product license
12 application, or PLA, and one for the establishment license
13 application, or ELA.

14 The Center is moving to eliminate the
15 establishment filing. In the future a single application
16 filing will result in the issuance of a single biologics
17 license.

18 As part of President Clinton's 1995 National
19 Performance Review, FDA announced that it would eliminate
20 the establishment license application filing for a group of
21 specified biotechnology products. FDA also committed to
22 develop a single harmonized application form for all
23 licensed biological products and all drug products.

24 In the Federal Register of May 14, 1996, FDA

1 published a final rule entitled Elimination of the
2 Establishment License Application for Specified
3 Biotechnology and Specified Synthetic Biological Products.
4 The rule eliminated the establishment license for the
5 products specified in the rule. It replaced the
6 establishment and certain other standards in the biologics
7 regulations located in Title 21 of the Code of Federal
8 Regulations, part 600 with a firm's demonstrated compliance
9 with regulations covering current good manufacturing
10 practices.

11 Specific information filed in the chemistry and
12 manufacturing control section of the harmonized
13 application, coupled with a prelicense inspection, replaced
14 the establishment application filing. An interim
15 application form was adopted for filing the BLA for the
16 specified biotech products.

17 The May 14, 1996 final rule covered
18 biotechnology products in the following categories:
19 therapeutic DNA plasmid products, therapeutic synthetic
20 peptide products of fewer than 40 amino acids, monoclonal
21 antibody products for in vivo use, and therapeutic
22 recombinant DNA-derived products.

23 Although the majority of products regulated by
24 the Office of Blood do not fall into one of these

1 categories, we have had our first biologics license
2 application review and licensure. The Genetic Institute's
3 recombinant factor IX, a product that you helped us review
4 at your December meeting, was licensed last month. A
5 biologics license application was filed for that product,
6 and Genetics Institute was issued a single biologics
7 license. I might add that door-to-door review time for
8 that biologics license application was four and a half
9 months.

10 The May 1996 final rule declared the specified
11 biotech products be exempt from certain standards found in
12 21 CFR, part 600. The exempted regulations are in 600.10,
13 sections (b) and (c), qualifications of personnel and
14 restrictions on personnel and specific duties; 600.11 which
15 describes the physical establishment, equipment, animals,
16 and care; 600.12 covers records; and 600.13 regarding
17 retention sample requirements.

18 In 21 CFR, part 610, the following regulatory
19 requirements are exempted from the specified biotech
20 products covered by the final rule: general safety
21 requirements, dating periods, and labeling standards,
22 including proper name, package label, and the legibility of
23 type.

24 Additionally, the rule expanded the definition

1 of manufacturer as defined in 21 CFR 600.3(t). Unlike the
2 previous slides that pertain only to the specified biotech
3 products covered under the elimination of the ELA rule,
4 this regulatory change pertains to the manufacture of all
5 biological products addressed in 21 CFR 600 through 680.

6 Who is the manufacturer is important because
7 the manufacturer is the party who becomes licensed.
8 Previously the definition of manufacturer restricted its
9 usage to one who was actually engaged in the manufacturing
10 process. The new definition also includes any legal person
11 or entity who is an applicant for a license where the
12 applicant assumes responsibility for compliance with the
13 applicable product and establishment standards. The
14 expanded definition provides for much greater flexibility
15 for the industry.

16 The applicant may or may not own the facilities
17 in which the product is manufactured. Additionally, the
18 new definition eliminates the requirement that each
19 contract facility, engaging in significant manufacture
20 obtain a separate license.

21 The practical results of the change in
22 definition of manufacturer are the facilitation of contract
23 manufacturing under license, the elimination of the
24 requirement for a separate license for the contractor,

1 although we still intend to maintain the licensing options
2 of shared and divided manufacturing for those who prefer
3 this licensing arrangement. It allows a product innovator
4 to be licensed even if the innovator is not engage in the
5 manufacturing processes, and it simplifies the application
6 process, we hope.

7 While the May 16, 1996 final rule addressing
8 the elimination of the establishment license and use of the
9 interim biologics license application pertains only to the
10 products specifically covered by the rule, the intention to
11 harmonize the application process between the Centers for
12 Biologics Evaluation and Research and Drugs Evaluation and
13 Research for all drugs and biologics was committed to as a
14 reinventing government, or REGO, initiative.

15 A draft form number 356h was developed for this
16 purpose and published in the Federal Register for comment.
17 The 60-day comment period ended December 1, 1996. Two
18 comments were received and they were both supportive.

19 The form will also be published by the Office
20 of Management and Budget for a final comment period. It is
21 my understanding that this has not happened yet but is
22 anticipated shortly.

23 The harmonized form is, in essence, a cover
24 sheet for filing an application. The meat of the

1 application is addressed by filing attachments to the form
2 that are addressed in a listing on the second page of the
3 form. The most significant for biological products are the
4 sections that request information pertaining to the
5 chemistry and manufacturing control for the product and the
6 establishment description section. It is important to note
7 that for the biological products not covered by the May
8 1996 final rule establishment standards are retained.

9 For each product category, guidance documents
10 addressing the content of the CMC and establishment
11 description sections are being developed. This guidance is
12 necessary before implementation of the single application
13 filing. Upon clearance by the Office of Management and
14 Budget, we anticipate publishing in the Federal Register a
15 start date for use of the form which is the form 356h.
16 When the form is available for use and appropriate guidance
17 is available for filing the single application form,
18 manufacturers may file the single biologics application for
19 biological products not specifically covered by the May 16,
20 1996 final rule.

21 Currently our regulations in 21 CFR 601 require
22 the issuance of a product license and an establishment
23 license. These regulations will need to be revised to
24 facilitate a single license issuance. However, this will

1 not interfere in the interim period with an applicant's
2 ability to file a single license application.

3 Last but definitely not least, the CBER
4 licensing database must be upgraded to accommodate the new
5 filing mechanism, and I believe we're looking toward the
6 end of this year for those changes to occur.

7 In CBER we are currently preparing CMC guidance
8 documents and establishment description guidance documents.
9 As these documents are prepared and cleared by the Center,
10 they will publish for comment in the Federal Register. So
11 far two have published. The CMC for the biotech products
12 specified in the May 1996 rule published in October. In
13 January a CMC and establishment description guidance for
14 the manufacture of autologous somatic cell therapy products
15 published.

16 CMC and establishment description guidance
17 documents are being prepared in the following areas: human
18 plasma derived products and animal antisera for therapeutic
19 use, bacterial and viral vaccines, licensed in vitro test
20 kits, allergenic extracts and patch tests, autologous cell
21 products, which did publish in January, naturally derived,
22 highly purified protein therapeutic products for in vivo
23 use, and blood and blood components.

24 The categories of primary interest in the

1 Office of Blood Research and Review are the ones covering
2 human plasma-derived products and animal antisera for
3 therapeutic use, the licensed in vitro test kits, and the
4 blood and blood components.

5 The majority of the CMC documents currently in
6 draft form follow closely the Center for Drug Evaluation
7 and Research's established CMC guidance documents for drug
8 products. The categories covered by the CMC guidance
9 include description of the drug substance and drug product,
10 characterization of both the substance and final product,
11 identification of the manufacturer or manufacturers,
12 methods of manufacturing and packaging, validation and
13 process controls employed in the manufacturing, use of
14 reference standards, release specifications, and testing
15 requirements, the container closure system and requirements
16 for shipping, the stability protocol and environmental
17 assessment.

18 Unlike the specified biotech products covered
19 by the May 1996 rule, other biological products will
20 include preapproval review of some establishment issues
21 beyond what is covered in the CMC section guidance. For
22 the most part, the establishment description guidance
23 documents cover water systems, heating, ventilation, and
24 air conditioning, contamination and cross-contamination for

1 multiple product manufacturing facilities, animal
2 facilities, and formulation and filling operations. It is
3 important to note that the information that will be
4 requested for preapproval review is less than what is
5 currently requested on the establishment license form in
6 use, form 3210.

7 The format and information requested for review
8 of applications for product license by the Office of Blood
9 Research and Review are compatible with the CMC and
10 establishment description guidances just described for both
11 the therapeutic hematologic products and the in vitro
12 diagnostic test kits. However, the paradigm is
13 sufficiently disrupted in the blood and blood components
14 category. The categories for review are not applicable for
15 this group of products and, if they could be made to fit,
16 do not offer simplification and streamlining of the
17 application process.

18 Therefore, we have taken the transition from
19 use of the product license applications and establishment
20 license applications as an opportunity to effect change in
21 the licensing process. This is part of an overall
22 evaluation of blood program regulation. It is an effort to
23 optimize efforts by both the agency and industry to assure
24 blood quality and safety.

1 In terms of the BLA for blood and blood
2 components, we have been considering several issues. First
3 is the scope of the BLA. We currently license separately
4 seven blood component products. Each has its own
5 application form, plus the addition of some supplemental
6 application forms. The total number of application forms
7 for products licensed by the Office of Blood is 17 I
8 believe.

9 We have grappled with what scope of component
10 manufacturing should be covered within a single
11 application. After considering several options, we have
12 settled on the number 1. That is, one application will
13 cover a full range of transfusable and for manufacturing
14 use components prepared by common methods within a blood
15 establishment.

16 For example, a new blood establishment who
17 wishes to be licensed for whole blood, red blood cells,
18 plasma, and platelets prepared by both whole blood and
19 apheresis methods will file one biologics application that
20 describes what is requested and how the components are
21 prepared and controlled. In the past such a request for
22 licensure would require the filing of six separate
23 applications.

24 We also considered the issue of facilities.

1 With the establishment license application, each separate
2 facility was essentially individually licensed even if part
3 of a larger licensee. With FDA's demand in recent years
4 that licensees standardize operations across its license
5 and maintain more centralized control over operations, we
6 have been faulted by the industry for not acknowledging
7 industry's attempts to better standardize operations and
8 maintain centralized control by allowing a more flexible
9 licensure scheme.

10 With the elimination of the establishment
11 license, we will no longer use the term "licensed
12 location." Facilities will be evaluated within the context
13 of the single application filing based on the extent of
14 manufacturing occurring at the facility and the impact on
15 safety and quality of the product prepared in the facility.

16 As mentioned earlier, the structure of the BLA
17 in terms of CMC and establishment description sections
18 applicable to other biological products are not helpful for
19 blood and blood components. For the most part, the
20 components are well defined. The role of licensing is to
21 ensure that the component is safe and processed in a manner
22 to ensure a component of consistently high quality. In
23 addition, there are blood donor issues that cross-cut the
24 range of blood components.

1 Our future goal is to use the licensing process
2 to monitor a licensee's ability to maintain quality
3 oversight of its own operations, but we are not there yet.

4 Approximately two years ago, the blood industry
5 worked together to form the Coalition for Regulatory
6 Reform. It was established to communicate with the FDA
7 concerning regulatory issues and represents all parts of
8 the blood industry.

9 In October of 1995, the coalition met with FDA
10 and presented suggestions for reform in several areas. One
11 of the areas addressed licensing. Because of regulatory
12 restrictions and ongoing commitments made in reinventing
13 government initiatives, some of the suggestions were not
14 viable at the time, but the suggestions have not been
15 ignored or forgotten. As much as possible, we have taken
16 the coalition's ideas into account as we've proposed
17 regulatory changes and developed the content of the BLA,
18 particularly the CMC and establishment description
19 guidance. We have recently met with a task force from the
20 coalition and asked for their continued dialogue as we
21 develop the content of the application.

22 Another regulatory initiative that impacts on
23 licensure is the Center's revision of the regulation that
24 covers what additions or changes to an approved application

1 need to be reported to the Center and whether review and
2 approval of the change is necessary before implementation.
3 This initiative is a rewrite of regulations found at 21 CFR
4 601.12. Although I will not discuss this today, it is a
5 very important initiative in terms of regulatory reform.

6 The proposed rule with categories for post-
7 approval reporting was the focus of an open public meeting
8 last April. The final rule is to publish soon.

9 One of the members of the Coalition for
10 Regulatory Reform asked that I clarify that under the
11 single application/single license concept, the conditions
12 of licensure will depend upon the content of the original
13 application. Changes in operations and functions will
14 continue to be subject to reporting under the terms of
15 601.12 but under the revised rules should be less
16 restrictive than in the past.

17 As mentioned earlier, changes in licensure for
18 blood are one part of an overall review of the way we
19 regulate blood. In the licensing arena and in the short
20 term, we plan to establish and implement the biologics
21 license application. In addition, we continue to stress
22 accountability in the review process by assessing our
23 performance in meeting review milestones under a program of
24 managed review.

1 We also continue to develop and upgrade our
2 automated data processing support which is an essential
3 element in improving and streamlining our operations.

4 In the medium term, we will evaluate the impact
5 of our initial changes in the licensing process by
6 reviewing the output, basically review of findings of
7 inspections, review of reported errors and accidents,
8 evaluation of recall situations, and by listening to both
9 the blood industry and the affected public.

10 In the longer term, as I mentioned earlier, our
11 goal is to be able to use the licensing process to evaluate
12 and monitor a licensee's ability to police itself through
13 an appropriate and viable quality program.

14 In addition, whereas for other biological products
15 the trend is to move away from defined product standards in
16 the regulations, we see a need to codify as product
17 standards some of our current licensing criteria and
18 recommendations found in our blood memoranda. We see this
19 as a way to clarify expectations and remove from the
20 license application review and approval process those
21 procedures that should be standard operations in the
22 preparation of blood and blood components.

23 Thank you and are there questions?

24 DR. SWISHER: Questions? Charles?

1 DR. AUGUST: You used the term "CMC" a lot.
2 What does that stand for?

3 MS. GUSTAFSON: Chemistry and manufacturing
4 control. I'm sorry. I mentioned it at the beginning.

5 DR. SWISHER: Is conceptually this process
6 you're going through converging in any way with the
7 movement or so-called consensus based regulation?

8 MS. GUSTAFSON: There are parts of the industry
9 that want to use a more consensus based, in fact, the
10 negotiated rulemaking. I think we would like to have not
11 quite that formal a process, but we are trying to get more
12 input in decisionmaking. The agency has recently published
13 a procedure called Good Guidance Practices that defines the
14 way that we will seek public guidance on all policy
15 documents basically that provide guidance to the industry.

16 DR. SWISHER: Other questions or comments from
17 the committee?

18 (No response.)

19 DR. SWISHER: If not, thank you very much.

20 MS. GUSTAFSON: Thank you.

21 DR. SWISHER: There is a designated open public
22 hearing on this topic, and let the record indicate that
23 that public hearing is now open. No one has asked for
24 reserved time to speak, but we will have a few minutes if

1 anyone does care to make a brief contribution to the
2 record.

3 Hearing none, we'll close the open public
4 hearing and open the topic for discussion by the committee.
5 Does anyone care to lead off this discussion?

6 (No response.)

7 DR. SWISHER: We find ourselves in a slightly
8 passive mood here. Did we expend all our energy on the
9 first topic?

10 The thrust of my question was about so-called
11 consensus based rulemaking, which this does seem to me to
12 be a step in that direction. Trying to find ways to smooth
13 the interface between the regulated community and the FDA
14 because in a sense they both have exactly the same mission
15 and the same commitment. The problem tends to arise on the
16 issues of procedure and, to some extent, on the issues of
17 philosophy.

18 My own very personal feeling is that this is a
19 good step in that direction and that further moves along
20 these lines should be very seriously considered as
21 regulations are developed, particularly in your so-called
22 mid-term and long-term perspectives.

23 The committee is not asked for any specific
24 response or guidance on this matter. Does that fulfill our

1 requirement here, Jay? Okay.

2 With that, we will move on to the next issue
3 which is the discussion of the problem of patient
4 notification. Here the introduction and background will be
5 given by Mark Weinstein.

6 DR. WEINSTEIN: I'd like to make a progress
7 report on public notification of recalls and withdrawals.
8 I will first summarize the steps the FDA has taken to
9 examine and improve public notification. I will then
10 discuss current initiatives that the agency is undertaking
11 to continue this process, and finally I will outline some
12 of the challenges that lie before us.

13 In March of 1996, a task force was formed to
14 examine issues of public notification of recalls and
15 withdrawals. It consisted of representatives of the Food
16 and Drug Administration, the National Heart, Lung, and
17 Blood Institute, and the Centers for Disease Control and
18 Prevention.

19 Through April and November of 1996, meetings of
20 this group were held to discuss current procedures and
21 responsibilities of these governmental groups regarding
22 this topic.

23 In November of 1996, this group sponsored an
24 informational meeting entitled Notification of Plasma

1 Product Withdrawals and Recalls to discuss public
2 notification of withdrawals and recalls of plasma-derived
3 products. The meeting was held at Masur Auditorium at the
4 NIH. The goals of this meeting included informing the
5 public about available notification resources, describing
6 the roles and responsibilities of public health service
7 agencies, manufacturers, distributors, and private
8 organizations in the notification process, and stimulating
9 discussion about improving the notification system.

10 The following are initiatives that the agency
11 is considering taking as a follow-up of this meeting.

12 The first is to improve the capacity to track
13 blood product by lot number to the consumer. FDA is
14 examining the concept of requiring manufacturers to be able
15 to track blood product derivatives by lot number from the
16 manufacturer through the chain of distribution, including
17 distributors, home health care institutions, pharmacies,
18 hospitals, and/or physicians, down to the patient
19 recipient. There is precedent for this requirement.
20 Products such as vaccines can now be tracked by lot number
21 to the consumer.

22 FDA does not need to seek additional statutory
23 authority to apply rulemaking procedures to pursue this
24 objective. FDA is now in the process of assessing what

1 actions are necessary to see that this objective is
2 achieved.

3 FDA is considering requesting that
4 manufacturers develop plans to ensure that end users of
5 blood products are notified about recalls and withdrawals.
6 At the November meeting, Deputy Commissioner Mary
7 Pendergast defined the responsibilities of manufacturers to
8 conduct recalls and notification. It is the primary
9 responsibility of manufacturers to conduct recalls and
10 carry out notification. That includes reaching the product
11 end users where appropriate. FDA has the responsibility to
12 enforce the manufacturers' notification and recall
13 responsibilities.

14 The FDA will continue to provide forums for
15 dialogue to develop policy in this area. The present
16 meeting is one opportunity for manufacturers, consumer
17 groups, and other interested parties to present their plans
18 for progress in this area.

19 Another initiative is to encourage new
20 technologies for notifying consumers about recalls and
21 withdrawals. The FDA has already initiated new procedures
22 for informing the public about recalls and withdrawals of
23 blood product derivatives. They include information
24 delivery through a toll-free 800 number, Internet web site,

1 facsimile on demand, and an automatic electronic mailing
2 list service by Internet. These methods, for the most
3 part, require that the consumer requests information.

4 FDA is considering proposing that manufacturers
5 see to it that custodians of the product be actively
6 notified about recalls or withdrawals. Actively means that
7 the final custodian of the product will be sent a message
8 directed specifically to that person informing that person
9 about the recall or withdrawal. Methods such as telephone
10 communication are attractive because they are fast and do
11 not require expensive equipment.

12 Another strong desire expressed at the meeting
13 is that public health service agencies define and/or
14 clarify present operating procedures for performing safety
15 hazard assessments. Task force groups consisting of
16 members of the FDA and CDC are now in the process of
17 reviewing these procedures. These groups will provide
18 information about the roles and responsibilities of the FDA
19 and CDC in investigating and evaluating adverse event
20 reports. They will identify groups within FDA and CDC that
21 are responsible for the evaluation of adverse event
22 reports, describe conditions under which interagency
23 notification about adverse events is to occur, and points
24 of contact within each agency. Lastly they will present

1 algorithms that are to be used to decide when to pursue or
2 to conclude an investigation.

3 I will now give you a brief outline of our
4 current procedures for investigating and evaluating adverse
5 events particularly from the viewpoint of the Office of
6 Blood Research and Review. This is simply a brief,
7 incomplete summary of some of our procedures.

8 The process can be divided into four major
9 parts: initial receipt of information, initial evaluation
10 of the health hazard risk, further investigation, an
11 iterative process, and finally resolution of the issue. We
12 will look at each of these steps starting with initial
13 receipt of information.

14 Receipt of information occurs from many
15 sources, including consumers, manufacturers, the CDC,
16 health professionals and other control agencies. This
17 information can enter the FDA through many different
18 portals including the MedWatch system, through monthly
19 reports to the Division of Biostatistics and Epidemiology
20 or direct calls to personnel in the Office of Blood
21 Research and Review, the Office of Compliance, among other
22 places.

23 Whatever the source of information and its
24 entry into the FDA, the information is added to a MedWatch

1 database and is directed as rapidly as possible to a hazard
2 evaluation team in the Office of Blood Research and Review.
3 This group is composed of physicians, product specialists
4 and personnel from the Division of Biostatistics and
5 Epidemiology and from the Office of Compliance. The office
6 directors in OBRR and Compliance are notified of the
7 situation.

8 The tasks of this group include discussing the
9 status of the situation with the product manufacturer to
10 learn what has been done to resolve the issue and recommend
11 further action. Secondly, there is an assessment of the
12 health hazard. Thirdly, informing other groups within the
13 FDA and the Public Health Service about the situation and
14 requesting their help if appropriate, and also assessing
15 what further actions need to be done to reach closure.

16 The actions of the hazard evaluation team will
17 depend in part on the information that is available
18 initially. Information to be gathered includes product
19 information, identifying the manufacturer, lot number, all
20 products implicated, plasma tree, and product disposition.
21 Was the product properly manufactured and virally
22 inactivated? Is product available for testing for the
23 presence of the infectious agent?

24 Information also is needed to be gathered about

1 the particular patient, the epidemiological and statistical
2 information, for example, the case report of the affected
3 patients, including description of the incident, the time
4 of occurrence, and all people involved, as well as other
5 reports of a similar nature from MedWatch and other
6 databases.

7 The information should be sufficient to provide
8 answers to the following questions. Is a given product
9 responsible for the adverse event? If so, what is the
10 health hazard and extent of the problem?

11 In the case of transmission of hepatitis A, C,
12 or HIV, algorithms that were developed by the FDA, CDC, and
13 the National Hemophilia Foundation may be used to help in
14 deciding whether there is sufficient information to link a
15 product to a clinical event. As an example, in the case of
16 a single report of a serologically positive test for HCV in
17 a patient who receives a plasma derivative, an investigator
18 should find out whether the patient has had a negative
19 serological test for the virus before the reported positive
20 test.

21 If the patient did not have a prior negative
22 test and there were no confounding data to suggest a
23 linkage of the product to the infection, like a positive
24 IgM antibody test indicating a recent infection, the case

1 might not be investigated further because a causal
2 connection could not be made between the product and the
3 incident. However, the information would still be added to
4 the MedWatch database for further reference.

5 In many situations that come to the attention
6 of the FDA, there is insufficient initial information to
7 clearly implicate or exonerate a product from being the
8 cause of an adverse event. The Office of Blood Research
9 and Review, the Office of Compliance, and if appropriate,
10 the Office of Emergency Operations work together to gather
11 additional information and to notify responsible
12 individuals. Activities include collecting samples for
13 testing by the FDA and CDC, inspecting MedWatch records for
14 past reports, inspecting the manufacturers batch records,
15 contacting the CDC to get reports of similar incidences,
16 and to get advice on the potential health hazard of the
17 given situation, and finally putting the product on lot
18 release hold if appropriate.

19 The decision of the FDA to request recall of
20 the product by the manufacturer is based on a number of
21 factors, including health hazard assessment, viral
22 inactivation procedure, batch record review and GMP audit,
23 evidence of infectious agent in the product, and the
24 quality of the information available.

1 Now, in many instances, manufacturers may have
2 already taken steps to investigate and resolve adverse
3 event reports. The FDA may only have to see that a
4 manufacturer has carried out their own recall or withdrawal
5 procedures properly.

6 Now, this outline gives you a sense of the kind
7 of information that will become available when the various
8 task forces have completed their job within the CDC and NIH
9 and FDA regarding the explicit description of our emergency
10 procedures and our recall procedures.

11 The last initiative that I will discuss is the
12 one that I believe offers the greatest challenge to the
13 agency, that is, deciding when the public should be
14 notified about an adverse event. PH agencies, in
15 conjunction with interested parties, will define conditions
16 under which public notification of an investigation should
17 occur. Some consumer groups wish to have a role in
18 deciding when public notification of an ongoing
19 investigation should take place.

20 A model of consumer group participation in
21 adverse event surveillance occurred through a contract
22 sponsored by the FDA that included the FDA, CDC, and the
23 National Hemophilia Foundation. From 1987 to 1996 through
24 contracts with the FDA and CDC, the NHF provided

1 surveillance of HIV and later HCV and HAV in the hemophilia
2 population through voluntary participation of hemophilia
3 treatment centers. The FDA, CDC, and the NHF jointly
4 reviewed cases brought to their attention and CDC and NHF
5 made recommendations about pursuing cases based on the
6 previously mentioned algorithms. Currently the CDC is
7 providing surveillance of hemophilia treatment centers.

8 One possibility for the future is to involve
9 consumers in an advisory capacity in the same way as in
10 this model system. However, there are a number of concerns
11 about the system that have yet to be resolved. These
12 include deciding which consumer groups or individuals
13 should participate, keeping information confidential until
14 a consensus decision is reached, deciding which products to
15 include, and setting a precedent for the evaluation of
16 other products regulated by the FDA.

17 Another possibility is to involve consumers,
18 manufacturers, distributors, and the medical community to
19 better define the conditions under which patient
20 notification should occur. Once certain thresholds are
21 crossed, the public would be notified about a recall or
22 withdrawal. These matters are as yet unresolved.

23 We look forward to working with all concerned
24 parties to better define what those thresholds should be

1 and the general problem of improving notification of
2 withdrawals and recalls.

3 DR. SWISHER: Are there questions from the
4 committee to Mark?

5 DR. LINDEN: As a public health official, I
6 used to regularly get electronically FDA recall notices at
7 least once a week, if not more often -- I don't know how
8 frequently -- which were very, very helpful to me. Then
9 recently we were notified that that system has been
10 discontinued, and we're apparently supposed to seek out by
11 fax now, going to a paper system, which is just not
12 working. It seems to me that's a big step backwards, from
13 an electronic system to go to a paper system. Why was the
14 electronic system eliminated? Why would the agency take
15 that step?

16 DR. WEINSTEIN: I'm frankly surprised by your
17 comment because, in fact, we have improved our electronic
18 system for notification.

19 MR. ELLENGOLD: I'm Mark Ellengold. I'm acting
20 Deputy Director of the Center. My normal job is Director
21 of the Office of Communication, Training, and Manufacturers
22 Assistance.

23 I believe you're talking about changes made by
24 the Division of Federal-State Relations on what used to be

1 called the NRSTAN Network and then they had some other
2 systems. We're not really involved in that other than to
3 feed information into it for use by the agency. I will,
4 after this meeting, transmit your concerns to the people in
5 Federal-State who do run that system.

6 That is in part the reason we developed our
7 automated system ourselves, and if you're having a problem
8 getting hooked up with that, you can give me a call and
9 we'll take care of that and add you and anyone else on your
10 staff that you believe should be added.

11 DR. LINDEN: Okay. Thank you.

12 MR. DUBIN: Just a request, Mark. I would
13 request that everybody on the BPAC be handed a copy of the
14 1978 regs. I'm aware that there are people sitting at the
15 table that have not read them. We know them front to
16 cover, inside out, and I think it's the only way we've
17 learned how to cope with some things to understand what the
18 rules are very clearly, and I think we're being asked to
19 evaluate standards of communication, questions of patient
20 notification, when should the public know. I think
21 everybody at the table should be on a level playing field
22 in terms of understanding those regs and what they mean.

23 DR. HOLLINGER: Corey, what is done now in
24 terms of notification when something comes up like you

1 commented on earlier today?

2 MR. DUBIN: I can say what has been done with
3 us, but I want to say that real quickly and defer to Mark
4 because I don't want to at all step in the place I don't
5 belong.

6 One of the things that has happened over the
7 last year is, for instance, when certain things have been
8 pending, the NHF, the Committee of Ten Thousand have
9 received telephone calls or faxes. For instance, we've
10 come into the loop to the degree where when the transferrin
11 issue happened with Baxter Hyland and there was a question
12 of what was to be done, both the NHF and the Committee of
13 Ten Thousand were in that loop, had discussions with Mark
14 about what was happening.

15 All in all it seemed to be a pretty good
16 process. I know some questions have been raised out of
17 that regarding at what point patients should be notified,
18 confidentiality. I think it was successful in the sense
19 that we released nothing and I know the NHF released
20 nothing until we had clearance from the FDA to do so. I
21 think in some way it was a good process, and that has
22 happened on a number of recent things that have happened.
23 I think certainly it has brought our community into the
24 loop as one of the primary user communities, if that

1 answers your question.

2 MS. PIERCE: If I can add to that. What has
3 happened is that up to recently it was more of an issue,
4 when the trigger happened, that the consumer groups were
5 notified and information went out via a number of different
6 avenues. Recently more information has been given out
7 earlier. But what currently happens when that information
8 comes out to the consumer group, there's a number of
9 electronic boards on the Internet. There are fax networks
10 that go out to the treatment centers and to chapters and
11 other groups. But up to that point, then it gets real
12 dicey in terms of the time frame of moving from those
13 points to the actual consumer that's using the product.

14 MR. DUBIN: I think one of the things we're
15 concerned about, as Mark knows -- the Committee of Ten
16 Thousand, our regulatory team, met with some of the FDA
17 staff this week and had a big discussion about this. We're
18 certainly pleased to be in the loop. I think what we're
19 concerned about -- and I think the NHF is also concerned
20 about this -- is we want to be in the loop but we want to
21 make sure per the regs that the responsibility for
22 ultimately notifying the end user happens in such a way so
23 it doesn't end up that a fax in Corey Dubin's bay or Val
24 Bias' bay or Rich Coleman ends up being the way that we've

1 got to worry about notifying an end user in Seattle that
2 there's a serious problem with the product in his or her
3 refrigerator.

4 So, I think we're really concerned about
5 developing a system where the lines of responsibility and
6 authority are absolutely clear in terms of what the
7 manufacturer's role is, what the FDA's role is, and what we
8 can do to assist, but I think we want to be careful to
9 understand that clearly.

10 I think that's part of why twice today I've
11 raised the regulations because the 1978 regs are pretty
12 clear. They're pretty direct and pretty clear. I think
13 part of the issue is are we working from a clear
14 application of those regs across the board in all
15 instances, and I think those are some of the issues that we
16 have. Again, I think it's imperative that everybody on the
17 committee knows these regs back and forth because we're
18 going to be asked to make decisions that directly relate to
19 these regulations.

20 REV. LITTLE: Yes. Along those lines you
21 raised the issue of which consumer groups to involve, and I
22 think that as a consumer of blood products -- I do not have
23 hemophilia -- I know there are many consumers of blood
24 products where there just is not the organization or maybe

1 even numbers or the political know-how or whatever to have
2 this information available. I agree with Corey if there is
3 some kind of central responsibility that can be made
4 available to all consumers of blood products, because I'm
5 very concerned that in these meetings there are many, many
6 consumer groups not represented or not even formed into
7 groups because of the different diseases they have.

8 DR. SWISHER: Kenrad, did you have a question?

9 DR. NELSON: Yes. This was fascinating. I
10 just wondered how do you deal with an international
11 situation, a product that, let's say, is sent to Luxembourg
12 or Bosnia or somewhere like that from the U.S.? I know,
13 particularly with the clotting factor, it has been an
14 important way that viruses have been sent out of the United
15 States and vice versa. How does that work?

16 DR. WEINSTEIN: Well, we just had a situation
17 like that in fact where a situation occurred. The National
18 Institute of Biological Standards and Control in the UK
19 informed us about a seropositive lot of plasma, HIV
20 positive lot, and they notified us about some products that
21 were made from that material. Of course, this occurred at
22 3 o'clock on Friday, which is the usual time that these
23 sorts of things happen.

24 In fact, everything that you saw outlined here

1 occurred very rapidly. We immediately called the
2 manufacturer about the situation, asked the manufacturer
3 what they had done about it. We had field people in the
4 plant that very day beginning to collect samples. We put
5 all material on hold. We pursued this policy of trying to
6 find out what products were made from this material. We
7 had to know what other distribution points there might have
8 been in the UK and throughout Europe. We wanted to know if
9 product was sent there. We wanted to alert other countries
10 about the situation. We have good relations with other
11 countries and when information comes in to us, we act as
12 expeditiously as possible.

13 DR. SWISHER: I have a question. In your
14 planning, let us suppose that a manufacturer brings to your
15 attention a "problem." You go through this evaluation and
16 you come to the conclusion that the trigger has not been
17 met, and therefore a recall and notification is not
18 necessary. Is there anything in your planning that would
19 prevent the manufacturer from doing just that, recalling
20 the product?

21 DR. WEINSTEIN: Oh, the manufacturer can
22 certainly recall -- withdraw their product on their own
23 initiative.

24 DR. SWISHER: So that it would not prevent the

1 manufacturer from, in effect, using either the existing
2 channels or other channels that they might develop for
3 themselves for notifications that they decided were in
4 their interest from the business point of view and
5 specifically from the medical/legal liability point of
6 view.

7 DR. WEINSTEIN: I think that if we encourage
8 the recall, we will examine the plan that the company has
9 for their recall and notification process here. We approve
10 that plan. Usually the way that this works is that a
11 company will provide us with information about how they
12 will be delivering information. We often have a chance and
13 opportunity to look at their press comments and how they
14 will go about informing the public.

15 DR. SWISHER: In a sense that's the other side
16 of the question that Corey had asked. It is perfectly
17 clear that a clear-cut separation of responsibilities and
18 authorities is important, but should that in a sense
19 preempt other kinds of initiatives that might be outside
20 these standard channels that might be useful in the
21 dissemination of information that might or might not be
22 useful to the end consumer?

23 MR. DUBIN: Well, I think, Scott, that's
24 basically what we've done is supplemented the lines of

1 responsibility and authority that exist with our structures
2 on the Internet and things of that nature because it really
3 has helped to disseminate information.

4 DR. WEINSTEIN: Usually if we feel the company
5 has not provided enough information, we will go ahead and
6 supplement --

7 DR. SWISHER: But in effect, you're not
8 planning a preemptive process that finds, in a sense, a
9 single channel and a single program.

10 DR. WEINSTEIN: There will be multiple means of
11 communication. The FDA, as I've pointed out here, has a
12 set of informational tools here as a supplement to what we
13 anticipate that manufacturers will produce.

14 DR. SWISHER: It turns out sometimes the most
15 efficient way to disseminate information is to let it flow
16 along natural water courses, and highly prescribed systems
17 that control information and decisionmaking may in some
18 ways be counterproductive at some point. It doesn't mean
19 that you shouldn't have them, but it means that they should
20 not prevent the development of new and novel approaches to
21 information transfer.

22 DR. WEINSTEIN: Oh, we encourage that. We want
23 that.

24 DR. SWISHER: Carol?

1 DR. KASPER: Reading the material that we had
2 before the meeting, I gathered that for some products there
3 is not accurate record keeping of lot numbers used. The
4 specific example cited was albumin used in emergency rooms.
5 For products that are used on a nonemergent basis like
6 clotting factor concentrates, it's standard for pharmacies
7 to record lot numbers. I think it's not very good practice
8 if they don't.

9 That might also be true that the lot numbers
10 might be recorded for gammaglobulin which has been
11 problematic lately, which leads to the issue of who has the
12 information to know which patient might have been dispensed
13 or received a particular product. I think it isn't the
14 National Hemophilia Foundation or any other committee or
15 often not the treatment center if that's not where the
16 patient got the product. If the physician prescribes it
17 but the patient gets it from somebody else, a home care
18 company, whatever -- with hemophilia it's very often a home
19 care company. The physician doesn't know the lot number.

20 It seems that rather than bombard each patient
21 with all of these notifications, what we have done in the
22 past is traced a lot and notified those patients. The
23 entity that's likely to know the lot is the pharmacy,
24 whatever pharmacy it is.

1 So, I like the idea of that avenue. I see the
2 Red Cross has a statement here presuming that the
3 hemophilia center knows all the lots. No, not if they go
4 through home care companies. We don't know the lot.

5 DR. SWISHER: We need another whole
6 presentation before maybe we extend our discussion, and
7 that's the response from the industry. I do not have the
8 name of whoever it is that will make that presentation.

9 DR. KASPER: Could I add something? Given that
10 in the last few weeks there have been several product holds
11 or withdrawals, you don't want to bombard patients because
12 they'll start to think you're crying wolf. You want to be
13 sure that you're notifying them appropriately.

14 We also occasionally have a problem, though, of
15 relatives with the same disorder sharing product, sort of
16 the under the table, gee, my cousin is not insured and I
17 am, so he'll use it. But then I think that's so dicey. I
18 don't know how to deal with that.

19 DR. KHABBAZ: I wanted to make an additional
20 comment in view of the discussion on the importance of
21 having different channels and different bodies
22 communicating the kind of information, that is, the
23 importance that the messages communicated be coordinated,
24 that we don't have industry, FDA, CDC, NHF communicating

1 separately different information and that the information
2 be clear. I think in our haste to communicate, there's a
3 danger of doing more harm, for instance, in times when we
4 are concerned and we're erring on the side of concern,
5 communicate that there's a danger, and that can have a
6 very, very harmful --

7 DR. KASPER: I agree. They've been muddy.

8 MR. DUBIN: I've got to give FDA credit on this
9 one, though. I think on the last few where we've
10 communicated together, there has been real clarity, if we
11 were going to make a release, between what NHF was saying
12 and what we were saying. I think in that sense there has
13 been some very good coordination, and I think there has
14 been a strong commitment from all sides to be very careful
15 about what and when gets reported and that the information
16 is correct and concise and directly to the point because of
17 the ramifications of what it means to miscommunicate with
18 people. So, I think in that sense it has functioned pretty
19 good and I want to be clear about that.

20 There are other questions that we need to
21 address vis-a-vis responsibility, but I think in that sense
22 this informal link is positive and I think we've all
23 demonstrated an ability to communicate with each other with
24 much care and restraint and make sure thresholds are

1 crossed before things go out and things like that. So, I
2 think that has been okay.

3 DR. SWISHER: Let's hear the industry response,
4 and would you please identify yourself?

5 MS. DUNST: I'll introduce myself. I'm Isabel
6 Dunst, also known as Liz Dunst, and I'm here as special
7 regulatory counsel to IPPIA.

8 Let me start with a disclaimer, although I'm
9 not sure I like these disclaimers to be on tape, and the
10 disclaimer is that I'm not an FDA lawyer. I'm a health
11 care lawyer, and I think it's for that reason that IPPIA
12 asked me to assist them in their proposal.

13 Clearly the issues of product recall and
14 patient notification raise very substantial questions of
15 the issues of the obligations of manufacturers and others
16 under the Public Health Service Act and under the FDA Act.
17 But an effective system for recall and patient notification
18 involves not only the manufacturers and the drug
19 wholesalers but, as we've heard from others, pharmacies and
20 home health care companies and hospitals and clinics and
21 physicians and other health care providers. These entities
22 operate not only within the FDA structure and the PHS Act
23 but under a wide variety of other state laws and really in
24 an integrated health care delivery system. It's this

1 broader perspective that I hope to bring to you in
2 presenting this.

3 For purposes of our presentation, we've divided
4 this into two parts, first, patient notification and,
5 second, product recall, although obviously we recognize
6 these two things intersect with each other and this will
7 become clear.

8 Also my New Yorker comes out when I start
9 talking, so somebody should say, slower, if I'm going too
10 fast.

11 In considering how to meet the goals that we're
12 talking about, I think there are a couple of things we want
13 to keep in mind. First, there's a wide array of plasma-
14 derived therapeutic products we're talking about and the
15 distinction between the distribution of our products versus
16 what I would call the distribution of the traditional
17 pharmaceutical industry. Some of the products, such as the
18 coagulation products, have a more limited total
19 distribution and are distributed in a way that I think more
20 easily allows us to have an effective system being
21 developed. There are other plasma-derived products such as
22 albumin that have dramatically, as we know, larger numbers
23 of products distributed with a much larger network of
24 entities involved in the process. In addition, as FDA is

1 aware, the plasma-derived products are also used in other
2 therapeutic products, either as manufacturing aids or as
3 excipients.

4 Last November during the meeting that Mark
5 talked about, the industry testified that it would present
6 a proposal at this meeting to respond to the need to
7 improve the system of product recall and patient
8 notification.

9 Since that time, the industry has been busy.
10 We've been studying ourselves. We've been studying the
11 performance in this arena. We've been studying the various
12 distribution avenues that we have for product. We've been
13 studying the federal and the state laws and the regulatory
14 schemes that impact these issues, and it's out of that
15 study that has come the proposal that I will present to
16 you.

17 This is not a final step. We think it is a
18 constructive step. A final step is going to require I
19 think that all of the interested parties, including the
20 FDA, work toward the common goal that I think we all have
21 and that's the most effective product recall possible and a
22 patient notification system that gets critical information
23 to patients. Let me start with patient notification.

24 I think it's fair to say that the industry

1 heard the message that the FDA and that the patient groups
2 in November gave to the industry that notification of
3 consumers of plasma-derived products must improve and that
4 the industry has a critical role to play in the process.
5 There is presently no statute and no regulation that
6 requires that manufacturers notify specific patients. In
7 fact, as we'll go through it, although I don't want to get
8 into a large legal debate, there are some legal,
9 logistical, and privacy issues which create substantial
10 barriers to specific identification and notification of end
11 users.

12 But nonetheless, the industry believes that it
13 has a positive role to play, along with others in notifying
14 patients under the appropriate circumstances and to
15 facilitate this, there are a couple of things that the
16 industry is committed to doing.

17 First -- and this we commit really by the end
18 of 1997 although we're already starting to work on it, the
19 following steps as an adjunct to product recall and to the
20 notification system.

21 First, the establishment by the industry of a
22 well-publicized industry web page with standard formats so
23 that each company would input on a same-day basis the
24 detailed recall information so there would be access to

1 that by individuals. The web page would have hyperlinks to
2 other web pages, to FDA, NHF, IDF, the physicians on-line
3 pharmaceutical net, and that would facilitate wider access
4 and knowledge by all of a recall.

5 Second, the establishment by IPPIA of an
6 official network of what we might call user group
7 designated contact persons that would be contacted directly
8 by the manufacturers upon a recall to assist in patient
9 notification, and the industry would be prepared to discuss
10 with those groups the sharing of costs to implement a
11 patient notification strategy by such groups.

12 Third, the association would urge that FDA
13 sponsor a meeting of those in the distribution chain, that
14 is, the hospitals and the pharmacies and the home care
15 companies, treatment centers, clinics, clinic patients and
16 their reps, to explore in detail other avenues of
17 information technology to assure increased notification and
18 to really facilitate the development of the regulatory
19 program, which we will talk about since we think a clear
20 regulatory program is required.

21 Let me turn to product recall. Again, you'll
22 see where product recall and patient notification intersect
23 in a variety of places in this proposal.

24 As the committee is obviously generally aware,

1 a critical link in any recall of drug products is going to
2 be the manufacturers' performance of their responsibilities
3 under the GMP regs, and what that reg requires is that
4 manufacturers have written procedures describing the
5 distribution of the products that include a system by which
6 the distribution of each lot can be determined to
7 facilitate recall. Obviously the first step in such a
8 system is to assure that the notification to entities who
9 buy products directly from the manufacturers is as
10 effective as possible.

11 Now, again, the distribution avenues differ for
12 different members of the industry and for different
13 products, but the entities that buy direct from
14 manufacturers include, obviously, wholesalers as well as
15 entities that distribute to end users, what we call final
16 distributors, such as hospitals, treatment centers,
17 clinics, and retail pharmacies.

18 To the end of assisting in having our product
19 recall be more effective, we are proposing and we will
20 adopt the following steps as part of our proposal for
21 notification of our direct consignees. Each consignee will
22 be asked to designate an individual position, because
23 sometimes people change, but a high level position within
24 the entity who will serve as the contact person when we

1 have a recall for purposes of instituting recall
2 procedures. This person will be contacted and it would be
3 their responsibility within the entity for carrying out the
4 buyer's responsibilities upon recall.

5 Second, the provision of postcards or other
6 appropriate materials to direct consignees, that allow
7 them, to confirm that they've received the recall notice
8 and that they have carried out their responsibilities to
9 notify their consignees.

10 Third, the development of electronic or other
11 technical systems to assure that we can do this in a more
12 effective or most effective way.

13 Fourth, the appropriate level of effectiveness
14 checks of all our direct consignees.

15 Finally -- and it was mentioned earlier -- I
16 think that the industry has become aware of the need for
17 education among its consignees, most notably hospitals,
18 about the need for education about what to do in a recall.
19 To help fill this need, the association is committed to
20 working to develop some general education materials that
21 could be provided to consignees, for example, through the
22 web page or through some other things we've been thinking
23 about on effective recall procedures. The FDA was pretty
24 effective on MedWatch and we would welcome their active

1 participation in helping on this education effort.

2 I want to turn next to recall from those who
3 purchase from the manufacturers direct sales, that is,
4 those who buy from the manufacturer and then distribute to
5 others who go to the end users. We'll call this the
6 distribution tier.

7 We've had discussion today and there has been
8 much discussion over the last several months concerning the
9 legal responsibilities of plasma derivative manufacturers
10 to notify patients of recalls. I think it's important from
11 the industry's point of view to understand that it is our
12 view that the FDA current laws and regulations, as opposed
13 to the nonbinding recall guidelines, do not explicitly
14 require that records be kept down to the patient level by
15 the manufacturer, by a drug wholesaler, by a pharmacy, or
16 by a health care entity, or a health care provider. This
17 lack of clarity stands in stark contrast to the clarity of
18 the recordkeeping obligations that FDA has implemented by
19 regulation for blood and blood products and for certain
20 medical devices.

21 But what we would like to do now is to spell
22 out what we think is an approach for the notification of
23 those who buy from distributors which we believe builds
24 upon the existing system, the existing structure within the

1 health care entity and which we believe can be more
2 effective for patients, more cost effective for the system.

3 In developing this, we really started from the
4 premise that building upon an existing and strengthening an
5 existing system is preferable to creating an entirely new
6 system. So, let me talk about what we think this system
7 could be.

8 Within the existing system, let us start with
9 the concept of contractual obligations that would assist
10 the industry in meeting our goals. Let me put on my other
11 lawyer hat to say that while the industry is considering
12 the inclusion of these type of provisions in the contracts
13 with people to whom we sell directly, it can't do so as an
14 industry without significant risk of being found in lawyer
15 terms as having a concerted refusal to deal. We cannot
16 ourselves adopt these as an industry standard unless we get
17 the FDA to impose such requirements as part of a
18 substantive and binding regulation.

19 So, it has got to be clearly understood that
20 while an individual company may enter into contracts today
21 as it sees fit, as an industry we need FDA's support and an
22 FDA rulemaking to mandate these requirements, but we do
23 think these are the kind of requirements that will make an
24 effective system within the health care delivery system

1 that we have today. There are seven of them. I'll go
2 through them relatively quickly.

3 Immediate suspension of distribution upon --
4 this is again at the distributor tier. Immediate
5 suspension of distribution of the recalled product by the
6 distributor upon request.

7 The distributor would notify its customers.
8 The manufacturer would be providing the distributor with
9 the form of the letter to be used which contains
10 instructions about what to do, but upon receipt, the
11 distributor would have a responsibility of going down in
12 the chain.

13 The manufacturer would assist the distributor
14 with the mailing and the shipping and reasonable
15 administrative expenses incurred by the distributor in
16 connection with the recall.

17 Obviously the distributor would cooperate in
18 any recalls by providing relevant product tracking
19 information to the manufacturer so we can be of assistance.

20 The fifth one is a lawyer's thing.
21 Representation and warranty that in carrying out their
22 responsibilities, they'll comply with the Prescription Drug
23 Marketing Act, and I'll get to what their requirements are
24 in a minute.

1 Distributors have to keep records adequate to
2 generate distribution, sales, and customer reports
3 necessary to trace lot numbers to its buyers, and a
4 downstream requirement that down the next stream they will
5 have the same requirements for people to whom they
6 distribute.

7 It was pointed out in the November 19th meeting
8 that the current regulatory scheme that already exists for
9 this distribution tier, i.e., drug wholesalers, already
10 contains a requirement that distributors establish and
11 adhere to written policies for recalls and for withdrawals.

12 But if you look at those regulations, they
13 really lack any clarity that's necessary to assist in doing
14 this type of activity. The PDMA regulations issued by FDA
15 simply state you have to have such a policy. It does not
16 spell out any detail on what they have to include, such as
17 requiring that the distributor include the lot numbers when
18 selling to physicians or others or notification of those to
19 whom the wholesaler has sold the product that are subject
20 to recall.

21 The PDMA does set out a minimum statutory
22 requirement. States are free to embellish upon that.
23 While I haven't looked at all 50 states, I've worked with a
24 number of them and I've worked with them. All the states

1 have done, by and large or almost universally, is just
2 repeat what FDA has in its PDMA regulations.

3 So, we would strongly urge that wholesalers be
4 explicitly required, as I have just said, to develop a
5 recordkeeping system so they could track, to notify their
6 direct sales, and that there be some standards for that
7 notification.

8 The last tier in the distribution system, what
9 I called the final distribution, the distribution to end
10 users, people who dispense drug directly to patients who
11 need to be advised of patient recall. Now, some of those
12 entities buy directly from manufacturers, but others buy
13 from wholesalers or somewhere else down the chain.

14 Again, let me make clear that in our view there
15 is no explicit law or regulation related to patient
16 notification regarding these plasma-derived products at
17 this time, but that is not to say that the industry doesn't
18 think that it's a goal to be achieved and it's not
19 appropriate.

20 What we would like to suggest -- and it was
21 actually also some of the comments made around the table --
22 is that patient-specific recall can best be handled at the
23 level closest to the patient, that is, the pharmacy or the
24 licensed health care provider who dispensed the product.

1 Again, we came to this proposal from an
2 examination of really the existing health care industry and
3 the statutory schemes that already exist within the health
4 care industry. Virtually all states have extensive
5 requirements for pharmacy-based patient records on drugs
6 dispensed and they really do provide an opportunity for
7 immediate retrieval of information regarding those patients
8 who have received prescription drugs from the pharmacy.

9 Now, although the pharmacies do keep detailed
10 records, in the states we have reviewed, it doesn't appear
11 that there is an explicit requirement that the lot numbers
12 be associated with a specific prescription, although I can
13 tell you from talking to a number of large pharmacy chains,
14 in fact they do keep that as a matter of good policy, but
15 we have not found it as a statutory or regulatory
16 requirement.

17 We also have not located an explicit
18 requirement that pharmacy notify patients who may have
19 received the prescriptions. Again, in talking to people in
20 the industry, there are many who in fact view that as their
21 responsibility and do it and use their own patient records.
22 But it's the association's view that this kind of direct
23 patient notification again is best handled at the level
24 with the direct patient contact.

1 We would note, although someone I think said it
2 wasn't quite what I had been told, but at least it was my
3 knowledge that treatment centers already have fairly
4 extensive medical records, and to the extent that they
5 dispense to patients inventory that is intact to patients,
6 then the lot number would be something that would be known
7 to the patient.

8 In proposing this, that is, that patient
9 notification be at that level, I want to say that we are
10 not unmindful of the regulatory scheme that FDA adopted
11 with respect to medical device tracking. Under that
12 regulation, while the reg itself doesn't talk about product
13 recall, there is a system in place under that regulation in
14 which information flows up to the manufacturer, patient-
15 specific information, such that if they needed to do a
16 recall, the manufacturer would have the patient-specific
17 information.

18 But it is the industry's view that there are
19 substantial factual differences between these that make the
20 adoption of that system both inefficient and inappropriate
21 to have that go up to the manufacturer level, and there are
22 two major reasons.

23 First, the amount of data and information that
24 would need to go up to the manufacturer on each patient by

1 hospitals, by treatment centers, retail pharmacy, and home
2 care companies, you are really need to going to have some
3 network system that doesn't now exist to connect those
4 entities with a manufacturer. A manual system is just not
5 going to work I don't think.

6 Many pharmacies, on the other hand,
7 particularly mail order pharmacies that are utilized by
8 many individuals who have need for chronic medications,
9 already have computerized databases. They already have
10 systems for patient notifications which we believe could be
11 effectively used for this purpose.

12 Second, the release of patient-identifiable
13 information to the manufacturer raises some significant
14 patient confidentiality concerns. As many of you know,
15 there is a big effort right now in implementing Kennedy-
16 Kassebaum to deal with issues of medical records and
17 patient confidentiality. In addition, in virtually every
18 state -- or maybe I shouldn't say it that strongly. In
19 most states, state pharmacy laws already would in fact
20 prohibit the provision of information to the manufacturer
21 unless they got specific patient consent.

22 Again, let me just go back. Since in fact the
23 manufacturers do sell to some people who do sell to end
24 users, we again would propose - oh, I skipped something.

1 Because we in fact do have some direct
2 consignees who are final distributors of the product, if
3 one had the FDA backing which you need from an antitrust
4 point of view, because otherwise you can't all agree that
5 you won't do business with a company that doesn't do that,
6 we would impose the requirements that the final distributor
7 has to maintain the records necessary to trace lot numbers
8 to patients, that patient labels would need to include the
9 lot number, and that they would notify patients of any
10 product recall.

11 So, to implement this, there are a couple of
12 regulatory actions that we would ask the FDA to undertake.
13 Amending the PDMA to deal with the requirements on
14 distributors. I would note that the FDA does have
15 currently a PDMA regulation. You have a proposed rule.
16 It's not yet finalized. It does amend some of the PDMA
17 requirements, and I can't speak obviously for the FDA
18 lawyers, but that may be a vehicle to do this quickly
19 because that is an existing rulemaking. And for final
20 distributors, amending 351(d)(1) and (2) to deal with the
21 issue of the end users.

22 I recognize that what we have proposed here is
23 really a multi-tiered system. I do think, however -- the
24 industry thinks -- that this is much more consonant with

1 the existing system. It will establish an effective system
2 of recall down through the tiers of distribution to the
3 individual patient without creating an entirely new overlay
4 of rules and responsibilities.

5 If the agency decides to adopt a product recall
6 and patient notification policy, we think it is incumbent
7 on the agency to provide a clear regulatory framework to do
8 this. As I hope we've been able to make clear, the
9 industry alone can't on its own create a system that
10 operates through the various levels of distribution. It
11 needs to be able to work in a concerted, multi-party
12 approach.

13 The industry reaffirms its position that
14 product recall would be as effective as possible and that
15 patients be notified of critical information. We believe
16 these are common goals that we're all involved in. The
17 industry, as it has in the past, pledges to continue to
18 work with FDA and the patients and their representatives,
19 as well as the distributors and the other parties in this
20 system who really have to be brought into the system if
21 we're going to have one that's effective.

22 We urge FDA to begin the rulemaking phase of
23 this proposal as soon as possible, maybe after the meeting
24 that we've suggested, and to put the finalization of this

1 on a priority track.

2 We do recognize at the same time that these
3 final regs take time, and so as we have set out in the
4 proposal, there are clearly things that the industry
5 pledges now to do in helping to develop a better
6 communications network to facilitate the flow of
7 information to meet our mutual goals.

8 Thank you.

9 DR. SWISHER: Are there questions of Ms. Dunst?

10 (No response.)

11 DR. SWISHER: The system that you present
12 seemed to me to terminate the information in the pharmacy.
13 What closes that final link to the patient?

14 MS. DUNST: Well, it's either the pharmacy or
15 the physician or the treatment center, whoever is the final
16 dispenser. We would need to have a regulation that
17 requires the pharmacy to in fact use the existing systems
18 they have and in fact notify patients. That's what would
19 close that link. At the moment, although many pharmacies
20 tell me at least that they do do this, there is no
21 obligation, A, that they keep the lot number or, B, that
22 they notify patients. So, that obligation would need to be
23 imposed.

24 DR. SWISHER: Does the pharmacy determine

1 whether or not the transmission of that information to a
2 given individual patient is in the patient's best interest?

3 MS. DUNST: I don't know the answer to that. I
4 don't think so. I think under this system, that's
5 something one would have to look at. The same thing is
6 true of pharmacies.

7 DR. SWISHER: That's obviously a provocative
8 question.

9 MS. DUNST: Right.

10 DR. SWISHER: But I think it's not without
11 precedent that issues like this arise.

12 A question of Ms. Dunst?

13 MS. PIERCE: Actually this is addressed to the
14 FDA, something that has been presented here that I've
15 gotten quite confused about, and that is from this
16 presentation, there seems to be a huge gap between our
17 responsibilities and regulations and guidelines in terms of
18 information about a problem with a product going from the
19 manufacturer to the end user. I'm sorting throughout all
20 this information that was put in here and presented today.

21 Is there really no one responsible under FDA
22 guidelines or regulations for making sure that information
23 gets from the manufacturer to the patient using it?

24 DR. EPSTEIN: Well, I think that this probably

1 isn't the right place and time to have a lawyers' debate
2 over what the reg means. I think the problem is that the
3 FDA believes that the preamble to the 1978 recall reg
4 squarely places on the manufacturer the responsibility for
5 effectiveness of the recall to whatever is the level
6 necessary.

7 Now, I think the problem is that over time
8 there has been some ambiguity regarding the agency's
9 expectations and the degree to which manufacturers have or
10 have not complied with the law as written or interpreted.
11 So, I would have to say that in 1997 there's certainly room
12 for legal debate.

13 On the other hand, Mary Pendergast, who is the
14 Deputy Commissioner, made quite clear at the November 19th
15 workshop that it is FDA's interpretation of the regulation,
16 as explained in the preamble, that that is a manufacturer's
17 responsibility.

18 Now, having said that, clearly there are
19 current gaps in the system which I think have just been
20 very clearly delineated. Whereas the FDA may hold the
21 manufacturer responsible, the system could benefit from
22 regulations that more clearly define the responsibilities
23 of distributors.

24 I think that the problem that's being pointed

1 out is that information may flow and get stuck. FDA may
2 take the point of view that, well, manufacturers shouldn't
3 have contracts with distributors that aren't poised to
4 carry through, and I think that that's an option that can
5 be exercised at the present time. But it's being suggested
6 to us that there are better solutions yet, which is to
7 close the gap on legally defined responsibilities, all the
8 way down the chain.

9 So, I think whereas there are these points of
10 debate from a legal point of view, the system can be
11 harmonized and there probably is need for additional
12 regulation.

13 MS. PIERCE: How long would it take to
14 determine those regulations and then implement them? FDA
15 regulations.

16 DR. EPSTEIN: Well, I don't think that I can
17 speak personally for the entire process. Promulgation of
18 regulations involves not just the Center but the agency,
19 not just the agency, but the Department, not just the
20 Department but OMB, the administration. There are
21 provisions for expedited rulemaking. There are provisions
22 for promulgating rules as final in their interim stage and
23 so forth. So, I think that there's some homework to be
24 done here, and I'm not prepared to commit to a time line.

1 I am prepared to state that this issue has the
2 highest level of visibility within the agency and a very
3 high priority has been attached to it. That's why we have
4 brought it to public discussion both through recent
5 workshops and BPAC meetings. We have had ongoing meetings
6 with various interested parties who have requested those
7 meetings.

8 So, we certainly are trying to move this
9 forward, but it would be both difficult and unwise for me
10 to forecast a time frame.

11 DR. NELSON: The presenter, at least as I
12 interpreted it, mentioned that plasma derivatives or the
13 products that are being discussed currently are handled
14 differently from the distributors and the manufacturers'
15 responsibility than other medical products and devices.

16 MS. DUNST: No. I think I said that there are
17 special rules for certain medical devices, as well as for
18 blood and blood products. That was the distinction.

19 DR. NELSON: So, in other words, if you had a
20 mitral valve replacement, you'd know what the lot number
21 was, but if you had a plasma-derived product, you wouldn't
22 necessarily know.

23 MS. DUNST: Under the device regulations, there
24 are I think currently 30 devices, and to be honest with

1 you, I don't know if mitral valves are in that 30 or not.
2 But there are 30 devices that have been put in a special
3 category that in fact require lot number and patient name.
4 They're implantable devices, and that is a special category
5 and it covers about I think currently 30 devices. I don't
6 know how many there actually are, but there are 30 types of
7 devices.

8 DR. NELSON: So, if that's the case, it would
9 appear that decades of time that might require the
10 distributor's responsibilities to be changed would just be
11 to add products to a law or responsibility that already
12 exists. So, therefore, if somebody was interested, it
13 probably could be done more quickly is my conclusion.

14 DR. SWISHER: The example of a valve which goes
15 into a patient with the lot number recorded in the
16 patient's record and also transmitted back to the
17 manufacturer is an example of a pre-event intervention or
18 recordkeeping.

19 We're talking now about things that happen
20 post-event. Unless the proposal would be that in effect
21 every lot number would be identified and connected with an
22 individual patient in exactly the same way before it was
23 infused?

24 MS. DUNST: That actually is the proposal

1 because that's the way that a patient knows what lot
2 number. The hospitals are a difficult case. There is a
3 requirement --

4 DR. SWISHER: That provides the record, but the
5 idea of information in a sense directed to the patient is a
6 different issue.

7 MS. DUNST: The JCHO requirements on medication
8 recall and on patient records don't -- at least as I have
9 been able to look through them, the medication recall are
10 fairly extensive, but the medical record requirements with
11 respect to lot number being indicated at the hospital
12 pharmacy, at least from my looking at it, doesn't appear to
13 exist. But I must tell you I didn't talk to the AHA or the
14 JCHO before making the presentation.

15 DR. SWISHER: Carol?

16 DR. KASPER: I thoroughly agree with the two
17 recommendations, one, that the person who finally
18 dispenses, the entity that finally dispenses, a product to
19 the patient should record the lot number, but also in view
20 of recalls, that entity that has the information should
21 notify not only the patient but the prescribing physician.
22 I could imagine a scenario in which the patient is notified
23 and the doctor isn't, which is dumb.

24 DR. SWISHER: We still have some presentations.

1 Thank you very much, Ms. Dunst.

2 We have requests from four speakers for our
3 open public session on this topic. Let the record now show
4 that the open public session is open, and the first request
5 for time is Michael R. McConnell of the National
6 Notification Center. A handout has been distributed to the
7 committee members.

8 MR. McCONNELL: Good afternoon. My name is
9 Michael McConnell. I'm the head of the Health Care
10 Division of the National Notification Center.

11 As you can tell, it has been suggested that in
12 some cases of product recalls and withdrawals and other
13 types of situations involving blood products that patients
14 should get the information. There are many issues
15 surrounding this subject, but my purpose here today in this
16 time allotted is to address only the practical aspects of
17 end user notification and to bring to the attention of this
18 committee and this audience recent technological advances
19 that may have a bearing on this topic.

20 It is now possible to notify large audiences,
21 for example, all patients who have hemophilia or all
22 patients that have immunodeficiency diseases in a matter of
23 hours with confidentiality and with confirmation that the
24 message was received.

1 Now, a way to do this is to employ what's
2 called a high capacity voice messaging system. This can be
3 described as a reverse voice mail system. You all know
4 voice mail. Maybe you've come to hate voice mail.

5 (Laughter.)

6 MR. McCONNELL: With traditional voice mail,
7 you call in to get your messages. This, though, is
8 different from that. In this case the message is recorded
9 and then the message calls the person, the recipient.

10 With traditional voice mail, there's a problem
11 in that the person has to call in to get the message, and
12 secondly they have to be on a voice mail system. You have
13 to have signed up for it. You have to be on a system to do
14 that. With high capacity voice messaging, the system will
15 call the recipient.

16 How that works is that a message sender, if I
17 wanted to send a message to everyone in this room, first of
18 all, I would have to know all your phone numbers, but I
19 would dial an 800 number and record a message. Then the
20 system would dial all of you, the end user. The system
21 could then confirm that you were who you say you were, and
22 then the voice mail is delivered.

23 Now, why this may be of some interest to you
24 all is because as far as speed goes with the high capacity

1 voice messaging system, 30,000 messages can be delivered in
2 an hour. So, in the case of 10,000 or so patients with
3 hemophilia, that could be done in less than an hour. We
4 currently use the system to notify 60,000 pharmacies of
5 drug recalls, and that usually takes about 4 hours. Of
6 course, the last few always take a long time to get done.

7 Another important factor is confidentiality.
8 Using a touch tone pad allows many different ways of
9 confidentiality. The most obvious one is entering a PIN
10 number of some kind. However, there are other systems to
11 use confidentiality, including speech recognition where you
12 recognize a spoken password, and then also voice
13 recognition which is kind of like voice printing, like
14 fingerprinting where a certain particular voice pattern,
15 which I apologize for my voice today, can be recognized.

16 Also, the system can then use the system for
17 confirmation. The touch tone interactivity allows that the
18 confirmation that the notice was received rather than the
19 notice being delivered to dead air.

20 The message is consistent. All recipients get
21 exactly the same message because it's the same message
22 that's recorded and delivered to everyone, as opposed to --
23 and I don't want to pick on our friends in the mass media,
24 but when you give it to Dan Rather, you kind of lose

1 control of what the message is.

2 However, the system is customizable. The
3 previous point said that all recipients get the exact, same
4 message but that's not entirely true because the system can
5 be set to send a different message to patients than it does
6 to physicians than it does to pharmacies. You can kind of
7 customize it depending upon the audience.

8 Then lastly it's easy and probably another word
9 that should be there too is "universal" in that all you
10 need to make it work is a telephone and all you have to do
11 is pick it up and say hello and the system will work.

12 Now, another important aspect in all of this is
13 cost. It seems in this technological day and age that
14 anything is possible if we're willing to pay for it.

15 Now, given a very important caveat, let me say
16 here that we have not yet had much defined for us yet as to
17 what the requirements of a system would be for end user
18 notification, but given that caveat, previously when I had
19 discussions with people at the FDA, they asked what
20 something like this might cost, and I quickly back-peddled
21 and said we didn't know. All these things would need to be
22 defined. So, we did the ball park and throw your arms
23 around it kind of thing, and we've finally come up with
24 this. The costs for notifying end users would range from

1 about \$25 to \$75 per patient per year.

2 Now, as for the timing on a system like this,
3 it's currently fully operational and it is used to notify
4 pharmacies in cases of drug recalls. Again, if certain
5 issues can be addressed, we could be fully operational for
6 blood product end user notification in about 60 days.

7 There are many issues and I take no credit for
8 this. You've heard all these issues brought up already by
9 Mark Weinstein and others.

10 The first one, ensuring confidentiality. I
11 think that that probably could be addressed. That is a bit
12 of a technological issue, but I think we've pretty much got
13 several options for that.

14 The other issues that are up there, though, are
15 much more philosophical in nature. Who is the sender of
16 the notification, and really what that is is we need to
17 know who is our client here. Who is responsible for all
18 this? Is it the manufacturer, the FDA, the CDC, the NIH?
19 Is it the NHF? Is the IDF?

20 What triggers initiation of notification?
21 That's very unclear to us and we would need very clear
22 direction on those kinds of things.

23 And who covers the cost? There's that nasty
24 word "cost" again.

1 While it is impossible to address all the
2 aspects of this system in the time allotted, we could go
3 into much more detail at a later date and in a different
4 forum. Our purpose here today is to bring to your
5 attention that end user notification is practical, is real,
6 and I hope this information has been of some benefit to
7 you.

8 Thank you very much.

9 DR. SWISHER: Would you stay at the podium for
10 a moment please? Are there questions? This is a pretty
11 novel approach to this problem that I have not heard of
12 before. Are there questions? Mr. Cheng?

13 MR. CHENG: So, how would you get the phone
14 numbers for the end users?

15 MR. McCONNELL: What we've currently done with
16 pharmacies is we get all the numbers ahead of time and then
17 we keep them and maintain them in a registry or a database.

18 MR. CHENG: So, you would be updating them
19 every few weeks?

20 MR. McCONNELL: We update them weekly in cases
21 of pharmacies. It's a monstrous task but it's pretty
22 important, so that's what we do.

23 In the case of patients, we would have to get a
24 registry or a list of patients from I don't know who, from

1 the Hemophilia Foundation, from the Immune Deficiency
2 Foundation.

3 MR. CHENG: So, would you need to have a
4 consent from the patients, I mean, for pharmacies to give
5 you that phone number, or how does that work?

6 MR. McCONNELL: To give the patient's phone
7 number?

8 MR. CHENG: Right.

9 MR. McCONNELL: Oh, I think that's a question
10 that you all would have to answer.

11 DR. SWISHER: Other questions?

12 One of my questions is, when your phone rings
13 in my house, how do you distinguish your organization and
14 your message from a survey taker or telemarketer, which in
15 our house results in instant hang-up?

16 (Laughter.)

17 MR. McCONNELL: I think that that is one of the
18 practical aspects that would have to be worked through, but
19 the message could simply say this is the National
20 Hemophilia Foundation with an important message for a
21 patient in this household. I could say something as obtuse
22 as this is a message saying, don't forget your Aunt Sadie's
23 birthday tomorrow, which could be a code, if you wanted to
24 maintain a certain amount of anonymity or confidentiality.

1 That's the code that I use in order to know that there's a
2 product recall.

3 What we do with pharmacies now is that we say
4 that this is an urgent drug recall. Please bring the
5 pharmacist to the phone to receive the message. When
6 you're ready for the message, press 1. If this is not a
7 good time to receive the message, press 2 and we'll call
8 you back in 15 minutes. That message keeps looping over
9 and over again until the pharmacist comes to the pharmacy
10 phone and receives the message. Then they press 1 and then
11 it goes through and gives them the details about the
12 recall.

13 DR. SWISHER: Blaine?

14 DR. HOLLINGER: And what if they don't have
15 touch tone?

16 MR. McCONNELL: We've identified the pharmacies
17 in the United States that don't have touch tone, and we do
18 this speech recognition. It actually recognizes spoken
19 words. That's not a very high tech and exact science, but
20 it does work. You just have to speak clearly.

21 Yes?

22 MS. PIERCE: If someone gets a message and say
23 they're not home, it's on their answering machine, or if
24 they are home and they get a message but they can't talk at

1 that time, it sounds like you have set up a code that they
2 can call back. Now, do they get an actual person or is
3 there some sort of system that they just sort of get into
4 the correct recorded message? Is that available 24 hours a
5 day with a person backup?

6 MR. McCONNELL: First of all, the system can
7 tell the difference between a live human voice and an
8 answering machine or voice mail. So, if we call your home
9 and get a live person, then it can play one message that
10 says, we have an important message about a product recall.
11 When you're ready for the message, press 1. If it detects
12 that it's getting a voice mail or an answering machine, it
13 can just say, there's an important message for you about a
14 product recall. Call 1-800, blah, blah, blah. Then that
15 800 number can go anywhere we all wish it to go. It can go
16 back to the manufacturer. It can go to the Hemophilia
17 Foundation. It could come to the National Notification
18 Center, and then we could screen and play the message or
19 deliver it to a live operator. There are many options
20 there open for that.

21 MS. PIERCE: And is that available 24 hours a
22 day, a live operator?

23 MR. McCONNELL: Sure, or can be anyway.

24 MR. CHENG: What would happen if like a 5-year-

1 old child picked up the phone? Then you'll get a live
2 voice, but that information may not necessarily get passed
3 on.

4 MR. McCONNELL: That's right and that's where
5 we would need to then make sure that we were all
6 comfortable with the proper introductory message that said,
7 please do something in order to receive the message. If a
8 5-year-old child could understand all that and do it, then
9 we would be delivering the message to the 5-year-old child.
10 So, we would just want to make sure that we had, enter a
11 PIN number, speak a code word, say your name, whatever that
12 happened to be. Much like the child-resistant containers,
13 you try to build it so that they can't get in and sometimes
14 they're better at it than the adults, but that's another
15 topic.

16 DR. SWISHER: Thank you very much.

17 Have you considered trying to help the Internal
18 Revenue Service?

19 (Laughter.)

20 MR. McCONNELL: No, but we have been asked to
21 sell aluminum siding, and we've resisted that.

22 (Laughter.)

23 DR. SWISHER: The next speaker is Mr. John
24 Boyle of the Immune Deficiency Foundation.

1 MR. BOYLE: Good afternoon. My name is John
2 Boyle.

3 Nineteen years ago this April, my son, who was
4 6 months at the time, was diagnosed as having X-linked
5 agammaglobulinemia, a primary immune deficiency disease.
6 Although the condition was and is life-threatening -- and
7 we had six weeks in intensive care to prove that -- there
8 is an effective treatment for it. It involves a blood
9 product, which is why I'm here today.

10 In 1980, two years after our son was diagnosed
11 as immune deficient, my wife, myself, and a handful of
12 other foolish people formed a national organization, the
13 Immune Deficiency Foundation, to support advances in the
14 care and treatment of these diseases. I am here today both
15 as a parent of an immune deficient patient and as a trustee
16 of an organization dedicated to the well-being of all
17 patients with primary immune deficiency diseases.

18 Since this group is an important segment of the
19 blood using population, I want to tell you a little bit
20 about them to characterize what is needed and what is
21 possible in terms of patient notification.

22 The term "primary immune deficiency disease,"
23 as many of you may know, is an umbrella that covers over 70
24 specific diseases. Collectively the NIH estimates that

1 approximately 500,000 Americans are affected by immune
2 deficiency diseases. However, the number of diagnosed
3 cases is a fraction of that. Many of these cases are
4 asymptomatic and others have symptoms but the underlying
5 conditions are not recognized.

6 How many diagnosed cases are there? No one
7 knows for certain, but IDF has recently taken steps for the
8 first population estimates of these diseases. As a first
9 step towards a national patient survey, IDF identified the
10 medical societies that are most likely to represent
11 physicians who treat patients with primary immune
12 deficiency diseases. We identified approximately 17,500
13 physicians that we thought as mostly. We mailed these
14 physicians a screener to try to ascertain whether they had
15 any patients and how many patients with primary immune
16 deficiency diseases.

17 To date the survey has identified over 1,200
18 specialists who follow approximately 17,000 patients with
19 primary immune deficiency diseases, and in order to be sure
20 we knew what we were talking about, we had them identified
21 in terms of specific diagnostic category so we don't pick
22 up things that are not primary immune deficiency diseases.

23 Now, this represents only a fraction of the
24 patient population because only 15 percent of the

1 specialists returned this survey, and when we compared
2 physicians whom we knew treated patients with primary
3 immune deficiency diseases with the respondents to this,
4 less than half had responded. So, the minimum estimate is
5 the number of patients with primary immune deficiency
6 diseases who are followed by specialists is probably more
7 in the range of 35,000 just based on doubling this number
8 for the specialists who haven't reported yet. We're
9 continuing the survey and we'll know more at a later point
10 in time.

11 This does not deal with the broader issue of
12 the primary care physician, and many patients with primary
13 immune deficiency diseases are not followed by specialists,
14 but by primary care physicians.

15 In an unrelated national survey of primary care
16 physicians, 12 percent reported seeing patients with a
17 family history of primary immune deficiency diseases. That
18 would translate into a population projection of
19 approximately 25,000 primary care specialists.

20 I raise this because of some of the issues in
21 terms of notification, numbers involved. In total, you're
22 talking about several thousand specialists and tens of
23 thousands of primary care physicians who are treating
24 patients with primary immune deficiency diseases.

1 Now, the vast majority of these patients
2 receive intravenous gammaglobulin. We can document that
3 because we have undertaken the patient side of this survey.
4 The survey to date has over 2,000. We're up to 2,000 here,
5 and as you can see from the slide that's in front of you,
6 over 70 percent have been treated with IVIG for their
7 condition. If we make a conservative estimate that the
8 number of patients with primary immune deficiency diseases
9 who have been diagnosed is something on the magnitude of
10 50,000 and if 70 percent have received -- and most of these
11 are receiving -- IVIG, then you're talking about something
12 on the magnitude of 35,000 IVIG users. You have to think
13 about that in terms of not only our patient population but
14 issues of recall. Clearly this makes treatment of patients
15 with primary immune deficiency diseases the primary FDA
16 approved application of IVIG for a specific patient
17 population.

18 In addition to the number of immune deficient
19 patients using IVIG, there are three other characteristics
20 of this patient population that bear directly on your
21 considerations.

22 First, when I was first told my son had an
23 immune deficiency disease, my assumption was, that was it.
24 In point of fact, with treatment this is a relatively

1 healthy population, and as you can see, despite the fact
2 that this patient population goes back to some of the first
3 diagnosed in the early 1950s, overall almost 7 out of 10
4 would describe their current health status as good or
5 better. It's not as good as the general population where
6 you would be talking about something like 85 percent or
7 more saying good or better, but still it's a relatively
8 healthy population.

9 One other measure is that less than a quarter
10 have been hospitalized in the past year. If you go to the
11 general population, 10 percent will be hospitalized in any
12 given year. So, once again, it's a relatively healthy
13 population if treated.

14 However, there are a number of serious problems
15 in treatment and cost, and health insurance is certainly
16 one of them. If you look at that population, if you look
17 very quickly at this, basically what you're looking at is
18 approximately a half who have had insurance applications
19 denied, canceled, conditions excluded, treatment denied,
20 and so on. I raise this issue because cost, which is an
21 implication of notification and other blood product stuff,
22 is a major issue of this population.

23 In order to pay for the patient's medical
24 treatment, these are not free riders. What you'll see is

1 over half have used their savings, sold their stocks and
2 bonds, their cars, their house, borrowed from the bank and
3 borrowed from others. So, once again, cost is a major
4 factor and resources.

5 This bears directly on treatment because if you
6 look at compliance with therapy, what you're looking at is
7 almost 2 out of 5 who have reported some failure of
8 compliance with medically indicated therapy because of cost
9 or insurance. If you look at the third one down, which
10 actually translates to I didn't take IVIG in the amount and
11 as frequently as it was prescribed, you're talking about 10
12 percent of all. That would be about 15 percent of those
13 who were IVIG users.

14 Now, what you're looking at is a potential
15 tragedy of people who can be healthy with treatment who,
16 for cost and other reasons, are not necessarily getting
17 that treatment.

18 Against that backdrop, let's talk about patient
19 notification of withdrawals and recalls. The present
20 system depends entirely on pharmacies to remove recalled
21 products from the system in a timely fashion. We have a
22 lot of anecdotal evidence from our members that this does
23 not always occur. We know that at least in some instances,
24 major medical centers did not receive recall notices for

1 their recalled products because we informed the physicians
2 who went down there and found them in the pharmacy ready
3 for dispensing. We know that in at least some instances
4 these major medical centers did not keep any lot numbers
5 that would permit any type of patient identification.

6 If you talk to some people, they'll tell you
7 the system doesn't work. Actually we don't know if the
8 system doesn't work. We know that there are specific
9 instances in which it doesn't. To the best of our
10 knowledge, there is no evidence about how well the current
11 system, upon which the safety of tens of thousands of
12 primary immune deficient patients at least, is working.

13 If the current recall system is to be
14 preserved, we urgently need an independent test of the
15 speed and completeness of the recall system. To the best
16 of my knowledge, I see no evidence of that. Such a test
17 would identify weaknesses in the current system that might
18 be remedied, and equally importantly, it would answer very
19 legitimate patient questions and concerns about the
20 effectiveness of the system in protecting the health of
21 patients.

22 No patient will accept having received an
23 unsafe product after it has been recalled. If the current
24 system does not assure virtually immediate and universal

1 patient protection from recalled products, then it must be
2 supplemented or replaced. A supplemental system would
3 emphasize prescribing physicians as the second line of
4 defense and infusing patients as the last line of defense
5 against unsafe products.

6 The total number of patients and physicians
7 involved in IVIG, which I've shown you up there, in
8 addition to any complete enumeration of these populations
9 -- I've told you that our guesstimate is that there are
10 probably 50,000 primary immune deficient patients.
11 Unfortunately, for the previous speaker and for ourselves,
12 I don't have a list of those 50,000 patients. I have a
13 list of probably about 10 percent of that population.

14 The total number of physicians, on the other
15 hand, in terms of specialists, I have a list of 1,200,
16 which is going to cover a fair portion, eventually maybe
17 2,500, but we don't know the primary care physicians.

18 So, in the absence of any complete enumeration,
19 we can't get -- and nobody that I know of can get -- to all
20 of the end users.

21 Nonetheless, an improved physician and patient
22 notification system is possible and potentially very
23 beneficial as a supplemental system. As indicated earlier,
24 we've already identified 1,200 physicians who treat 17,000

1 immune deficient patients. We are continuing our efforts
2 to identify the vast majority of specialists who treat
3 these patients. A supplemental notification system based
4 on 2,000 to 3,000 specialists who see the largest number of
5 IVIG patients would provide a significant improvement over
6 the present system in which prescribing physicians are not
7 necessarily notified by pharmacies of recalls affecting
8 their patients. The notified physician provides a check on
9 pharmacy notification and action on the product recall.

10 The Immune Deficiency Foundation has already
11 created several disease registries for immune deficient
12 patients. As a result of its current patient survey, IDF
13 is developing a voluntary listing of thousands of immune
14 deficient patients. We do not expect our patient listings
15 ever to cover the entire patient population. Nonetheless,
16 a large but incomplete listing of patient notification
17 could provide some immediate benefits for product safety.

18 Prescribing physicians frequently do not
19 dispense the product, which may be administered by a nurse,
20 a home health care technician, or the patients themselves.
21 If the patients are informed of product recalls and if
22 patients can check those lot numbers against products that
23 they are receiving, then failures in product recall can be
24 identified and stopped before they hurt the patient.

1 Moreover, if patients can record lot numbers, then we can
2 identify who received tainted products distributed before
3 the recall notice. This will facilitate early testing and
4 treatment of affected patients and peace of mind for
5 unaffected patients. In addition, patient monitoring
6 provides an ongoing system of quality control over the
7 pharmacy-based recall system.

8 The success of a supplemental system of patient
9 notification, even based on a sample basis, requires more
10 than making recall information available to patients.
11 First, product information needs to be displayed in a
12 uniform fashion on bottles and bags that the patients see
13 so that they can record lot numbers and compare them to the
14 current recalls. It's not sufficient to put them on boxes
15 that the patient may never actually see in the clinic.

16 Second, health professionals would have to
17 accept patient review of the product before infusion as
18 necessary and appropriate behavior. In other words, tell
19 them, yes, you can look at it. Don't just trust us.

20 Third, patients would have to be trained how to
21 check their product against current recalls and record
22 product information for future recalls.

23 Finally, a means to communicate recall
24 information to patients in a timely fashion would have to

1 be established.

2 These steps in improving patient notification
3 of product recalls could save lives and reduce unnecessary
4 product related injuries. It would also help to reassure a
5 patient population whose faith in the safety of their
6 product and the government regulation of product safety has
7 been shaken.

8 As we indicated earlier, immune deficient
9 patients represent a potentially healthy population if they
10 can be assured an access to an adequate supply of a safe
11 product. As I said earlier, there is a safe treatment. I
12 can prove that. I have the bill for college tuition for my
13 son that I have to pay. So, there is a safe treatment.
14 The important thing is to make sure that the safety of that
15 product is maintained and that we do things that helps us
16 better control the system.

17 Thank you.

18 DR. SWISHER: Are there questions of Mr. Boyle
19 from the committee?

20 (No response.)

21 DR. SWISHER: If not, thank you very much.

22 The next speaker is Dr. Fred Dauer who will be
23 speaking on behalf of the American Red Cross.

24 DR. DAUER: Thank you. My name is Fred Dauer.

1 I'm a medical officer with the American Red Cross.

2 At the November 19th FDA informational meeting
3 dealing with notification of plasma and product withdrawals
4 and recalls, the American Red Cross expressed its support
5 of a system that would provide early, accurate, and
6 complete patient notification of product recalls and
7 withdrawals so that patients can make informed decisions
8 about their treatment.

9 The American Red Cross is acutely aware of the
10 inadequacies of the information network that links
11 manufacturers' product lot numbers with final patient
12 consumers. Without federal regulations that mandate the
13 permanent recording of product lot numbers by intermediate
14 distributors, it is doubtful that current practices of
15 consignee notification will ever guarantee complete patient
16 notification in times of product recall or withdrawal.

17 In spite of these recognized inadequacies, the
18 American Red Cross has sought to maximize information
19 distribution about product withdrawals by notifying the
20 National Hemophilia Foundation who alerts their treatment
21 centers by means of the Medical Alert Bulletin; hemophilia
22 treatment centers directly in an attempt to spread the word
23 as quickly as possible; hemophilia treaters; the American
24 Association of Blood Banks who includes this information in

1 their FaxNet; and America's Blood Centers who includes the
2 information in their Newsletter.

3 In addition, the American Red Cross has
4 provided financial support to hemophilia treatment centers
5 to assist them in notification of their constituents. A
6 longstanding goal of the National Hemophilia Foundation was
7 the development of a home page on the Internet for the
8 dissemination of information of general interest to persons
9 with hemophilia and their families and for rapid
10 notification of product withdrawals. The American Red
11 Cross assisted NHF to realize this goal by providing
12 financial support in its inception.

13 At the same November 19th meeting, the National
14 Hemophilia Foundation asserted that the development and
15 enforcement of a primary notification system is the
16 responsibility of the Food and Drug Administration.
17 Further, they stated that the FDA should make industry
18 fully accountable for tracking all plasma products they
19 manufacture through their entire distribution pathway. The
20 American Red Cross firmly believes that patients have the
21 right to know about factors that might affect their health
22 in as expedient a manner as possible, and to that end, the
23 American Red Cross commits its support and assistance to
24 the development of that system.

1 Thank you.

2 DR. SWISHER: Questions of Dr. Dauer?

3 DR. KASPER: In that list of entities that you
4 notify if there's a recall, do you also notify any
5 pharmacies outside of hemophilia treatment centers that
6 have been dispensed and including home care companies?

7 DR. DAUER: Yes. We notify every consignee
8 that we have direct information that received the product
9 from us, but quite often it ends there.

10 Thank you.

11 DR. SWISHER: Questions?

12 (No response.)

13 DR. SWISHER: The last speaker is Mr. Donald
14 Colburn, representing the National Hemophilia Foundation.

15 MR. COLBURN: Thank you. I'm sure you are most
16 happy to hear that this was the last speaker.

17 On behalf of the National Hemophilia
18 Foundation, I would like to thank you for this opportunity
19 to present our position on this issue that's being
20 considered by the Blood Products Advisory Committee today.

21 These positions reflect some careful
22 discussions and input from members of the NHF Blood Safety
23 Working Group. As mentioned, my name is Donald Colburn. I
24 sit on that committee. I'm also a person with severe

1 hemophilia as well as the CEO of a hemophilia home care
2 delivery company.

3 NHF has been dealing with the issue of
4 delivering prompt and accurate notification regarding blood
5 products almost since its inception. The years have been
6 extremely difficult and tragic ones most recently, and I
7 think all of you are well aware of the reasons why.

8 NHF is committed to ensuring that consumers of
9 blood products have information about the products that
10 they're using in order to make informed and educated
11 decisions about their treatment. This is only possible if
12 they are provided crucial and possibly life-saving
13 information in as short a time period as possible.

14 On last November 19, 1996 at the FDA-sponsored
15 public meeting on notification regarding withdrawals and
16 recalls of blood products, Deputy Commissioner Mary
17 Pendergast stated that the blood product manufacturer is
18 responsible for delivering appropriate notification
19 regarding the withdrawal or recall of a specific blood
20 product to the end user of that product. Deputy
21 Commissioner Pendergast stressed that the FDA has
22 interpreted the Code of Federal Regulations' definitions of
23 an end user as the actual consumer of the blood product.
24 NHF applauded that statement and we clearly articulated our

1 support for this position at that meeting.

2 Since the November 19th meeting, the world of
3 hemophilia has had two voluntary recalls of different
4 products, a voluntary withdrawal of another, a quarantine
5 of a lot of product for potential HIV antibodies in the
6 plasma pool, as well as the continued suspension of
7 production at a manufacturer. NHF has issued seven medical
8 bulletins to its chapters, treatment centers, and volunteer
9 leadership since November.

10 It's pretty clear that this is an issue that
11 needs a degree of urgency attached to it. It's not like
12 we're sitting in a vacuum and nothing is happening. There
13 was one week I recall that we had I believe three in one
14 week, and that was pretty special.

15 During our presentation on the 19th, NHF
16 recommended that the FDA should develop and enforce a
17 primary notification system that mandates that the blood
18 products industry is fully accountable for tracking all
19 plasma products to the end user, the consumer, and his or
20 her physician. We recognize that it is extremely difficult
21 to develop a rational patient notification system in the
22 midst of a crisis, but we are concerned that FDA has not
23 brought together representatives from our organization,
24 CDC, NIH, and industry and other patient groups to develop

1 a patient notification system.

2 I'd like to conclude with the fact that NHF
3 requests that the FDA provide a clear, unequivocal
4 direction and guideline and leadership to the manufacturers
5 regarding the establishment and enforcement of a primary
6 notification system for implementation in six months with a
7 progress report in three months.

8 We will look forward to our continued role with
9 members of industry, the FDA, and the CDC to assist in the
10 formation of this system so that it will be sensitive to
11 the needs of our community as well as other chronic users
12 of blood derivatives.

13 Time is of the essence for this community as
14 well as many others. Each time a recall takes place and
15 it's an ineffective recall, we're left with a person who is
16 putting something into their veins that a whole lot of
17 professionals know they shouldn't be.

18 We can make systems work. It's not that
19 difficult.

20 Thank you.

21 DR. SWISHER: Questions for Mr. Colburn? Are
22 there questions?

23 (No response.)

24 DR. SWISHER: Thank you very much.

1 This concludes the open public hearing on this
2 topic. I must say we've gotten some very important input.

3 I'm now going to open the topic for discussion
4 by the committee. We have not designated a specific lead
5 discussant for this topic, but who would like to open the
6 discussion?

7 I'd like to point out that we're not being
8 asked for specific recommendations. Indeed, the primary
9 output of this part of the discussion by the committee will
10 be the sense of guidance and direction that the FDA staff
11 obtains from our discussion. If you have specific
12 recommendations, I think it would be very appropriate to
13 make those.

14 Who would like to open up?

15 REV. LITTLE: I'd like to refer back to
16 something that the presenter from the American Red Cross
17 said, and that's the statement, without federal regulations
18 that mandate the permanent recording, et cetera, it is
19 doubtful that current practices will ever guarantee
20 complete notification. It's something that I've been
21 hearing over and over not only from consumer groups but it
22 seems also from manufacturers.

23 I keep thinking of Saul Olinsky's distinction
24 between the world as it is and the world as it ought to be.

1 I think in the world as it ought to be, these things will
2 happen because they're the right thing to do, but the
3 reality is what's in that sentence.

4 I feel that unless there is something that is
5 clear, not a recommendation, but a requirement, that it's
6 really not going to happen. I can't even believe I find
7 myself saying this, but I think there have to be tight
8 requirements and regulation, otherwise it's just not going
9 to happen.

10 DR. SWISHER: Comment, Corey?

11 MR. DUBIN: I mean, I almost don't know how to
12 say this, so I'll just say it really directly. Given all
13 that happened and the level of money being made in the
14 blood products industry, it boggles me to have a
15 representative of, in essence, the four of you stand up
16 there and tells us you can't really afford the bill to get
17 notification all the way to the patients when the products
18 are ultimately products you're producing when there's a
19 problem.

20 Chrysler gets all the way down to my Cherokee
21 when there was a problem with the air bag. Notification
22 came to my front door and, in fact, Chrysler called me on
23 the telephone to boot. I wouldn't expect that from an auto
24 maker. I would expect it from fractionators.

1 I do think if we're talking about an investment
2 to establish a network, they should be able to weigh in on
3 it and get it done. It's absurd to me, when I know what
4 the structure is and what the level of money being pulled
5 in off plasma derivatives is, the level being made. I
6 don't know how else to say it.

7 DR. SWISHER: Carol?

8 DR. KASPER: I think it's not altogether a
9 matter of money, but a matter of systems.

10 I feel that I agree with Rev. Little, that
11 unfortunately one needs to have a mandatory recording of
12 lot numbers by the person dispensing, just as one has a
13 recording of the number of the blood bag when one gives a
14 unit of whole blood. There has to be someplace a recording
15 of the number so you can trace, and it has to be mandated
16 so that big, busy places don't just not bother or small,
17 sloppy places don't just not bother.

18 I think that the difference between the
19 notifications that we get when there's something the matter
20 with the car that we just bought is that the manufacturers
21 have no difficulty getting my name and address to tell me
22 to bring in my Olds that I just got because it's got a
23 faulty part. They have my name and address because I
24 bought it, whereas the manufacturers of Omniclot don't have

1 the names and addresses of persons with hemophilia. There
2 is no such thing as a national registry of persons with
3 hemophilia or persons with immune deficiency with names and
4 addresses, but it could be voluntary.

5 On the other hand, do you want your name and
6 address on a computer list and how many people with
7 hemophilia have said I don't want my name on a list
8 someplace which has been the problem with registries. We
9 had one in California for a while for hemophilia. It was
10 incomplete because of people who didn't want to be on it,
11 but we haven't even tried lately because there has been a
12 lot of resistance to such a thing.

13 There could be a voluntary list, but that might
14 leave off the people who need a personal notification, and
15 personally, in spite of the elegance of this telephone
16 system, I think the final notification is going to wind up
17 being personal in order to be effective.

18 DR. HOLLINGER: Carol, how would you do that?
19 If people don't want to do it voluntarily, how would you
20 notify them personally?

21 DR. KASPER: I think there are a lot of people
22 who don't want to be on some kind of nationwide
23 computerized name and address list, I have hemophilia.
24 There are a lot of them who have shrunk from that because I

1 have a brother with von Willebrand's. He's old enough now
2 and retired. None of his employers ever knew it, and he
3 would never have been employed in any of the jobs he had if
4 they knew it, nor would he have been insured. So, for all
5 those reasons, people don't want to be known.

6 So, people don't want to be on a registry.
7 They could be on a volunteer basis. So, I think the way it
8 might work -- certainly if a patient for whom I have
9 prescribed Omniclot or whatever, if I am notified that this
10 is a recalled lot, then I think it's my obligation as a
11 treating physician to notify that patient in such a way
12 that I know he got the message and I got a feedback, yes, I
13 understand this, and I have a chance to answer questions.

14 Now, whether it's the physician's
15 responsibility or the pharmacy's responsibility, it might
16 be a double-layer thing for the gammaglobulin or the
17 whatever. The pharmacy delivering the product for home
18 care might have to tell the patient and tell me. I don't
19 know exactly how to design this system.

20 I think it's safer to have belt and suspenders
21 because I've known of instances in the early days of HIV
22 and lookback with whole blood, particularly with whole
23 blood, where the physician prescribing the whole blood
24 refused to notify the recipient. It was voluntary. They

1 said, I don't want to let this patient know that I'm the
2 one that prescribed the blood that was HIV positive. So, I
3 think there needs to be a sort of belt and suspenders
4 system, the pharmacist and the prescribing doctor.

5 DR. SWISHER: Dr. Piliavin?

6 DR. PILIAVIN: I agree with both Violet and
7 Carol to some extent.

8 Obviously we haven't had very long to think
9 about this, but this is a human systems problem. It's not
10 a technical or medical problem. I think there does have to
11 be some sort of requirement first that the lot numbers be
12 written down. We have got to know who's got the Cherokee
13 basically. And it is easy to know who's got the Cherokee
14 because you paid good money for it and it's a big item and
15 there are laws that say that the manufacturers must inform
16 people about recalls and that they must pay for it.

17 So, the question is how to get close to that
18 system. The first step clearly is knowing who got the
19 product.

20 Then the question of course is, well, how do
21 you get to the people who got the product? Well, I would
22 make a second requirement that the organization that sold
23 the product, the pharmacy, the home care people, whoever
24 was the person who took the money from the consumer, should

1 be the one with the responsibility to inform them and
2 penalties if they do not. One knows enough about human
3 behavior that one does the things that are going to cost
4 the most if you don't or get you the most if you do.
5 Altruism only goes so far, and most people are not in
6 business for altruism. So, I'm not saying they're in it to
7 hurt people intentionally, but there has to be some sort of
8 incentive to get them to do what will cost them money and
9 time and effort. But it seems to me that it's the
10 organizations that are making the money from the product
11 who ought to be responsible for getting the information to
12 the patient.

13 Now, I also like that phone system. The phone
14 system is really cool. My son is in computer systems and I
15 think he would really love to hear about that. But the
16 place I could see that being used here would be with a list
17 of the people who dispense the product rather than the end
18 user, if you wanted to get to people quickly.

19 In terms of the cost of the system -- see, I'm
20 building a whole system here as I talk -- I think the cost
21 of the phoning of those people might be -- because there
22 will be costs all along. The cost of phoning them might be
23 on the manufacturer whose product is problematic. Then the
24 cost of informing the ultimate consumer would be on the

1 head of the person who sold it to them, who also presumably
2 made a profit. That would be my system.

3 DR. SWISHER: Corey, I think you were next.

4 MR. DUBIN: I'll let Ben go.

5 MR. CHENG: I just wanted to bring up one sort
6 of similarity that we're going through with HIV drugs right
7 now. I realize we're talking about a whole range of
8 products here.

9 The Merck protease inhibitor -- when the drug
10 got approved, they did not have enough drug to go around
11 for everybody. So, they hired a specific pharmacy -- and
12 you can probably do this with a clinical research
13 organization -- who handled the distribution of the drug so
14 that they ensured that whoever got on drug were guaranteed
15 to have access to the drug for as long as they wanted it,
16 so that there would not be any lag time when they would not
17 be on drug because of drug resistance and everything else
18 that develops.

19 So, perhaps following a model like that, having
20 a CRO who handles a particular product, every time IVIG or
21 whatever gets prescribed, dial an 800 number, and the CRO
22 gets the lot number for that particular patient. You'd
23 just have a patient ID number and not a name. The CRO
24 handles the database. So, if there is a recall or

1 whatever, the CRO can then contact physician and patient.

2 DR. LEITMAN: I'd like to comment on the
3 telephone notification. For a very specific reason, I'm
4 not sure that's the best way to handle this in that the
5 message that comes across is so different depending upon
6 what's risky in the product that was transfused. As in
7 1994, I think there was a very real recall of, I think it
8 was, Baxter IVIG for hepatitis C transmission involving
9 several hundred individuals in the U.S. and some in Europe.
10 That's a message that has a very specific counseling set of
11 messages that go with it.

12 But the message that you got a product that was
13 derived from someone who has one family member who died of
14 Creutzfeldt Jakob's disease or two family members where the
15 risk is so remote as to be impossible to quantify it, and
16 maybe it's not a risk at all, I don't think you can get
17 that across to a patient adequately by telephone
18 notification. In some cases it's a positive antibody
19 result that's unconfirmed and it breached FDA criteria for
20 product release, but everyone know there's no real risk.

21 So, the risk involved in all of these
22 contaminated or problematic units varies from very real to
23 nonexistent, and the telephone message is not the way to
24 get that across.

1 I agree absolutely with what Dr. Kasper said.
2 There's a physician involved in prescribing all these
3 drugs. They're prescription medications, and the
4 pharmacies have the names. I believe they're supposed to
5 have -- perhaps someone can correct me -- the phone numbers
6 of the physicians that write prescriptions for patients.
7 So, if the database could include the physician and the
8 physician's number, I think that's where the responsibility
9 should lie.

10 DR. NELSON: This is really a knotty problem.
11 If you look at, as a physician, how well have physicians
12 complied with certain laws like reporting infectious
13 diseases and how well do they communicate all kinds of
14 things to their patients, their wives, and all kinds of
15 things, it's really a difficult problem. But they're going
16 to have to be involved because they are I think legally
17 responsible for this product that they prescribe to a
18 patient.

19 It's not going to be easy because some
20 physicians will make a judgment that's erroneous, that
21 well, hepatitis C isn't a big deal. What will we treat it
22 with? So, I don't have to notify this person. Some will
23 say, Creutzfeldt Jakob, gee, I'm going to tell all my
24 patients to do serial 7's before they go to bed at night

1 just to make sure that there's not something going wrong
2 there. It's not an easy problem.

3 DR. SWISHER: Of course, one very interesting
4 possibility is that the physician is an endangered species.
5 Today we have health care providers. More and more of the
6 functions of the --

7 DR. NELSON: I'm afraid to admit this but I
8 think they might do better because I think that they might
9 be less likely to make their own interpretation. They
10 might follow an algorithm better than a physician would I
11 suspect. Their lawyers would tell them which algorithm to
12 follow and they probably would follow it.

13 DR. SWISHER: Dr. Linden?

14 DR. LINDEN: Yes. I'd like to just reiterate
15 the observation that the weak link here that needs to be
16 addressed is the end user facility or physician, whoever is
17 dispensing the product. In New York, which is one of the
18 most heavily regulated areas of the health care industry,
19 several years ago we tried actually to impose a requirement
20 that for plasma derivatives the dispensing entity would
21 need to record in a logbook form the lot number and so
22 forth so that a recall would be facilitated. And we got
23 tremendous negative letters during the public comment
24 period primarily from pharmacists who said this isn't

1 necessary, it's too much trouble. When we sort of
2 questioned that, since we were primarily talking about
3 albumin and immune globulins, they basically said these
4 products are never recalled. Well, certainly we have seen
5 recently that that is not the case, but that was the mind
6 set that we found.

7 We actually wound up with a compromise that for
8 factor concentrates, it would be mandated and the rest we
9 were not able to get that through even in our state.

10 I think that the mind set just needs to be
11 changed, and I'm not sure how that can be accomplished.
12 You can mandate, but I'm not sure what compliance would be
13 and I'm not sure whether FDA has the authority to do that.
14 These are all good questions, but that is really where the
15 problem is. There is a mind set that it's not necessary to
16 keep a log book record. Otherwise you're relying on the
17 patients trying to actively seek out information which may
18 mean for the patients with hemophilia, an educated,
19 motivated group, that's possible or the immune deficiency
20 group, but for patients who got albumin on a one-time
21 basis, you would never capture that population.

22 DR. SWISHER: Dr. Piliavin dealt with the
23 question of how to change the mind set, and it seemed to me
24 that there was some combination of carrots and sticks

1 there.

2 DR. PILIAVIN: Yes. But Jeanne is quite right.
3 Unless the FDA has the carrots and the sticks, it's not
4 going to work. There has to be somebody who has the power
5 to say you have to do this and follow it up.

6 DR. SWISHER: Joel?

7 DR. VERTER: I find the whole discussion
8 fascinating. I was trying to think about why this was
9 brought before the committee. I think we're an advisory
10 committee, and I dare say that not a one of us doesn't
11 advise the FDA to work with the manufacturer, the
12 Hemophilia Foundation, and all the other worthy
13 organizations we heard from today to find some system to
14 solve the problem.

15 I also dare say that it's probably going to be
16 impossible to find anything near a perfect system when
17 you're dealing with a human cohort. I could sit here
18 probably and we could all sit here for hours trying to
19 design systems, and every time one of us puts something up,
20 you bring something else, especially as someone mentioned
21 earlier, the unfortunate legal system in this country.

22 If I was a doctor and someone said to me,
23 you're now giving IVIG to your patients. Anytime I call
24 you, you better contact every one of your patients. I

1 might think about referring IVIG patients to someone else
2 because of the cost, not only the cost of my time but the
3 potential costs from the legal system if someone was out of
4 town and I couldn't get a hold of them.

5 So, I think this is a monumental problem. On
6 the other hand, I agree with everything that has been said.
7 Someone needs to sit down and out of good will come up with
8 some way that 90 plus percent of the system will work,
9 recognizing that it won't work in some other cases, that a
10 good effort was made and no one is going to lose his shirt
11 because that extra 10 percent wasn't notified given that
12 good will was tried.

13 DR. SWISHER: It may be an example of where the
14 very best is an enemy of the good.

15 Jerry?

16 DR. HOLMBERG: Yes. I just want to make a
17 comment that I think maybe the answer was 19 years ago when
18 the comment was in the preamble and just enforcing that of
19 the 1978 preamble to the drug labeling and tracking.

20 I can tell you anecdotal stories also and I
21 think where I became acutely aware of this was about 1986
22 doing a lookback with heat-treated factor VIII and found
23 out that pharmacies don't track lot numbers. Here we are.
24 1978 was -- if it was in the preamble, it's not being

1 enforced. We've gone through a real hysterical period of
2 time with the retroviruses.

3 So, I think that the message that we have given
4 today is loud and clear to the FDA that there needs to be
5 enforcement of the intent of those regs.

6 MS. PIERCE: It's also vital that there is very
7 clear information from the manufacturers and the FDA
8 concerning an episode through down to the treating
9 physician and the patient so that you get clear, precise
10 information -- that's what's available -- in order to help
11 your patient make a decision. I think that's vital because
12 you don't want the physician sitting there getting a phone
13 call saying this is going on and then that's all they get
14 also. There needs to be I think very clear, concise
15 communication.

16 DR. KHABBAZ: I'd like to add I think I'm very
17 glad to see the discussion we've had today and the
18 presentations. I'd remind us all that that's not the first
19 time we've discussed this. In fact, a couple of meetings
20 ago the question of notification and patient notification
21 came up. At the time there was quite a bit of skepticism
22 about who and what and the need. I think we've made
23 progress I think through the meeting that the FDA held and
24 the airing of the issues and industry going back and

1 researching. I think we've made progress, and I think I
2 sense an agreement as to the need to close the gap and
3 reach patients and mechanisms to do that. I tend to agree
4 that the physician and pharmacist involvement is important.
5 So, I think we're on the right track. We just need to
6 close the gap.

7 DR. AUGUST: On the basis of some recent
8 experience I had with my own hospital pharmacy wherein they
9 reported to me that they did not keep lot numbers of a
10 certain product that I was interested in simply because the
11 FDA didn't require it or it wasn't mandated, I think that
12 it won't happen unless the FDA says it has to happen.

13 The other comment I would make is that many of
14 the patients who are at risk are those who are receiving a
15 product, be it IV gammaglobulin or factor VIII, repeatedly
16 over time, and they obviously are individuals with chronic
17 illnesses who come into I think hopefully fairly good and
18 intimate relationships with one physician or a small group
19 of physicians. I would be more sanguine than many of us,
20 that in this context, patient counseling and giving of
21 information about this would happen better rather than
22 worse.

23 Now, that may or may not be true, but certainly
24 I think it's a situation where, on the surface of it in any

1 case, it favors the likelihood that information about
2 tainted products and recalls and so forth would be more
3 likely to be transmitted simply because physicians feel
4 more comfortable talking to those sorts of patients than
5 physicians having lesser contact with other groups of
6 patients.

7 DR. SWISHER: As both the authority and
8 responsibility in the health care system has become more of
9 a "team" operation, I think the interesting thing is that
10 the physician feels less and less responsibility for this
11 kind of communication. I think that's one of the current
12 disasters of medical practice. As a practicing physician
13 in the past, I would be incensed if I were not in that link
14 of communication in dealing with my patient for which I
15 have in my own sense a global responsibility, including
16 such things as dealing with the issue of health care
17 reimbursement and insurance and all of these other matters.
18 But today I think the way things are going in the practice
19 of medicine, as I understand it from reflections for
20 example, from my son, there is less and less incentive,
21 less and less tradition of the physician fulfilling this
22 kind of a role. I must say I personally regret that very
23 much.

24 Paul?

1 DR. NESS: I was just thinking that perhaps
2 there's a lesson we can learn here via the lookback
3 experience which we've all been in transfusion services and
4 hospitals and donor centers going through. For a number of
5 years, it was viewed as largely voluntary, but recently the
6 Medicare reimbursement regulations are now saying it's no
7 longer voluntary and it's actually a condition of law that
8 when lookbacks are given to the transfusion service that
9 the patient be notified or the treating physician be
10 notified, and there's a whole set of documents that have
11 been issued to the public saying what has to be done. If
12 this is something that needs a systematic approach, that
13 might be an example we could use here.

14 MS. PIERCE: Dr. Swisher, if it's okay, Mr.
15 Colburn has an additional comment which I think would be
16 helpful to the committee discussion, if that's all right.

17 MR. COLBURN: Thank you. I appreciate it. I'm
18 going to twist my hats around and I'm going to talk to you
19 as a president and CEO of a hemophilia home care delivery
20 company.

21 This is a box of product. As you know, I have
22 hemophilia. I carry it with me. How many here sitting
23 around the table have ever seen it, a box of it?

24 (A show of hands.)

1 MR. COLBURN: Good. That's good.

2 On the back of it here, as is on every
3 particular brand product, it says: "Caution: U.S. federal
4 law prohibits dispensing without prescription." If I was
5 careless enough to throw this box away, on the back of the
6 little bottle here of the medication it says: "Caution."
7 My glasses aren't good enough. It just says the same thing
8 that I just read you.

9 I think the point that I want to make here is
10 that this system that everyone is so concerned about
11 setting up exists. What has happened over the years is it
12 has been changed, moved from one department to another.

13 Basically what you have here, when you utilize
14 terms like "dispensed without a prescription," there is not
15 a state in this Union that I'm aware of that a pharmacist
16 is not required to keep a log of every prescription filled
17 with the lot number when dispensed and to keep those
18 records for three years. Somewhere we've gotten into a
19 group of folks who dispense without keeping records. We
20 already have the laws.

21 I guess my challenge would be how do we make
22 what we have work. So, I hope there is some clarification
23 here because there is a system in place that works pretty
24 fairly well when it's utilized.

1 My company deals only in hemophilia and
2 hemophilia-related products. We don't have many women with
3 bleeding disorders. I would say that probably twice every
4 year I get this large notification of a product withdrawal
5 from a birth control pill. We don't carry any, never have,
6 never even dealt with the manufacturer. In fact, actually
7 we get a whole series of product recalls on products that
8 we do not carry. The reason that we get them is we are a
9 registered pharmacy, and if this can't go out without a
10 prescription, if this can't be dispensed without some
11 pharmacist putting his initials next to the log or whatever
12 the system is in any given state -- but there is a system,
13 trust me -- then that needs to be fixed so that that works
14 because there is a way for it to work.

15 When you get that, the reason that you are
16 compelled when you own a company to take a look at that
17 recall notice was explained a little bit earlier. I think
18 you mentioned it, Dr. Nelson, and that's, yes, I have this
19 other non-pharmacist consultant that works with me and
20 charges me about \$200 an hour, and he's called an attorney.
21 He says, if you get a recall notice and you don't notify
22 your clients -- well, I won't tell you what he says.
23 Actually he takes a lot longer to say what I just said. I
24 never understood that.

1 I guess what I'm trying to say is that there
2 are systems that exist for this today. My challenge would
3 be how can we make those systems work because they're
4 there.

5 DR. KASPER: Don, are those state laws or
6 federal laws? I think what we're asking for is there may
7 be states that don't have the laws, there may be states
8 that don't push it. If the FDA also has a regulation, it's
9 federal, so you can say the Feds are going to get you, the
10 states are going to get you.

11 MR. COLBURN: Well, on the back here it says,
12 "U.S. federal law prohibits dispensing without a
13 prescription," which then, as soon as the prescription is
14 written, technically all the laws that I'm familiar with
15 for pharmacies, Massachusetts, Connecticut, Illinois,
16 California, require that that dispensing physician or
17 pharmacist has to keep the same paperwork, which again goes
18 back to that same log. By the way, as most of us are
19 probably are, most docs don't. They just hand something
20 out if they have it, and they don't keep a record of it.

21 But my question is, how many folks are really
22 handing out biologics in their practice of medicine on a
23 daily basis unless they're set up with something that
24 should have the ability to record the lot numbers?

1 DR. LINDEN: Can I just throw another 2 cents
2 just to remind people we're not talking only about blood
3 banks and pharmacies here. We have a larger problem in
4 that a lot of products are given in bulk to other usually
5 physicians in the OR or the ER or maybe it's a hemophilia
6 treatment center or whatever, so that even if we could get
7 at the pharmacies per se keeping all of their records,
8 their disposition log is going to say X number of bottles
9 of albumin went to the OR or whatever. Then to actually
10 get those sites, you're talking a really tough road here.

11 MR. COLBURN: I will agree that there's a weak
12 link in the wholesale laws of most states as well as
13 federally, but many of them come back to a pharmacy.

14 DR. SWISHER: Kenrad?

15 DR. NELSON: I personally think there is a need
16 for the FDA to do something, even though the federal law
17 says you can't dispense it without a prescription from a
18 physician. Even though the 1978 law may cover this,
19 clearly it ain't happening. The reason laws are made is to
20 correct a problem. It's pretty clear I think we're all
21 convinced that there's a problem here. I think the FDA
22 needs to explicitly make a regulation or law or whatever
23 requiring whoever dispenses to keep for X number of years
24 the lot number, and if that's found not to be done, then

1 there's a penalty. Then the manufacturer and the physician
2 and everybody else, if the lot number is there and a recall
3 is issued -- then things will fall into place.

4 But currently the law is a little bit vague and
5 interpreted differently by lawyers for different clients or
6 different people. Clearly if the intent of the 1978 law is
7 not being followed, I think it needs to be fixed. I can't
8 speak for the committee, but that's kind of the way I sum
9 up what has been presented.

10 DR. SWISHER: Is it really an issue then of the
11 law or is it an issue of compliance?

12 DR. NELSON: Well, I don't know what it is, but
13 if it's only an issue of compliance because two lawyers are
14 interpreting it differently, then it needs to be stated in
15 such a way that every lawyer will interpret it in the same
16 way.

17 (Laughter.)

18 DR. SWISHER: With that, we can say nirvana
19 would have arrived.

20 (Laughter.)

21 DR. PILIAVIN: Joel and I were sitting here
22 having a side conversation. No, I'm not designing it. He
23 pointed out that somehow Federal Express has no problem in
24 tracking a package from the person who sent it to the

1 person who gets it. They have those little bar codes and
2 trackers. If you could set up a system like that, then it
3 could get recorded right back at the manufacturer, if there
4 was some way of tracking it to the point of the person who
5 took it home. The technology is there.

6 DR. SWISHER: And for \$1.25 they will confirm
7 that they delivered it by sending you back that same little
8 sticker.

9 DR. KASPER: If we're going to describe
10 methods, I saw something lovely in Singapore. They had all
11 these bottles of gammaglobulin and concentrate and so on.
12 They also had a little "pull off the sticker gummed-back"
13 piece of paper that identified the lot number. You put it
14 on the patient's chart. Nobody has to transcribe anything
15 and you avoid errors or crummy handwriting. It was a
16 really neat deal.

17 DR. SWISHER: It could be even machine-
18 readable.

19 Well, I think we could continue on this topic
20 well beyond dinner, which is an issue for those of us
21 staying in this hotel as to where we're going to go. I
22 think we need a little extra time to think about it.

23 I'll ask Jay if his voluminous notetaking has
24 helped, has been neutral, or has actually made the problem

1 worse.

2 DR. EPSTEIN: I think we appreciate all the
3 comments.

4 DR. SWISHER: There's a diplomat.

5 We will adjourn until tomorrow morning.

6 Tomorrow morning the single topic, at 8:30 I'll point out,
7 is to receive the report of the site visit for the
8 Laboratory for Plasma Derivatives. We will see you all
9 then.

10 (Whereupon, at 5:12 p.m., the committee was
11 recessed, to reconvene at 8:30 a.m., Friday, March 14,
12 1997.)

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