

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21

VOLUME 1

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Thirty-fourth Meeting

_____ /

The above-mentioned meeting of the Advisory Committee on Blood Safety and Availability was held on Thursday, May 29, 2008, commencing at 8:35 a.m., at The Hilton Rockville Hotel, 1750 Rockville Pike, Rockville, Maryland 20852, before Robert A. Shocket, a Notary Public.

REPORTED BY: Robert A. Shocket

1 APPEARANCES :

2

3 PARTICIPANTS/MEMBERS :

4

5 ARTHUR W. BRACEY, M.D., Chairman

6 JERRY A. HOLMBERG, Ph.D., Executive Secretary

7 RICHARD J. BENJAMIN, MBChB, Ph.D.

8 ANN MARIE BENZINGER

9 WILLIAM DUFFELL, JR., Ph.D.

10 JAY S. EPSTEIN, M.D.

11 ANNE MARIE FINLEY

12 MICHAEL G. ISON, M.D., M.S.

13 HARVEY KLEIN, M.D.

14 DR. FERNANDA LESSA

15 ILEANA LOPEZ-PLAZA, M.D.

16 KLAUS NETHER

17 GREGORY J. POMPER, M.D.

18 GLENN RAMSEY, M.D.

19 LINDA THOMAS-WADE

20 DARRELL J. TRIULZI, M.D.

21 (Appearances Continued on the Next Page)

1 APPEARANCES CONTINUED:

2

3 GUEST SPEAKERS/PRESENTERS:

4

5 ABU ALAYASH, PH.D.

6 TERESA AYRES

7 RICHARD BENJAMIN, M.D., Ph.D.

8 LAURENCE CORASH, M.D.

9 LARRY DUMONT, M.B.A., Ph.D.

10 LESLIE HOLNESS, M.D.

11 MICHAEL JACOBS, M.D., Ph.D.

12 LAURENCE LANDOW, M.D.

13 WILLIAM G. MURPHY, M.D.

14 ELIZABETH ORTIZ-RIOS, M.D., M.P.H.

15 RUTH SOLOMON, M.D.

16 DONALD WRIGHT, M.D., M.P.H.

17 PUBLIC PARTICIPANTS:

18

19 DR. MICHAEL BUSCH

20 DAVID CAVANAUGH

21 MICHAEL FITZPATRICK

1 P-R-O-C-E-E-D-I-N-G-S

2 DR. BRACEY: I would like to call the
3 meeting to order. Good morning. My name is Dr. Bracey
4 and welcome to the 34th meeting of the HHS Advisory
5 Committee on Blood Safety and Availability. We have
6 several new members joining the committee and I would
7 like to personally thank them for admitting the time
8 and dedication to our work and public service. Over
9 the years this Committee along with those in the field
10 has engaged in successful efforts to markedly improve
11 the safety of blood and its derivatives. More recently
12 tissue transplantation has been added to our sphere of
13 action. While transfusion associated viral disease,
14 particularly HIV and HCV is largely contained, much
15 work remains to be done to achieve our goal of
16 maximizing the blood and tissue safety.

17 This morning we will hear reports from
18 various matters important to our charges including a
19 recent conference on hemoglobin-based, oxygen-based
20 carriers, vascularized allografts and adverse event
21 reports, including fatalities reported to the FDA. In

1 the afternoon we will hear a series of updates on
2 bacterial contamination platelets. Tomorrow we will
3 review an evolving area of study, the effect of blood
4 surge on patient outcomes. There's no doubt that blood
5 is a life-saving fluid for those with severe hemorrhage
6 and oxygen-delivering deficits; however, many
7 uncertainties exist regarding the balance of benefit
8 and risk of blood transfusion for many patients in
9 current medical practice. I look forward to your
10 thoughts on these important issues. We are at a point
11 where we are going to have the roll call so I will wait
12 for the Executive Secretary to return for the roll
13 call.

14 DR. HOLMBERG: Good morning. I'm already
15 in violation of the one of the things I was going to
16 mention, and as soon as I finish with the roll call I
17 will silence my cell phone. But I would ask that
18 everyone else silence their cell phones so that it's
19 not a distraction throughout the meeting. I have been
20 in several meetings where if a cell phone went off they
21 fine them a certain amount money and that went into the

1 research scholarship fund but I don't think as a
2 government agency we can do that.

3 At any rate, it's a pleasure to have you
4 here. I have received notification that several people
5 will be either late getting here this morning or they
6 are currently jammed up in traffic, which I personally
7 experienced last night, two and a half hours trying to
8 get home last night. So, at any rate, that's what we
9 have to deal with here in the Washington, D.C. area.
10 If I can just have you respond and we will recognize
11 those people, as other people as they come into the
12 room. Dr. Benjamin?

13 DR. BENJAMIN: Present.

14 DR. HOLMBERG: Ms. Benzinger?

15 Ms. Birkofer? Dr. Bloche? Dr. Bracey?

16 DR. BRACEY: Present.

17 DR. HOLMBERG: Dr. Duffell?

18 DR. DUFFELL: Present.

19 DR. HOLMBERG: Ms. Finley? Dr. Haley is
20 not here. He's a new member and we will get around to
21 introducing the new members in just a minute and also

1 having a swearing in ceremony but Dr. Haley was not
2 able to join us this morning. Another new member is
3 Dr. Ison.

4 DR. ISON: Here.

5 DR. HOLMBERG: Dr. Kouides? Dr. Lopez?

6 DR. LOPEZ-PLAZA: Here.

7 DR. HOLMBERG: Mr. Matyas will be late.

8 Klaus Nether?

9 MR. NETHER: Present.

10 DR. HOLMBERG: Klaus is another new member.

11 Dr. Pierce is unable to join us today for medical

12 reasons. And Dr. Ramsey?

13 DR. RAMSEY: Present. Good morning,

14 everyone.

15 DR. HOLMBERG: Ms. Thomas-Wade?

16 MS. THOMAS-WADE: Present.

17 DR. HOLMBERG: Dr. Triulzi?

18 DR. TRIULZI: Here.

19 DR. HOLMBERG: Okay. And Dr. Pomper is

20 here?

21 DR. POMPER: Present.

1 DR. HOLMBERG: At my age, my eyesight has
2 just sort of went right over the piece there after I
3 recognized Dr. Pierce but Dr. Pomper is also a new
4 Committee member, coming to us from Wake Forest. For
5 the nonvoting members, Dr. Kuehnert is not able to
6 attend today but Dr. Leesa will be filling in for him.
7 Dr. Epstein?

8 DR. EPSTEIN: Here.

9 DR. HOLMBERG: Dr. Klein?

10 DR. KLEIN: Here.

11 DR. HOLMBERG: Commander Libby is not able
12 to join us today but we have Colonel Lopatka. Dr.
13 Bowman is not able to join us today. He will be here
14 tomorrow. And Dr. Solomon?

15 DR. SOLOMON: Here.

16 DR. HOLMBERG: And Dr. Ortiz-Rios?

17 DR. ORTIZ-RIOS: Here. Here.

18 DR. HOLMBERG: Okay. I think that there is
19 a seat up here in the front, if you want to join us up
20 here, Dr. Rios? And, Ms. Benzinger is with us here.
21 Thank you. Okay. I will count up the members in a few

1 minutes to make sure that we do have a quorum and I do
2 want to remind every one of the Committee members that
3 we do require to have a quorum of the voting members.
4 The government representatives are not part of that
5 quorum and the government representatives are not
6 voting members.

7 Tomorrow as we draw close to 5 o'clock I
8 would appreciate people trying to be remindful of the
9 quorum, the need for a quorum so that if there are
10 recommendations that they can be voted on with the
11 quorum in place.

12 I also want to just remind a few of you of
13 different administrative logistic situations here in
14 the building. I hope this meeting solely is amenable
15 to everyone. We have met here before in various
16 government agencies and they have recently remodeled
17 and I think that this is going to a very good meeting
18 location. The restrooms are outside the door of the
19 room here. Also I would like to direct your attention
20 to the exit signs and during the breaks please locate
21 the nearest emergency exit.

1 I also want to just explain a little bit
2 about the conflict of interest. The Committee, for
3 those that are new to the Committee, I would like to
4 briefly go over a little bit about the historical
5 aspects of the Committee being formed. The Committee
6 was actually formed out of the result of an IOM report
7 and the Secretary of Health and Human Services deciding
8 that there needed to be an internal and external
9 committee, advisory committee to the Secretary. And,
10 because of the internal task force that followed up on
11 the recommendations of the IOM report, they recognized
12 that there would be conflict of interest with the
13 various people that were at the table, to talk about
14 the policy issues on transfusion, blood safety and
15 availability.

16 With that in mind, all the special
17 government employees are required to fill out annually
18 a form that discloses all the financial aspects of
19 potential conflict of interest. If there are conflict
20 of interest, these are evaluated and taken through
21 legal counsel to see whether a waiver is needed. We do

1 have various individuals on the Committee that do have
2 waivers to the conflict of interest. And, I would just
3 ask that if after during the discussions we have
4 anything that comes up that you would feel that your
5 other involvements may be perceived as a conflict of
6 interest, I would appreciate you disclosing that at the
7 time so that everyone has full disclosure. I would ask
8 the public to do the same, that if you ask for time at
9 the microphone that you recognize who you are, and the
10 organization that you represent, any potential conflict
11 of interest.

12 With that, I think that that's all that
13 needs to be said on those matters. I've already
14 mentioned about the cell phones and I will silence mine
15 in just a second. But I am very pleased to have with
16 us today Dr. Don Wright. Dr. Wright has been with the
17 Office of Home Health and Science since December and he
18 is the Principal Deputy Assistant Secretary for Health.
19 And, so, with that I'll turn it over to Dr. Wright.

20 DR. WRIGHT: Good morning. It truly is my
21 pleasure to be with you this morning. I believe this

1 is the second Blood Safety and Availability Advisory
2 Council meeting that I have been able to attend. I so
3 appreciate the expertise that comes from this group,
4 the recommendations that come from this group. I did
5 want to pass on words of welcome, not only for myself
6 as the Principal Deputy Assistant Secretary but on
7 behalf of Dr. Garcia, who is our new Assistant
8 Secretary for Health. He was Senate-confirmed a couple
9 of months back and has been in that capacity for a
10 couple of months now. In addition, Secretary Levitt is
11 very appreciative of this Committee and the tremendous
12 value that comes from our advisory committees on a
13 whole host of topics.

14 I have had the opportunity to review so
15 many of your biographical sketches and I'm just amazed
16 at not only this advisory committee but all our
17 advisory committees and the amount of expertise that we
18 really do have access to here at HHS. We had an
19 opportunity recently to look at, go back historically
20 and look at this particular advisory committee and the
21 various comments, recommendations, opinions that have

1 been issued by this particular Committee and actually
2 what happened with them.

3 And I think we were very pleasantly
4 surprised and pleased to see that a very large number
5 of the recommendations that you have made, the comments
6 that you have made have actually been translated into
7 public policy and what we do at the department of HHS.
8 So, again, thank you so much for your time, your
9 expertise, your willingness to serve. There is a very
10 good product at the end of the day because of the time
11 and commitment that you make to this particular
12 Committee.

13 I understand that this is the first
14 Committee meeting that we have had since the Secretary
15 had a reappointment and new appointments and we have
16 numerous or two new reappointments. Dr. Bracey,
17 sitting here to my right, we were thrilled that he has
18 agreed to stay at the helm for another year and serve
19 as Chair of this Committee. A great deal of good work
20 has occurred under his leadership and we anticipate
21 that that will continue in the future.

1 Dr. Pierce also has been reappointed to
2 this Committee. He represents the Hemophilia Committee
3 but due to a medical concern was unable to join us
4 today. As Dr. Holmberg mentioned, we have three new
5 appointments, Dr. Haley, who cannot be here with us
6 today, Dr. Pomper, who is from Wake Forest University,
7 and we're very pleased to have him join with his
8 expertise, and then Dr. Ison from Northwestern
9 University; they will be our new appointments.

10 In addition to that, the Secretary has made
11 two appointments to our representative categories.
12 Clearly the American Red Cross is a huge stakeholder
13 when we talk about blood safety and availability. And
14 Dr. Benjamin has been appointed to that position to
15 represent the American Red Cross. And in addition to
16 that, Klaus Nether from the Joint Commission, someone
17 that, an organization that is heavily involved in so
18 many hospital issues has been appointed to the
19 representative category as well.

20 I have a few more comments that I want to
21 make about the agenda and talk to you about what are

1 some of the concerns that the department, HHS, has as
2 it relates to blood safety and availability and what we
3 really want to hear from you, what we want you to weigh
4 in on and share your opinions and any recommendations
5 that you have. But before we actually get to that part
6 of the opening, I really do need to make this legit,
7 so, if you have been reappointed or are you're a new
8 appointee, we need to have a swearing-in ceremony over
9 to the right here. So even if you're being
10 reappointed, we need to take care of this housekeeping.

11 Put your right hand on the Bible and repeat
12 after me. "I -- and your name -- do solemnly swear
13 that I will support and defend the Constitution of the
14 United States against all enemies, foreign and
15 domestic, that I will bear truth, faith and allegiance
16 to the same, that I take this obligation freely,
17 without any mental reservations or purpose of evasion
18 and that I will well and faithfully discharge the
19 duties of the office of which I am about to enter, so
20 help me God." Thank you all for your service.

21 (Applause)

1 DR. WRIGHT: Well, once again thanks to all
2 of you who have been willing to share your time and
3 your medical expertise with HHS. I assure you that the
4 work of this Committee is very important to what we do
5 at HHS and I think you can look back with a great sense
6 of pride at the service that you all have on this
7 Committee and how your expertise is used to really
8 drive healthcare policy and to make some of the very
9 crucial decisions that we have to make at the
10 Department of HHS.

11 I have had an opportunity to review the
12 agenda for this meeting and clearly there's a number of
13 issues that are going to be discussed but there are two
14 areas in particular that are of great interest to the
15 Department of HHS. One is the issue of bacterial
16 contamination of platelet concentrates and, you know,
17 the rates of bacterial contamination and sepsis as it
18 relates to the storage period for those. And I know
19 that's a very important agenda item and we're going to
20 be very interested in the opinions, comments, and
21 recommendations that come on, in regard to that, but

1 also the other issue that's very important to us is the
2 clinical significance of red cell age in transfusions.
3 So, those are the two agenda items that we will really
4 be looking at closely.

5 As it relates to bacterial contamination of
6 platelet concentrates, I think one of the questions
7 that we really want you to weigh in on is the risk
8 associated with bacterial contamination of platelet
9 concentrates acceptable, is the current risk acceptable
10 and if it's not acceptable, where do we go from there?
11 You know, what do we need to do if the risk is
12 unacceptable?

13 As we move onto the issue of red cell age
14 as a variable in transfusion outcome, I think that we
15 would really like to hear from this Advisory Committee
16 on the current data, does it support that using red
17 cells as long as 42 days is acceptable or should that
18 be of a shorter duration. And, you know, indeed if you
19 lower that number from 42 days to a smaller number, how
20 is that going to be affect the blood availability in
21 this country which is so important?

1 As I was talking to Dr. Bracey early today,
2 very frequently I think we find ourselves at HHS
3 wanting to make the best decisions based on the best
4 science, and in reality sometimes the science is not
5 complete. It's not exact. And, so, that would be
6 another area that we would be very interested to hear
7 from you. Are there areas of research or are there
8 gaps in our knowledge about the clinical significance
9 of the 42 days that need to be filled with research?
10 Again, blood availability is a huge issue for this
11 Committee so we would be very interested to know if
12 that were shortened, how will that affect blood
13 availability. And then last of all, should the blood
14 industry be doing anything to produce, improve red cell
15 products?

16 So, two huge issues as it relates to sepsis
17 and bacterial contamination of platelet isolates and
18 then the clinical significance of the age of red cells
19 at the time of transfusion and what that ideal number
20 is. Both of those issues are very important to the
21 Department and we'll be looking to your comments and

1 any recommendations you have in regard to that.

2 I know this a busy Committee so I don't
3 want to take much of your time but I did want to just
4 kind of open it up to the floor for a few minutes to
5 ask you if you have any questions you would like to ask
6 the Principal Deputy Assistant Secretary for Health.
7 As I told you earlier, I'm still somewhat of a new kid
8 on the block. I think I was just a couple weeks new
9 when I met with you last time and now I'm almost six
10 months into the job. But are there any questions that
11 I could field? Yes, Dr. Bracey.

12 DR. BRACEY: Yeah, if I could start off. I
13 always harken back to one of the comments of one of our
14 previous members, Dr. Jerry Sandler, and that is that
15 an important component of this, formation of this
16 Committee was the establishment of in essence a Blood
17 Tzar, central spokesperson for blood safety in the
18 U.S., and clearly that is the role that the Assistant
19 Secretary holds.

20 We are in a period of change, and change
21 that sometimes presents the opportunity for lack of

1 clarity in terms of spokespersons. And my
2 understanding is that with your nomination that you
3 represent that stability of the system and the ability
4 to serve as a spokesperson for the safety of blood.
5 Could you comment a little bit on how the position of
6 the Blood Tzar continues throughout political change?

7 DR. WRIGHT: Sure. That's actually a very
8 common question. As I meet with advisory committees at
9 this time in our history, it's no secret here in
10 Washington that there's about to be change. Regardless
11 of which political party triumphs in November we're
12 going to have a change in Administration and there's
13 always a large number of new faces when that occurs. I
14 think the one thing that you need to know about me is
15 I'm not a career -- I mean I'm not a political
16 appointee; I'm a career employee. A decision was made
17 that when they were looking for the Principal Deputy
18 Assistant Secretary over the years that had been,
19 depending on the time in our history, had been either a
20 career position or a political appointee position and
21 the decision was made that we needed some stability in

1 this job and consequently they decided to put someone
2 that was career in this position.

3 So, I'm a career employee and will be here
4 as we make this transition from the current
5 Administration to whatever the future Administration
6 is. And it's my hope that I can provide some
7 consistent leadership, some ongoing leadership to the
8 advisory committees, which work is very important. It
9 doesn't see these normal timelines that we see in
10 Washington so often. You will continue to function
11 just in the same manner that you were before and it's
12 just my hope that I can provide the leadership to this
13 community during that period of time.

14 With a change of Administration there may
15 be a period in which we do not have an Assistant
16 Secretary for Health. It's very common as they go
17 through the nomination process and then ultimately
18 being senate-confirmed, and I will, as the Principal
19 Deputy, I would be serving in that capacity as the
20 Acting Assistant Secretary in the interim, much as I
21 did and was serving in that capacity when I met with

1 you six months ago. So, it's my hope that I can
2 provide some consistent leadership and really serve as
3 the Blood Tzar which the Assistant Secretary for Health
4 is responsible for during the interim.

5 DR. BRACEY: Thank you. Other questions?
6 Dr. Duffell?

7 DR. DUFFELL: My question deals with
8 reimbursement, payment for blood. I mean, this
9 Committee over the years has dealt with a number of
10 safety issues and there is no free ride. All these
11 things, including one that we will be talking about
12 today, pathogen reduction technology, have a cost with
13 it, but, you know, we hear that the community out there
14 is still struggling with a realization of what the true
15 cost of blood is in the Medicare, Medicaid system and
16 in private insurance and things of that sort, what
17 initiatives might be underway in the future that are
18 going to take a proactive stance towards that rather
19 than one that's reactive to a crisis of some sort,
20 which, and some would already say is already occurring.

21 I mean, if you look at some of the

1 compliance issues that some of the blood centers are
2 having to struggle with and the costs associated with
3 bringing things back into compliance and doing the
4 right things, safety screening and all that, so.

5 DR. WRIGHT: I hear your question. I hear
6 your frustration that is there and I hear that so
7 frequently as I move around. I have to admit that I
8 don't have the expertise to answer your particular
9 question. The Center for Medicare and Medicaid
10 Services are the ones that set up the payment profile
11 and I regret that those individuals are not here to
12 answer your question.

13 As our technology improves, as our concerns
14 about safety improve, obviously there's cost associated
15 with that. And the hospital, patient care community,
16 managed care community is always concerned about that.
17 I'll certainly pass on to CMS that particular question,
18 and perhaps it's something that they could address at
19 one of the upcoming meetings if they're going to look
20 at payment reimbursement as it relates to those issues
21 that obviously have an increased price tag associated

1 with them.

2 I will tell you that one of the struggles
3 that we have here not only in Washington but as we look
4 at healthcare across the nation is the escalating cost
5 of healthcare. I think the Medicare Trust Fund will
6 release their annual report, as they're required to do,
7 that indicates that, you know, unless changes are made,
8 the Medicare system will be insolvent in 2019. That's
9 not too far down the road. And, so, we as a nation
10 have some huge decisions to make, ones that will have
11 to be quite courageous by the next Administration. If
12 you think our next President potentially serving for
13 eight years, regardless of which political party he
14 represents, that brings us right up to a period of
15 time, that would bring us to 2016 and the last couple
16 of reports from the trust fund have indicated
17 insolvency in I believe in 2018 or 2019. So clearly
18 we're going to have to address these funding issues on
19 a large scale.

20 DR. BRACEY: Additional questions for Dr.
21 Wright? If not, thank you very much for joining us

1 this morning.

2 DR. WRIGHT: Thank you.

3 DR. BRACEY: Now we would like to again, so
4 that you are reminded of our charges that were
5 presented by Dr. Wright, put up the slide. We do have
6 a slide that has the charges. And again under the area
7 of red cell storage, the first question is the current
8 data support, a change in medical practice -- well,
9 let's just wait until it comes up.

10 Okay. So, let's go to the bacterial
11 contamination first. And then that is, again is the
12 risk associated with bacterial contamination of
13 platelet concentrates, is subsequent detection of the
14 bacterial contamination acceptable for both apheresis
15 and whole blood derived platelets, and, secondly, if
16 the risk associated with bacterial contamination of
17 platelet concentrates and the sensitivity of the
18 currently available detection systems is unacceptable,
19 what does the Committee recommend for next steps? That
20 would be the set of questions for bacterial
21 contamination.

1 Under red cell storage, number one, do
2 current data support a change in medical practice from
3 transfusing red blood cells stored for as long as 42
4 days to transfusing red cells that are stored for much
5 shorter periods of time? If so, what impact would the
6 shift in practice have on blood availability in the
7 U.S.?

8 And then secondly, is there a need for
9 additional research to evaluate if red cells stored for
10 longer periods of time are as safe and clinically
11 effective as red cells stored for shorter periods of
12 time?

13 And then lastly, to understand the nature
14 of the storage lesion. Then what impact would a change
15 in transfusion practice have on blood availability, and
16 then should the blood banking industry strive to
17 produce improved red blood cell products? So, please
18 keep those charges in mind and I think we have a
19 handout as well, that we will, either you have or will
20 be distributed.

21 Okay. With that I would like to move on

1 then to our first speaker. Our first speaker is Dr.
2 Abdu Alayash and actually we have two speakers, Dr.
3 Laurence Landow. Dr. Alayash received his Ph.D. in
4 biochemistry from the University of Essex and he has
5 extensive investigative research in the area of
6 hemoglobin and hemoglobin-based oxygen carriers. He is
7 currently serving in the laboratory of biochemistry and
8 vascular biology within the division of hematology.
9 Dr. Alayash?

10 DR. ALAYASH: Thank you. Good morning.
11 I'll try to summarize the preclinical presentation at
12 the recent workshop that the FDA, DHHS and the NHLBR
13 organized at the NIH. The workshop was held on the
14 29th and 30th of April at the NIH conference. And the
15 purpose of the workshop simply was to review the signs
16 of HBOCs, the current signs, and also look into ways
17 and means to push the field forward. The list of
18 individuals who actually organized the workshop is on
19 your right and, as you can see, these are very
20 prominent people in the field. Additional to this
21 list, Barbara Algreen and George Biro from Canada also

1 held throughout the organization of the workshop, the
2 program and so on, so forth.

3 My part here is really to summarize these
4 two sessions, the first session which occurred on the
5 first day and the second session, of the second day.
6 And again, as I said, it's largely the preclinical
7 preparation and my colleague Larry Landow, will deal
8 with the clinical component. And as you can see, the
9 first part, the first day, the focus was largely on
10 oxygen, physiology and biochemistry of hemoglobin and
11 HBOC. The speakers were Bunn, myself, Alan Schechter
12 from the NIH and George Biro from Canada.

13 The second session is a more futuristic
14 type of session, dealt with the issues of toxicity and
15 also ways and means to control it and new ideas as far
16 as where the field should go. And again, we invited a
17 number of speakers, Gladwin from the NIH, John Alston
18 from Price (phonetic), and -- (name) -- from San Diego,
19 Dr. Dominique Sharp from Switzerland and Joe Darnaro
20 who was an FDA reviewer.

21 Just to remind you very quickly what we're

1 dealing with, we're dealing with hemoglobin-based
2 oxygen carriers. These products are basically derived
3 from the red cells. The hemoglobin is purified and
4 undergoes a number of chemical modifications depending
5 on the company that produces it. Some opted for
6 cross-linking, as you know, once you take the
7 hemoglobin out of the red cells and obviously
8 dimerized, and to cross-link it is of course to
9 stabilize it. In some instances the hemoglobin is
10 cross-linked and the surface of the hemoglobin is
11 conjugated. In some instances the hemoglobin is
12 polymerized into a long chain. These are remember not
13 really truly a substitution for blood. They are meant
14 to basically carry oxygen and provide volume
15 replacement.

16 So, I'm going to go and summarize the
17 presentation by each speaker and I have chosen one or
18 two slides from each speaker, which really it doesn't
19 do justice for the fact I've been given about 20
20 minutes. And this is obviously going to be some bias
21 from my point, to see what slides I thought are picked

1 up. The case of Bunn, Franklin Bunn, as you know, he's
2 going to be speaking here tomorrow, the history of his
3 association with hemoglobin physiology and
4 biochemistry.

5 So he started out by giving us his
6 associations with early work on free hemoglobin and PD
7 clearance and the toxicity associated with that. He
8 then also talked about the current thinking about the
9 vasodilatory properties of red cells. Then he put this
10 question to the community, which basically saying that
11 the current thinking, which is primarily there are two
12 issues that are associated with toxicity of hemoglobin,
13 one of them is of course the nitric oxide, the
14 scavenging by the HBOC, which may ultimately lead to
15 vasoconstriction and impairment of blood flow and the
16 fact that most manufacturers aim at mimicking the red
17 cells when it comes to the oxygen delivery. Both of
18 these assumptions according to Bunn need to be revised.
19 And he basically presented the concept that was
20 initiated by Robert Winslow that basically says that
21 the oxygen affinity of hemoglobin needs to be designed

1 in a way to maintain the oxygen delivery, and according
2 to this hypothesis, that these HBOCs oversupply the
3 tissue with oxygen and that is responsible for the
4 vasoconstriction and hypertension. And accordingly
5 what you need to do is start with hemoglobin that does
6 not have high -- low oxygen affinity, rather small P50
7 high oxygen affinity. And that's basically the sort of
8 very quick summary of Bunn's presentation.

9 In my time I focused as always on the
10 oxidation of hemoglobin, which I believe is an
11 important issue that needs to be considered. I
12 reminded the audience at the time that of course
13 hemoglobin undergoes oxidation within the red cells but
14 as you all know, hemoglobin, within the red cells we
15 have sufficient enzymes to reduce hemoglobin back to
16 its functional form. When you take the hemoglobin
17 after the red cells, free environment hemoglobin of
18 course will undergo oxidation rapidly, and
19 additionally, the hemoglobin when you manufacture it,
20 when you add chemical agents that would also enhance
21 the oxidation, vasoactivity, has oxidation, oxidant

1 really has oxidation and so on, so forth.

2 And I gave an example about how the role,
3 form of chemical modifications may actually lead to the
4 oxidation of hemoglobin and also the demise of the
5 hemoglobin. And of course all of these put together
6 will ultimately affect the safety and efficacy of these
7 products.

8 I gave them a simple example, which a
9 recent experiment that we had done whereby to sort of
10 demonstrate the utility of these oxidation, in real, in
11 vivo. We use two animal rats and guinea pig. The rat
12 is able to synthesize ascorbic acid, which is a
13 powerful reducing agent. Guinea pig, like humans,
14 aren't able to produce -- and what we did we used the
15 same hemoglobin, we made an exchange transfusion, about
16 50 percent of the blood and then we gave them the HBOC.

17 Here you're looking at the ascorbic level
18 in the rat. And as you can see they maintain normal
19 level, and the guinea drops then drops and remains very
20 low. It consumes whatever little bit of -- that's
21 taken obviously on by official from the official

1 sources. But the important thing if you look at the
2 animal's blood and look at the oxidation of hemoglobin
3 clearly you can see the guinea pig did not control the
4 oxidation, it had reached a very high level of
5 hemoglobin by the rat, maintained a very good control
6 of oxidation, in fact, clearly shows that some of these
7 in vitro studies that we report in the past actually do
8 occur in vivo and have some value to what we are
9 discussing today.

10 John Alston, which is the second session,
11 presented one of the ways and means to control the
12 nitric oxide and oxidation of hemoglobin. And John
13 Alston from Rice University actually pioneered this
14 work. The focus of his work is primarily using
15 mutagenesis, site directed mutagenesis and he actually
16 focused on the heme pocket; this is the heme, that
17 surrounds the heme, and basically if you recall that
18 nitric oxide, which is the same size as the oxygen, go
19 all the way down to the back portion of the heme pocket
20 which is called the heme pocket here. And what John
21 Alston had done is basically replacing some of these

1 small amino acid into larger amino acid and he was able
2 to block the entry of nitric oxide but he maintained
3 the entry of oxygen to bind to the heme.

4 And of course Baxter at the time adopted
5 this technology and they actually produced one of the
6 first generation hemoglobin. And this is one of the
7 early experiments in which an animal was infused with
8 this recombinant hemoglobin, and here we're looking at
9 the -- resistant, which is the ratio of mean arterial
10 pressure over cardiac output. And as you can see in
11 the animals that are being transfused with these HBOC,
12 this is the normal time course of the vascular
13 responses and of course when you infuse them with the
14 newly recombinant hemoglobin you almost reduce it to
15 normal value. But unfortunately this particular
16 hemoglobin did not bind.

17 Further, again this is my own editorial
18 comment, knowing the chemistry of these hemoglobins is
19 because the oxidation was not resolved and hemoglobin,
20 or rather the heme is readily lost, even in spite of
21 the fact that you reduce nitric oxide binding.

1 Bit Allen Schechter from the first day
2 and Gladwin, who you will hear from tomorrow talked
3 about the new, a property of hemoglobin, as, not a
4 property, which says basically that hemoglobin will
5 undergo a transition from oxy to deoxy. It acts in
6 enzymatic fashion and can actually convert nitrite to
7 nitric oxide, and replacing nitric oxide, which
8 presumably will be scavenged by HBOC.

9 Mark presented a lot of data. This is one
10 of them, one slide, which has been taken actually from
11 a recent paper, in circulation. This paper was
12 published by Warren Zabel from Harvard. And what they
13 did basically is again my side believed, the one of the
14 known HBOC BCHLB, the fusion point is here. And as you
15 can see this is a typical hypertensive response in
16 animals and in humans, more or less. It peaks up very
17 quickly and it continues for about an hour and a half.
18 Then it goes down. This is without nitrite. Then they
19 added nitrite and this is the added nitrite as you can
20 see the blood pressure was brought back to normal. And
21 what they speculated, of course, nitrite, hemoglobin,

1 rather, recycled nitrite produced nitric oxide and that
2 led to vasodilation.

3 An interesting point here from my point of
4 view is when they looked at the oxidation of hemoglobin
5 in circulation they found out that the red cells
6 naturally didn't oxidize a lot because as you know
7 nitrite is an oxidizing species because the red cells
8 can do that because of its ability to reduce oxidation.
9 While the free hemoglobin in the plasma was oxidized in
10 the first ten minutes, almost 10 percent; unfortunately
11 they don't really show data what happens to the HBOC
12 after that -- which I would assume some higher level of
13 oxidation.

14 Mark Bizantaglata (phonetic) from San Diego
15 pioneered the work on microcirculation and he developed
16 this hamster skin fold whereby he can actually
17 visualize the microcirculation and he focused on the
18 functional capillary density where he looked at these
19 and used this value as an indirect index of tissue
20 oxygenation and so on, so forth. But Mark says
21 basically he used number of hemoglobins, number of

1 volume expanders, such as dextrans and a number of
2 hemoglobin that have been encapsulated with the lipids.
3 And his conclusion was HBOCs are fundamentally
4 different, which everybody, I guess, agrees with this.
5 And what he says basically is that the viscosity effect
6 should be taken into account, and particularly whatever
7 in terms of chemistry, you put on your hemoglobin and
8 you may actually counteract vasoactivity by increasing
9 the vasoactivity -- rather by increasing the viscosity.

10 The last scientific speaker was Dominique
11 Sharp from Switzerland who talked about haptoglobin.
12 And this is an area that unfortunately has been
13 forgotten by both industry and academia. Haptoglobin,
14 as you know, is an important endogenous protective
15 mechanism. And he also talked about CD-163, which has
16 recently been discovered, which is a receptor,
17 scavenger receptor on the microphages.

18 And what, according to Dominique, is that
19 initially (phonetic) when you infuse hemoglobin,
20 haptoglobin is activated and of course the CD-163, the
21 primary pathway is haptoglobin and the secondary

1 pathway is 163. The interesting data that he presented
2 is that when you use a chemically modified hemoglobin,
3 the chemistry of a given hemoglobin, or the surface
4 chemistry is very critical and it determines whether
5 the hemoglobin is picked up by haptoglobin or by
6 CD-163. And you can actually be clever with the
7 chemistry, the surface chemistry of the hemoglobin, you
8 can actually sort of enhance the uptake of hemoglobin
9 and that could be considered a way to sort of at least
10 control some of the toxicity associated with
11 hemoglobin.

12 I summarized George Biro and Kevin
13 Cavagnaro who talked about animal studies, and the
14 problematic issues that are associated with it and I
15 tried to put it here in these three bullets. Basically
16 what George Biro says, that we have really two camps,
17 industry, which is there are animal studies, largely a
18 GLP-level type of work by academia or nonGLP but
19 academia of course have more extensive expertise and
20 diverse expertise and what they recommended, that these
21 two camps need really to merge to sort of help in

1 designing a useful animal model and to work out at
2 least at the animal level the risk-benefit and that
3 these toxicology studies should be extended to sort of
4 mimic the human situation whereby, as you know, not
5 everybody who receives this product is healthy.
6 Particularly the focus should be on the vascular
7 system, particularly in those patients that we deal
8 with; normally the endothelia barrier is dysfunctional.
9 And of course also they're saying that based on the
10 huge amount of clinical experience now we surely should
11 be able to design a relevant and useful animal model
12 that could help both the regulatory agency and of
13 course industry as well. And I think this is the
14 basically summary that I have for you. Than you.

15 DR. BRACEY: Thank you, Dr. Alayash.
16 Questions from the Committee for Dr. Alayash? Yes, Dr.
17 Epstein.

18 DR. EPSTEIN: Yes, thank you very much, Dr.
19 Alayash, also for all of your personal work advanced in
20 this field. I guess my question is that there's a bit
21 of a gap between knowing we need more suitable

1 preclinical models and deciding what they really are
2 and I just wonder in your opinion, how close are we in
3 knowing what the right models are?

4 DR. ALAYASH: Well, as you know, it's
5 really very difficult to come up with one model that
6 addresses all these issues but I think we are there to
7 sort of be able to be selective, to at least choose a
8 model that will mimic some of the complex situations
9 that we deal with. The issue of oxidation, if you're
10 asking my own sort of the simplistic thoughts, I do
11 think that oxidation is very important. So really to
12 be able to mimic this the way we have chosen at least
13 to the animal the way they handle the oxidation, that
14 would be quite useful in plasma to really monitor what
15 happens in animal and follow oxidation such as rat or
16 animal cannot control oxidation. Devise a number of
17 additional questions asked in these two animals this,
18 and this is what we're doing these days actually in the
19 lab, trying to come up with these to two tracks in a
20 way to address some of the still outstanding issues as
21 far as the toxicity of these products.

1 DR. BRACEY: Yes, Dr. Klein.

2 DR. KLEIN: Dr. Alayash, the Planning
3 Committee wrestled with this and I wonder again if you
4 have any opinion on whether a series of animal models
5 could be designed but perhaps the testing could be
6 carried out by a third party that would be acceptable
7 to the regulatory agency and deal with the toxicity
8 we've seen with some of these agents in the past rather
9 than allowing data from each individual commercial firm
10 using different models to be used to go ahead with
11 clinical trials.

12 DR. ALAYASH: Again this issue has been
13 sort of dealt with. We've dealt with it for some time
14 and we have sort of tried to get industry primarily to
15 sort of go for an animal model. And one rule so to
16 speak, fortunately out attempt to do work successfully
17 and try to sort of not get drawn into this thing. And
18 that would be very logical, as I said, if we can find
19 an animal model which, by the way, it is very difficult
20 to find one animal model that can address all these
21 issues from the hypertension to organ damage as so on,

1 so forth, or at least a model that everybody within the
2 community could agree on and if we can have all these
3 hemoglobins given to one group of researchers, be it
4 government or otherwise, and study them all in one go
5 (phonetic). But again, like I said, approach the one
6 very successful with industry.

7 DR. BRACEY: Perhaps this would be better
8 directed to the next speaker but I'll ask. From all of
9 these experiments is there some benefit we can learn
10 regarding the usual practices that is supporting
11 hemoglobins, i.e., how much hemoglobin in animal or man
12 needs to have basically normal function?

13 DR. ALAYASH: Yeah, I mean all of these
14 animal studies you can design them as per all these
15 issues but it's not going to be one animal model that
16 gives you all of these answers. And we need to have
17 sort of more model to address these issues. If the
18 issues are not pharmacology, you can talk to a
19 pharmacologist, they can start with the size of the
20 animal, large animal, small animal, and so on, so
21 forth. It gets really very complicated. But from a

1 simple scientific question what we've asked is very
2 simple. What are the issues that we're dealing with?

3 Hemoglobin is a complex model. You can do
4 a lot with the test tubes but once you move that
5 experiment with an animal model things will become very
6 complicated and it's not very easy to address these
7 issues. And it takes us, for example, we've been doing
8 this for almost twenty years now. We have money, we
9 have support and nobody really telling us what to do.
10 Basically, give me people -- just doing for some time
11 but it's still, I still at this point, you haven't
12 really reached to that point where we can say, okay --
13 model, help you -- so on, so forth, but we haven't been
14 yet to that point. Give us a little bit more time and
15 a little bit more money and we might be able to do
16 that.

17 DR. BRACEY: Yes, Dr. Triulzi has a
18 question.

19 DR. TRIULZI: Yeah, can you comment on
20 whether you think the modification of human hemoglobin
21 or an engineered recombinant hemoglobin is more likely

1 to be the best source for hemoglobin-based oxygen
2 carrier because it impacts, obviously, blood supply is
3 going to be hemoglobin.

4 DR. ALAYASH: Well, actually, human or any
5 animal source would be ease to speaker and if you know
6 your chemistry you know what the chemistry does to the
7 hemoglobin, that should be fine. Genetic engineering
8 or genetically-engineered hemoglobin presents
9 additional problems. The two things with
10 genetically-engineered is even if you get the primary
11 sequence of the protein directly, the folding of the
12 protein, particularly with hemoglobin with four
13 subunits total 600 amino acids, somehow do not fold the
14 right way.

15 Additional problem with hemoglobin is the
16 fact the heme needs to be inserted in the right area in
17 the right orientation and with the recombinant
18 hemoglobin unfortunately nobody has actually solved
19 that problem. Although John Alston, the person who
20 is -- did understand this and he has some ideas as to
21 how to solve this problem.

1 DR. BRACEY: Thank you. Can we move on now
2 to Dr. Landow, Dr. Laurence Landow? Dr. Landow is a
3 board certified anesthesiologist and practitioner of
4 critical care medicine for over 22 years. He's an FDA
5 medical reviewer and his expertise is in hemoglobin --
6 hemoglobin-based oxygen carriers --

7 DR. LANDOW: Good morning, everyone. I'm
8 going to discuss the clinical sessions that were part
9 of this workshop. This is an overview, what took
10 place. First there was an FDA presentation of the
11 published data, all the data in the public domain
12 whether in journals, medical journals or press releases
13 and that was presented by Dr. Toby Silverman, who is
14 the branch chief. And she discussed unmet needs, the
15 settings and indications for HBOCs, the endpoints for
16 clinical trials and defining clinical benefit.

17 In the afternoon, representatives of
18 regulated industry gave presentations. The following
19 were represented: Apex, Baxter, Biopure, Enzon,
20 Northfield, Sangart. The next day there were the
21 following speakers who spoke about a clinical

1 assessment of safety and efficacy using the published
2 studies, and that included Dr. Demetrios Demetirades
3 from U.C.L.A., who is a trauma surgeon, Dr. Daniel
4 Freilich, who is from the Navy Medical Research Center,
5 John Holcomb, who is from the U.S. Army, Charles
6 Natanson from NIH, Edward Sloan from the University of
7 Illinois, who is an ER physician, and Gus Vlahakes, who
8 is a cardiac surgeon at Harvard. And the workshop
9 ended with a panel discussion by all of these members.
10 So the FDA presentation presented the following points,
11 first, that FDA believes there is an unmet need for
12 hemoglobin-based oxygen carriers. And Dr. Silverman
13 then presented some of the highlights of the FDA
14 guidance on blood substitutes. Among the items that
15 she mentioned were that HBOCs are likely to be used in
16 a wide variety of clinical settings such as oxygen
17 transport and blood pressure elevation, for example, in
18 shock so that clinical trial endpoints were likely to
19 be different. And therefore, because the endpoints are
20 different, it's very unlikely that a single trial could
21 address all the possible uses for a particular product.

1 She also highlighted the fact that the guidance calls
2 for a sequential approach to HBOC drug development.

3 Obviously we start off in phase one but
4 then the next step would be to administer the product
5 in highly monitored settings, i.e. usually the
6 operating room, in patients who are at very low risk of
7 experiencing an adverse event. And that is most
8 usually elective surgery patients, orthopedics, cardiac
9 surgery, et cetera. Then according to this paradigm,
10 once the product has shown a favorable risk-benefit
11 profile in these highly monitored settings, the next
12 step would be to permit studies where monitoring is
13 much more limited, such as in the ambulance, in
14 high-risk patients, trauma patients, for example.

15 In preparation for the workshop FDA
16 conducted two reviews. One was a review of all
17 information available in the public domain and we
18 reviewed the clinical safety data from all published
19 trials and press releases and that was available for
20 six of the eight commercial products. In addition, we
21 did an internal review which took around three months.

1 It was quite intensive, and we reviewed all of the data
2 that had been submitted by all of the HBOC companies,
3 since going back to, I believe, 1985 or 86, and that is
4 proprietary and we can't reveal that but that gives
5 some context to what I'm going to show you next. And
6 before I do, I just want to present this caveat about
7 the publicly available information. First, not all
8 trials that sponsors conducted have been published, and
9 second of all, not all enzyme elevations, for example,
10 pancreatic enzyme elevation, myocardial enzyme
11 elevations and so forth were captured as AEs or were
12 they captured in a uniform manner.

13 So, there are some limitations to what I'm
14 going to show you next. Now, this is a very busy
15 slide, just trying to highlight some. Major points
16 here. On the left column are the bedracodeine
17 (phonetic). That's how we code the particular safety
18 events. I know it's hard to read. This first line
19 here is death and I also want to draw your attention to
20 this line here, myocardial infarction. And then you
21 have these columns. They're entitled Apex, Baxter,

1 Biopure, Enzon, Hemosol, Northfield, Sangart,
2 Somatogen. And you can see they're color-coded.

3 The other point is T stands for test and C
4 stands for control. And I'm not going to go through
5 this cell-by-cell but there are circles around one,
6 two, three -- and I thought there was a fourth -- yes,
7 there is. One, two, three four, those are the only
8 cells in which the control group had a higher frequency
9 of a particular adverse event than the test control,
10 than the test arm. So, in other words, for almost all
11 of these cells, for almost all of these products, for
12 almost all of these events, the test arm had a higher
13 frequency than the control arm.

14 The next point I just want to bring out is
15 that some companies did not report their studies; this
16 one, for instance. And then the last point is to look
17 at the death rate of the products that did report their
18 studies. For Baxter it was 76 versus 38 and the sample
19 sizes are approximately equivalent. They're not
20 identical. Biopure, 166, I'm sorry, 25 versus 14.
21 Enzon did not get to this stage, had no deaths.

1 Hemosol, 1 versus 4, Northfield, I'm sorry, yes -- am I
2 in the right lane? Yes, yes, 1 versus 4 and then
3 Northfield, 73 versus 39, Sangart, 2 versus 0. As you
4 can see, these are the sample size in bold
5 corresponding to those death rates. And then the other
6 line I wanted just to point out is the myocardial
7 infarction, Apex, as I said before, did not present --
8 did not report rather in the public domain, Baxter was
9 6 versus 1, Biopure, 14 versus 4, none for Enzon, then
10 14 versus 7 for Hemosol, 29 versus 2 for Northfield, 2
11 versus 0 for Sangart and Somatogen did not have any
12 deaths. So I think there's a pretty clear picture here
13 which way the products are heading in terms of
14 toxicity.

15 Well, in the afternoon the industry
16 presented, given an opportunity to respond, Sangart was
17 the first company to respond and they made the
18 following points and I have to make the same provision
19 that Dr. Alayash made. These are my biased extractions
20 of what each company said. They spoke for twenty
21 minutes to thirty minutes and so I think if they were

1 here they might say this is not a complete
2 representation of what they wanted to say but I picked
3 out these items as the most relevant for this meeting.

4 So I would say that Sangart emphasized that
5 their product has a very high oxygen affinity, which
6 means that it limits oxygen release early on at the
7 arterioles and thereby allows greater delivery of
8 oxygen downstream to the tissues where it's needed.
9 They feel that their product is qualitatively and
10 quantitatively different from the other products. They
11 also feel that any increase in blood pressure
12 associated with the product is due to the oncotic
13 properties of the product since they claim that their
14 product does not scavenge nitric oxide.

15 And, finally, they did present safety data
16 from a phase two orthopedic trial that enrolled 90
17 subjects and they did mention that there were excesses
18 in the test arm. There were excess myocardial
19 infarctions, an excess of arrhythmias, including
20 ventricular arrhythmias, severe ventricular
21 arrhythmias. There was an excess of hypertension, GI

1 symptoms such as nausea and vomiting and elevations of
2 pancreatic enzymes when compared against the placebo.

3 The next sponsor was Northfield. They
4 spoke about their phase two in-hospital single arm
5 trauma study that was compared, that had as a control
6 the rate of morbidity and mortality, among Jehovah's
7 Witnesses. And they also spoke about their recently
8 completed phase three ambulance plus in-hospital trauma
9 randomized control trial which was conducted over,
10 under exception from informed consent.

11 Now, the results of that trial have been
12 released to the public and what they show is that first
13 there was an excess mortality in the test arm that
14 exceeded a prespecified noninferiority margin. And
15 second of all, there was an excess of myocardial
16 infarctions. Now, the company then claimed that they
17 had assembled a panel of experts to readjudicate the
18 myocardial infarctions on a post hoc basis and they
19 stated -- and we have not seen this data but they
20 stated that this panel was able to exclude myocardial
21 infarction in more of the test arm subjects than in the

1 control arm subjects.

2 The next presentation was from Prolong
3 Pharmaceuticals, formerly Enzon. They have a pegulated
4 hemoglobin that was developed in the mid-1990's and
5 designed to raise tumor oxygen tension and increase
6 radiosensitivity for susceptible tumors. They
7 completed two studies, or reported, rather, two phase
8 one studies. And it's interesting that the adverse
9 events that they reported are similar to all the other
10 HBOC adverse events reported, i.e., hypertension,
11 dysphasia, nausea and vomiting. And they stopped
12 development in the late 1990's.

13 The next presenter was Biopure. We
14 discussed this product at a December '06 Blood Products
15 Advisory Committee meeting. They admitted that there
16 was an excess of myocardial infarction, stroke, heart
17 failure, cardiac arrest and other SAEs noted in their
18 elective surgery studies but they claimed that the
19 etiology was due to underdosing, which led to ischemia,
20 or to overdosing, which would lead to live overload and
21 congestive heart failure. And that explains this

1 second bullet point. They concluded that further
2 trials comparing their product against red blood cells
3 were not warranted but that trials should continue
4 where blood is not immediately available or is not an
5 option.

6 The next sponsor was Baxter, which bought
7 out Somatogen, so we've combined them together. Their
8 products were DCLHb -- and recombinant hemoglobin 1.1.
9 And they described the excess mortality that they
10 observed in two phase three trauma studies. The first
11 was one that was conducted in the U.S. under exception
12 of informed consent, once again. The product was given
13 in the emergency room but the site had to be terminated
14 early because of excess deaths in the treatment arm.

15 The other study that was going on in Europe
16 was a little bit different, the product was given in
17 the ambulance but that study also was terminated early
18 because the company decided that it wasn't in their
19 best interest to continue funding these. But
20 interestingly enough, even in the European study there
21 was imbalance against the product in terms of

1 mortality.

2 The etiology of this excess mortality in
3 terms of Baxter, Somatogen's product is unclear. The
4 speaker stated that test subjects may have been
5 under-resuscitated due to inadequate dosing of DCLHb
6 but we even to this day do not know the true cause of
7 this.

8 I think this is the last speaker, from
9 Apex. They described a phase three trial in subjects
10 with volume refractory, pressor-dependent systemic
11 involuntary response syndrome but that trial was
12 stopped prematurely after 62 subjects been enrolled
13 because they found it difficult to find subjects that
14 would meet the entry criteria. Nevertheless, there was
15 noted to have an excess of MIs and myocardial ischemia
16 and what they said, they said the reason for this was
17 that the investigators were unblinded and therefore
18 biased and that they therefore over-reported MIs in the
19 treatment group. They also stated that there was an
20 absence of a prospective definition for myocardial
21 infarction and that when they had a consultant, an

1 outside consultant who is blinded, readjudicate HLD,
2 MIs and myocardial ischemia episodes, he found that
3 there were excess MIs in the placebo group. We have
4 not seen this data either so I cannot comment on it.

5 The next day was a new round of speakers,
6 starting off with Dr. Demetriades, head of trauma at
7 UCLA. He stated that HBOCs are promising agents but
8 that they require further study in nontrauma settings
9 before they go into trauma settings because of the
10 safety concerns raised in the elective surgery studies.
11 So he more or less supported our paradigm of going from
12 low risk, highly monitored settings to high risk,
13 poorly monitored settings. He also made the point that
14 he didn't believe blunt trauma and penetrating trauma
15 should be included in one trial. He said you should
16 separate the two groups because they have different
17 mortality rates and they die at different times and
18 since the product is given early on, it would be
19 difficult to attribute the death or more difficult to
20 attribute the death to the product when it was later,
21 when the death was later than when it was earlier.

1 So, he's arguing that penetrating trauma
2 should be the one that we study. He's arguing also,
3 rather differently from most other people, that the
4 blood pressure should be less than 80. Most of the
5 trauma studies that we have received have a criterion
6 of blood pressure less than 90. Doesn't sound like
7 much, but he last emphasized that point in many
8 conversations. And he feels that the control should be
9 hypertonic saline or red blood cells and he said they
10 should be less than two weeks old.

11 Dan Freilich from Navy Medical Research
12 Center, he stated that there are abundant preclinical
13 data from animal models that should be used to steer
14 the clinical trauma trials. They should, in other
15 words, support the conduct of allowing trauma trials to
16 be conducted. He said that these experimental studies
17 suggest a significant potential benefit of HBOC 201,
18 which is the product that he is advocating the use of.
19 He said that it's not fair and it's not correct to lump
20 all HBOCs together because they have different
21 physicochemical properties. And he said that trials of

1 HBOCs in patients with severe hemorrhagic shock where
2 mortality is high should be encouraged.

3 John Holcomb spoke next. He's from the
4 Army and he made a rather stunning statement. He said
5 that patients in Iraq -- not patients -- soldiers in
6 Iraq who survive to the hospital who don't exanguinate
7 on the spot do not present with an abnormally low
8 hemoglobin. Their mean hemoglobin -- he showed a table
9 -- was 11.5. And I thought that was amazing. Instead,
10 he believes that trauma-induced coagulopathy is the
11 real problem that should be addressed, not anemia. So
12 he's sort of an outlier from the rest of the group.
13 And he said there's an urgent need to identify patients
14 most likely to experience coagulopathy and that we
15 should be administering FFP and platelets much earlier
16 and in much higher volumes than we currently do.

17 So, he would, in other words, instead of as
18 soon as you hang the first unit of blood, he would
19 suggest that you hang the several units of FFP and
20 platelets and you continue in that sequence because you
21 have to treat the coagulopathy, because he feels it's

1 the coagulopathy that is killing soldiers on the
2 battlefield, not per se anemia. At least that was my
3 impression of what he said.

4 Then we got to Dr, Natanson from NIH, who I
5 think everyone's knows whose team has published a trial
6 in JAMA. It's a meta-analysis of 3711 patients from
7 published HBOC trials, encompassing five manufacturers.
8 The test for heterogeneity for mortality and MI was not
9 statistically significant, had a P value of 0.6, so it
10 was, they claimed in the article that it was fair to
11 combine all of these different products and different
12 studies and the results were there was an increased
13 risk of death with an odds ratio of 1.3, and a 95
14 percent confidence interval as you see there and an
15 increased risk of myocardial infarction. And when they
16 did subgroup analyses for the indication from which the
17 product was administered, the tetramer content and the
18 P50, it was consistent with the overall finding that is
19 just above.

20 And he stated that in his opinion -- and
21 there was accompanying editorial in JAMA that came to

1 the same conclusion -- trials of HBOCs should not be
2 allowed until the underlying mechanisms of toxicity
3 have been elucidated and corrected.

4 The next speaker was Edward Sloan. He had
5 been the principal investigator for the U.S. Baxter
6 trauma trial that had been stopped prematurely that I
7 mentioned earlier. And he has done a lot of
8 retrospective review trying to find out the etiology.
9 As you recall, we really don't know what happened in
10 that study, why there was an excess of deaths but he
11 found that blood pressure, base deficit, lactate, shock
12 index was not different from treatment groups; in other
13 words, there was no obvious etiology.

14 And he recommended the following, that
15 patients with TCS of three -- that's the worst head
16 trauma -- be excluded because they're going to die
17 whether the product is defective or not in the other
18 populations, and we should be looking at the
19 intermediate population. Many people have said this.
20 The people on the two extremes are not going to,
21 patients on the one extreme are going to die no matter

1 what; patients on the other extreme are going to
2 survive without the product. You want to get that
3 middle group and see if you can improve their survival.

4 The last speaker was Gus Vlahakes, from
5 Harvard. He's a cardiac surgeon. And he stated that
6 virtually all HBOC products elevate systemic and
7 pulmonary vascular resistance. And he stated that it
8 was his opinion -- he's been in this field for many
9 years -- that early on he felt that they could be of
10 benefit in trauma and cardiac surgery. But in a
11 cardiac surgery study that he cited using HBOC-201,
12 there was a savings of only one-half unit of red blood
13 cells and at the expense of the safety protrial that I
14 had shown you earlier. And he also made the point that
15 titration of the product to a blood pressure endpoint
16 could lead to under-resuscitation, so perhaps we're
17 looking at the wrong endpoints when we administer the
18 product.

19 The session ended with a
20 question-and-answer panel discussion. All the speakers
21 got up onto the dais and the panelists were asked about

1 clinical situations where they thought HBOCs might
2 still be useful. So some panelists stated that
3 mortality in any future trial would need to be a
4 hundred percent before they allow the product to be
5 used in subjects, in clinical trials, even, while
6 others thought young patients without comorbidities
7 would be appropriate since they theoretically would be
8 at less risk for these adverse events. The panelists
9 generally agreed that it would be difficult to test
10 these products against red blood cells given the safety
11 of the blood supply in this country.

12 They also agreed that much more preclinical
13 research is required but that these animal models have
14 limited usefulness unless, unless they are capable of
15 mimicking safety events noted in patients. That is the
16 problem -- I think someone just brought it up earlier
17 -- that these animal models do not reflect what we see
18 in patients and so they're noninformative and what we
19 need are animal models that do reproduce what we see in
20 patients and then we would compare in the future a
21 blood product, an HBOC product with control and we

1 could then evaluate whether there's a safety risk or
2 not. Thank you.

3 DR. BRACEY: Thank you, Dr. Landow, for
4 that extensive review. Questions from the Committee?
5 I had one question. Was there any discussion of
6 pharmacologic manipulation? Clearly we can do that
7 with the hemorrhaging group but perhaps the an anemic
8 set of patients, use of NO to perhaps counteract some
9 of the adverse effects of the hemoglobin sessions?

10 DR. LANDOW: Well, yes. I think that's an
11 active field of interest. As I recall, the person who
12 I remember speaking to the most about, that was Mark
13 Gladwin because that is his field of expertise. But
14 that has not been used in the clinical setting. I
15 think it's more experimental, benchwork currently.

16 DR. BRACEY: Additional questions? If not,
17 thank you very much.

18 DR. LANDOW: Thank you.

19 DR. BRACEY: Our next speaker is Dr.
20 Elizabeth Ortiz-Rios. Dr. Ortiz-Rios will present a
21 summary report of HRSA's vascular composite allografts.

1 Dr. Rios is trained in epidemiology, having a master's
2 in public health from Emory School of Public Health and
3 she has been at HRSA and CDC. Thank you.

4 DR. ORTIZ-RIOS: Good morning. I have a
5 very short presentation, a summary of the vascular
6 composite allografts. Just a little background, the
7 reasons for including vascular composite allografts as
8 organs, regulatory legislative issues, talk about the
9 Federal Register notice and the HRSA meeting that we
10 conducted on April 4. The Division of Transplantation
11 oversees the nation's solid organ transplant system,
12 which includes the Organ Procurement and Transplant
13 Network, OPTN, and the Scientific Registry of
14 Transplant Recipients, SRTR, oversees the C.W. Bill
15 Young cell transplant program in the National Cord
16 Blood Inventory and develop and implement national
17 programs to increase organ tissue, blood stem cell and
18 blood donation.

19 As, in response to the need of donating
20 increasing organ donation and improving transplant
21 organization allocation the Congress passed the

1 National Organ Transplant Act, NOTA, in 1984. And
2 through this act, NOTA and SRTR were developed or
3 established. NOTA also provided authority for the
4 Secretary of Health to regulate definition of human
5 organs as in, for example, in 2007, the intestines were
6 added to the definition of transplant organs and to
7 collaboration between HRSA and FDA, blood vessels to be
8 transplanted, with transplanted organ were also
9 including in the definition of transplant organs in
10 2007. Reasons for including VCAs in the definition of
11 organs, these are parts of the body such as limb or
12 face transplants, which are clinically and biological
13 dealt in the same manner as organ transplants. They
14 have short preservation time.

15 They have the potential need for allocation
16 rules, and also the need for immunosuppression to
17 prevent graft rejection. VCAs do not meet the FDA
18 definition of tissue and the oversight by HRSA of
19 program requirements would fit very well into the OPTN
20 role, which deals with outpatient rules, data
21 collection and patient safety issues, for donation and

1 transplantation. I think I already mentioned this,
2 just to add to the fact that there have been over two
3 dozen limb transplants and a couple face transplants
4 reported in the world and this number is likely to grow
5 rapidly and so the need for appropriate oversight will
6 be very important.

7 The purpose of, well, HRSA published a
8 Federal Register notice on March 3rd, 2008 for the
9 purpose of obtaining public input on whether HRSA
10 should include vascular composite allografts in the
11 definition of organ for the purpose of inclusion in the
12 Organ Procurement and Translation Network final rule,
13 and added to the definition of human organs covered by
14 the Section 301 of the National Organ Transplant Act,
15 NOTA. We sponsored a meeting on April 4th to which all
16 public and stakeholders were invited for discussions
17 about VCA issues. We had a good turnout, both
18 attending the meeting or over conference calls. We had
19 various presentations for what different programs are
20 intending to do on face transplants and hand
21 transplants, also futurist transplant, and we had OPO

1 -- as well as -- personnel. We also increased the
2 deadline to the July 2nd for the public to provide
3 written comments to HRSA. We have had a few comments
4 come in but we still have four more weeks to wait for
5 comments from the public so we will not be discussing
6 those today. And that's all I can say right now about
7 vascular composite allograft. Thank you.

8 DR. BRACEY: Thank you, Dr. Ortiz-Rios.
9 Questions or comments from the Committee? It appears
10 -- and let me see if I'm thinking right here -- that
11 obviously when one uses simply the definition of an
12 organ, that that's rather limiting in terms of the
13 clinical activities and so really in the broad brush of
14 what you're looking or seeking to do any vascularized
15 component of the body that would be transplanted from
16 one individual to another, come under your domain, just
17 to sort of cover the crafts as far as new clinical
18 interventions?

19 DR. ORTIZ-RIOS: Under the HRSA, yes, right
20 now is not on the horizon (phonetic) by FDA nor HRSA.
21 As we see that these are increasing we see also the

1 need to have some regulatory process in place and we
2 have been meeting, collaborating with FDA over the past
3 year and it was decided between the two agencies that
4 to have the Federal Register notice out there to have
5 input from the public and the transplant community.
6 Depending on the comments HRSA will decide how to
7 proceed. So, we'll be working with these comments in
8 July, when the deadline ends, to have comments from the
9 public.

10 DR. BRACEY: Thank you. Additional
11 questions or comments from the Committee?

12 DR. ORTIZ-RIOS: Thank you.

13 DR. BRACEY: If not, we are at the point of
14 taking a break so why don't we take a 15-minute break
15 and reconvene at a quarter after ten.

16 (There was a break in the proceedings.)

17 DR. BRACEY: Our next speaker is Dr. Les
18 Holness. Dr. Leslie Holness is the Chief of the Blood
19 and Plasma Branch of the Division of Blood Applications
20 at CBER. Dr. Holness is trained in anatomic clinical
21 pathology and oversees the reporting system for FDA

1 reported fatalities, which is a very important area in
2 terms of safety monitoring of blood transfusion in the
3 United States. And he will share with us the CBER
4 Blood Safety Team and annual summary report on
5 fatalities. Thank you.

6 DR. HOLNESS: I would like to thank Dr.
7 Holmberg and the Committee for inviting me to speak
8 today. Today's talk will be about the CBER internal
9 Blood Safety Team and its activity over the last couple
10 of calendar years and then we'll discuss how that is
11 associated with blood collection or transfusion for a
12 number of fiscal years. I'll say a brief word about
13 future adverse event reporting, and the bottom of the
14 slide, a good general link for reporting problems to
15 the FDA.

16 The CBER initiative for internal Blood
17 Safety Team began in July of 2006 and it grew out of
18 blood safety working group started the year before
19 under the direction of the CBER center director. Since
20 that time under the leadership of Dr. Jonathan
21 Goldsmith, deputy director of the office of blood, the

1 Blood Safety Team has been meeting every other week.

2 The goals of the Blood Safety Team are to
3 formalize center operation procedures, to make sure we
4 do things in a fairly uniform way, to establish roles
5 and responsibilities in the management of blood safety
6 issues, be certain about whose job it is, when it
7 happens so there that there are no errors of omission.
8 Third, to enhance internal and external communications
9 within CBER, the FDA, inside and outside government.

10 The major objectives are to improve CBER
11 responsibilities to blood safety issues through defined
12 cross-office collaboration creating increased
13 sensitivity to safety signals, to improve the value of
14 safety information and broaden public and regulated
15 industry access to the information, to improve the
16 processing of blood safety information through
17 establishment of a forum for review and evaluation
18 permitting discussions in a noncrisis mode,
19 facilitating anticipation of events, also, to enhance
20 external outreach, evaluation and risk communication.
21 In other words, things that occur in one hall being

1 picked up and transferred centrally to deal with these
2 issues, to make sure that the information we collect is
3 useful. As we all know, preparation is the better
4 response and management has the last minute to adjourn
5 a crisis.

6 This is a simplified staffing model of the
7 Center for Biologics. The blocks in yellow are the
8 offices that contribute permanent members to the Blood
9 Safety Team. This is the Office of Director, the
10 Office of Biostatistics and Epidemiology, the Office of
11 Communications, Training And Manufacturers Assistance,
12 the Office of Blood Research and Review, and the Office
13 of Compliance and Biologics Quality. Each office
14 contributes two to four individuals who serve for about
15 two years.

16 What are the activities of the Blood Safety
17 Team? The first is coordination of investigations of
18 potential shortages of blood products. Due to
19 manufacturing changes, investigation of the impact of
20 manufacturing changes and impact of potential recalls
21 on public health. Shortages may be due to reports of

1 adverse events of a clinical or technical nature. This
2 may lead to problems balancing supply and safety. In
3 the last couple of years we dealt with shortages due
4 reports of reduced stability. Part of the job is to
5 seek and explore regulatory pathways to avert
6 shortages.

7 The Blood Safety Team also reviews annual
8 fatality reports from whole blood and source plasma
9 establishments, under the regulations cited on the
10 slide, provides oversight for the annual reports and
11 reviews communication opportunities. We seek some
12 potential etiologies as to what puts a healthy donor at
13 risk for an adverse event and donation. We also try to
14 increase our understanding of adverse outcomes in
15 recipients that end up in fatalities, and to
16 eventually, we would like to develop mitigating
17 strategies to reduce the number of deaths associated
18 with transfusion.

19 The Blood Safety Team also reviews biologic
20 product deviation reports, BPDRs, under 606.171, and
21 potential enhancements to reduce reporting burdens.

1 The safety team provides oversight for the annual
2 report, reviews the benefit of continued implementation
3 of post donation information, PDIs. In the last couple
4 of years we've dealt with issues such as tattoos and
5 donor history of cancer and made recommendations for
6 consideration at the office in Centreville.

7 The Blood Safety Team evaluates
8 manufacturing issues and potential safety impacts, the
9 effect of breaches in cGMPs, bioburden excursions and
10 their impact on safety, purity and potency as bacteria
11 get into the starting product, and material of the
12 product, who has got the impact on safety, purity and
13 potency.

14 The Blood Safety Team also investigates
15 approaches to threats to the blood supply. We review
16 existing scientific information and support public
17 workshops. We've investigated the impact of outbreaks
18 of transfusion transmissible diseases on potential
19 blood donors. For instance, we've all heard of the
20 endoscopy-related hepatitis C outbreak in Las Vegas,
21 Nevada. We looked at the impact that we have on the

1 blood donors in that area. We've also looked at,
2 investigated the impact of adulterated pharmaceutical
3 ingredients. We've heard that heparin hyposulphanated,
4 adroitin sulfate was distributed to the market. It's
5 unusual but we have some heparin involvement, devices
6 used to screen donors to that effect and to diagnose
7 viral diseases.

8 This slide shows ongoing Blood Safety Team
9 challenges, development and formalization of the best
10 cross-office approaches to key safety areas. BPDRs
11 seek ways to increase the value to the FDA and
12 regulated industry, emerging infection diseases. We
13 explore improvements in informatics. We use data
14 mining with advanced algorithms to detect safety
15 signals. And we would like to have denominators such
16 as the number of red cells, platelets and FFP
17 transfusions each year and the number of first-time
18 donors and repeat donors who use the product each year.
19 A lack of a denominator makes it difficult to determine
20 scientific information. One of our goals is to improve
21 the role of hospital-based transfusion staffs of our

1 fellow government agencies to improve databases.

2 In summary, the Blood Safety Team functions
3 as a coordinated, agile interoffice team that evaluates
4 processes, investigates and responds to a variety of
5 blood safety issues and plays an important role in
6 external outreach and risk communication.

7 We move on to fatality data. The first
8 fatality annual summary report was posted on the CBER
9 Website in March. In the past this information was
10 released only through FOIA request and presented for
11 public presentation by FDA staff. This fatality data
12 is from October 1st, 2005, to September 30, 2006, in
13 other words, fiscal years. In 2005, there were 97
14 transfusion recipients, 8 donors, 14 cases in which the
15 transfusions were not ruled out, 21 cases which were
16 considered not transfusion related. In FY 2006 there
17 were 95 reports received, 81 transfusion recipients, 14
18 donors, 10 cases in which a transfusion was not ruled
19 out and 8 cases in which the transfusion was not
20 related to the patient's demise.

21 This is a combined fatality data for fiscal

1 year 2005, 2006 by complication. We had 51 percent
2 TRALI, 20 percent is the hemolytic transfusion
3 reaction, non-ABO, 12 percent microbial infections, 7
4 percent hemolytic transfusion reaction from ABO
5 antibodies, 7 percent transfusion associated
6 circulatory overload and 2 percent others. The other
7 includes one graft versus host disease and one
8 therapeutic platelets pheresis error. Okay. And also
9 there's one case of anaphylaxis.

10 This is the fatality data for 2007. There
11 are 94 reports received. This is raw data. We had 34
12 TRALI incidents, which is about the same as in 2006.
13 Hemolytic transfusion reactions, ABO versus non-ABO, 5,
14 TACO, 6 microbial infections, which includes 3 Babesia,
15 2 anaphylaxis cases, 1 hepatitis B case, which was
16 later transferred to the transfusion not ruled out
17 category and 13 non-transfusion related and 17 donors.

18 I'm sorry this is hard to see but this is
19 the complication stretched out through for fiscal year
20 '05, '06 and '07. What's interesting here is that you
21 have the same number of TRALI cases in FY '07 as FY

1 '06; however, since there are fewer recipient
2 fatalities, the percentage is 65 percent. It's much
3 higher.

4 This is another slide of basically the same
5 material. The fiscal years '05, '06 and '07 are listed
6 together in the last column, TRALI averaging about 55
7 percent over the three-year period, from '07, 55
8 percent, hemoglobin transfusion reactions 16 percent,
9 microbial infection, 12 percent, TACO 8 percent,
10 hemolytic transfusion reaction ABO antibody 7 percent
11 and 2 percent anaphylaxis and 1 percent other.

12 This is a schematic of the
13 transfusion-related fatalities for fiscal year '05 and
14 '06 by complication. TRALI, as you can see, represents
15 in both years for the most numbers, reports, followed
16 by nonABO transfusion, nonABO hemolytic transfusion
17 reactions and microbial infections. This is the same
18 slide of fiscal year '07 added. TRALI is about the
19 same for FY '06 and FY '07. Hemolytic transfusion
20 reactions dropped off. Microbial infections had
21 dropped slightly. The TACO dropped the same, hemolytic

1 transfusion reactions, non-ABO antibodies are about the
2 same as well as anaphylaxis and other.

3 These are the reports of TRALI by
4 implicated blood product. FFP for FY '06 is up almost
5 twice the number for FY '05. RBC TRALI stayed about
6 the same. TRALI from plasma, which includes FB-24, has
7 been reduced, FY '05 and FY '06, platelets pheresis has
8 been cut in half, and TRALI from multiple products
9 stayed roughly the same.

10 This is reports of TRALI by implicated
11 blood products, with FY '07 added. In FY '07 TRALI
12 returned from FFP to 12 cases but there's a spike in
13 RBC cases and there's also a spike in multiple products
14 cases with the rest of the plasma platelet pheresis
15 reduced.

16 Now, this is the fatality data for FY '06,
17 '05 and '07 by antibodies. The most frequent are
18 multiple antibodies, ABO antibodies, 31 percent. I
19 won't go through all these but what's interesting is
20 two-thirds of these antibodies were delayed hemolytic
21 transfusion reactions and of the remaining third

1 one-half were laboratory errors and the other half were
2 emergency transfusions for which a cross-match was not
3 available.

4 These are the organisms that were found in
5 the fatality cases. What's interesting here is the
6 *Eubacterium limosum* is anaerobe and the *Morganella*
7 *morganii* is anaerobe. The cases for FY '07 were about
8 the same with the addition of a streptococcus and
9 *Klebsiella*. This is a schematic of microbial infection
10 by implicated product, red blood cells increasing in FY
11 '06 from FY '05, pooled platelets stayed about the same
12 and platelets pheresis dropped from FY '05 to FY '06
13 from 6 to 2. This is a microbial infection by
14 implicated blood products with FY '07 added and FY '07
15 RBCs rose slightly to, almost back to the FY '06 level.
16 Pooled platelets stayed about the same and the platelet
17 pheresis stayed about the same, down from FY '05 to FY
18 '06 and FY '07.

19 The FDA is considering future adverse
20 reaction reporting to revise the proposed rule on the
21 safety reporting requirements for human drug and

1 biological products. The proposed rule was circulated
2 March 14, 2003. There was an extended time period
3 which closed October 14, 2003 and comments received are
4 still under review in the agency. Thank you.

5 DR. BRACEY: Thank you. Questions from the
6 Committee? Dr. Klein?

7 DR. KLEIN: Yes. How does the proposed
8 adverse events reporting and analysis fit with the
9 public-private hemovigilance initiative we've heard
10 much about recently?

11 DR. HOLNESS: I'm sorry. What's your
12 question, how does it fit with the --

13 DR. KLEIN: The hemovigilance, the
14 public-private hemovigilance initiative, biovigilance,
15 I suppose it's been called, where again if we're
16 looking at, I hope at national adverse events relating
17 to transfusion and analyzing them on a national basis.

18 DR. HOLNESS: Well, the team is headed by
19 Dr. Jonathan Goldsmith and he I believe is also on the
20 hemovigilance Committee as well, so, there's shared
21 information back and forth.

1 DR. BRACEY: I think, Dr. Epstein, you had
2 a comment?

3 MR. EPSTEIN: Yeah. What Dr. Holness says
4 is correct but let me elaborate just a little bit. As
5 you know we have over a period of two years a
6 discussion about strategic planning for the blood
7 system, and two working groups within HHS, one on
8 biovigilance, one on disaster preparedness. The
9 biovigilance group has been very active and is now
10 working in cooperation with AABB on the AABB initiative
11 on hemovigilance later to be expanded potentially to
12 biovigilance, including cells, organs, tissues. That
13 collaboration has resulted in a series of meetings in
14 which the interface between the private sector role and
15 the government role has been the principal focus. And
16 you may already know because I think it was made public
17 at one of our previous meetings that there is a pilot
18 program at a number of hospitals being established
19 with, you know, seed money to expand on the
20 epidemiology surveillance network existing in hospitals
21 to include transfusion event-related reporting.

1 Now, coming to your question, how does all
2 that interface with FDA reporting? Well, the
3 requirement to report serious adverse events related to
4 both donation and transfusion is not yet in place.
5 And, FDA through the cooperation with this Committee
6 has made known that the design of any hemovigilance
7 system will need to take into account the additional
8 requirements for mandatory reporting and that will
9 include appropriate design of data elements as well as
10 data system compatibilities with the FDA reporting
11 system to the extent that it is also electronic. So,
12 the issues are on the table but the resolution is not
13 yet at hand. But, the folks who are, you know,
14 involved in developing both the voluntary system,
15 government-mediated pilot and FDA reporting are all
16 talking to each other.

17 DR. BRACEY: Dr. Benjamin?

18 DR. BENJAMIN: I just have a question.
19 There appear to be some trends in the data, for one, an
20 increase in the hemolytic transfusion reactions over
21 the three year period. Another one I noticed was in

1 the TRALI caused by apheresis platelets have gone from
2 4 to 2 to 1. Has your Committee considered given that
3 -- active intervention -- to cause those D and P
4 climbs, why this, why that's happening?

5 DR. HOLNESS: Well, as far as TRALI is
6 concerned there is the initiative by AABB. They
7 produced some TRALI -- so that that may have had an
8 effect. Incidentally, for FOIA, just as a note the
9 TRALIs have gone down as well. So it may be
10 responsibility, there may be because AABB memos have
11 taken effect.

12 DR. BENJAMIN: The reason I focused on
13 platelets on TRALI was that the AABB memo got sent in
14 November of this year for apheresis platelets and so
15 there seems to be a decline over the last three years
16 that's preempting, you know, actually putting in place
17 at some cost to the blood centers. It would be
18 wonderful to understand what's going on.

19 DR. HOLNESS: My guess is that some of the
20 blood centers responding to tests their repeat
21 platelets donors early so that, you know, to get ready

1 for the 2008 deadline.

2 DR. BENJAMIN: I'm not sure it's happening
3 in the larger blood centers at all. I know the Red
4 Cross represents probably 30, 40 percent of the
5 apheresis platelet, mark, that's not the case, so, I
6 think it's worth looking at more closely.

7 DR. BRACEY: Dr. Holmberg, question or
8 comment?

9 DR. HOLMBERG: Dr. Holness, I was sort of
10 amazed at your numbers for the donor fatalities went
11 from 8 to 14 to 17 and in light of the most recent
12 paper from the Red Cross on the adverse events in the
13 younger population, can you elaborate a little bit more
14 on that?

15 DR. HOLNESS: Well, much of that data has
16 been taken with a grain of salt. The data includes
17 plasma, source plasma donors and some of the reporting
18 is a response of some, you know, media expanded, you
19 know, donors in the resource plasma industries that
20 died and so that there's a closer look at source plasma
21 donors who have died. But there's no real, in other

1 words, there's no real criteria in terms of whether the
2 source plasma donor has died, you know, as a result of
3 procedure or not. So, I think some of that is errant
4 reporting.

5 DR. BRACEY: I had a question in terms of,
6 there now is an initiative, the integration of data.
7 There now is an initiative from CMS so that when that's
8 a transfusion error, ABO, that will be reported, it
9 will not be aimed at the services. Is that information
10 currently, that information does not get to the FDA for
11 review?

12 DR. HOLNESS: It will if our, the rule that
13 I just mentioned at the last -- information as well.

14 DR. BRACEY: And then another point that
15 seemed curious though it's really in your data, over
16 the years the fatalities related to nonABO
17 incompatibilities seem unusual in terms of just my
18 clinical experience and I wonder if some of those may
19 be due to errant reporting or perhaps poor treatment.
20 And so does your group analyze the management of those
21 instances with a goal of having feedback in terms of

1 how to improve practices?

2 DR. HOLNESS: Well, there is some, we
3 talked to the hospitals involved and there's usually
4 inspection in the hospital involved to make sure that
5 their, the transfusion practices are current and
6 according to regulations. That's as far as we go
7 actually.

8 DR. BRACEY: Again, it's surprising that
9 the frequency is that high but it is what it is.

10 DR. HOLNESS: Yeah. Some of them are
11 delayed hemolytic transfusion reactions and it's very
12 hard to kind of figure out, you know, what exactly
13 happened, whether the patient didn't really have a
14 delayed hemolytic reaction or whether, you know, it's
15 just, you know, a problem that they missed in the
16 laboratory, with a laboratory rat.

17 DR. BRACEY: Additional questions or
18 comments from the Committee? Thank you very much.
19 Moving on, our next speaker is, oh, yes, Dr. Ruth
20 Solomon. Dr. Solomon is the director of the division
21 of human tissues in the office of cell, tissue and gene

1 therapies. Dr. Solomon will present on adverse
2 reaction reporting from human cells, tissue, cellular
3 and tissue based products. Thank you. Dr. Solomon?

4 DR. SOLOMON: Thank you. And thank you for
5 inviting me to speak at the meeting. I think we're
6 happy to see that tissues and organs are being
7 gradually introduced to this Committee. Okay. This
8 morning I will be discussing some background on the
9 regulation of cells and tissues, the Tissue Safety
10 Team, the challenges faced by the team. I will give
11 you some summary data on the adverse reaction reports
12 we received and also some Website addresses.

13 So, first what are HCT/P? That acronym
14 stands for human cells tissues or cellular or
15 tissue-based products. And, the definition is the
16 articles containing or consisting of human cells or
17 tissues that are intended for implantation,
18 transplantation, infusion or transfer into a human
19 recipient. This term covers a wide variety of cells
20 and tissues. For instance, musculoskeletal tissue,
21 bone, soft tissue, such as tendon, skin, human dura

1 mater, cardiovascular tissue such as human heart valves
2 like vessels, ocular tissues like cornea and sclera,
3 reproductive tissues, semen, oocytes and embryos,
4 hematopoietic stem progenitor cells derived from
5 peripheral blood and cord blood, and other cellular
6 therapies including one licensed product, Carticel,
7 which is an autologous chondrocyte product, and most of
8 other cellular therapies are under I&D currently.

9 We then excluded from this definition our
10 vascularized human organs which are overseen by HRSA,
11 blood or blood components or blood derivative products
12 which have a separate regulatory pathway, secreted or
13 extracted human products, such as milk, collagen and
14 cell factors, minimally manipulated bone marrow for
15 homologous use and not combined with another article.
16 Those are again overseen by HRSA. Ancillary products
17 used in the manufacture of HCT/Ps, cells, tissues and
18 organs from other animals, in vitro diagnostic products
19 and, as you heard, blood vessels recovered with an
20 organ intended for use in organ transplantation and
21 labeled for use in organ transplantation only. So,

1 recently, as you heard, those are considered organs
2 rather than HCT/Ps.

3 Over the years we have developed three
4 rules which are codified in 21 CFR Part 1271. They all
5 became effective fairly recently, May 25th, 2005, so,
6 we have rules for establishment of registration and
7 product listing, donor eligibility requirements and
8 current good tissue practice, which is similar to
9 current good manufacturing practice but it is focused
10 on infectious disease, preventing infectious disease
11 transmission. And the adverse reaction reporting that
12 I'm going to talk about today, the requirement for that
13 is found in the current good tissue practice part of
14 the rule.

15 The legal authority for regulating P cells
16 and tissues comes from Section 361 of the Public Health
17 Service Act, which says that the Secretary can
18 promulgate rules to prevent the introduction,
19 transmission or spread of communicable disease. Unlike
20 blood, which also gets its authority from Section 361,
21 blood also gets its authority from Section 351 of the

1 Public Health Service Act, which permits licensing of
2 the blood products. Tissues are not licensed.

3 So the regulatory pathways for HCT/Ps are,
4 there are three, in general, three pathways. There are
5 the cells and tissues, which we refer to as 361,
6 because they're regulated only under Section 361 of the
7 Public Health Service Act. For them there's no
8 premarket review and approval. They can just go on the
9 market without FDA reviewing anything. But the
10 establishments have to follow Part 1271 only and we
11 determine their compliance with Part 1271 on
12 inspection.

13 Then under this broad category, HCT/Ps,
14 they can also be regulated as biologic products. There
15 are certain criteria that will allow you to be
16 regulated solely under 361. If a product, an HCT/P
17 does not meet all of those criteria, then it is
18 regulated either as a biologic product, and again those
19 would follow the requirements in 1271 but also would
20 have other applicable regulations applying to them.
21 Those products, of course, have premarket review and

1 approval in the form of a biologics license application
2 and they have to show safety purity, potency and
3 effectiveness before going on market.

4 There can also be HCT/Ps which are
5 considered medical devices, so, those follow Part 1271
6 and the Medical Device regulations. Again they have
7 premarket review and either clearance or approval
8 through the 510(k) or PMA mechanism and they again must
9 show safety and efficacy before being marketed. So,
10 now I talk about adverse reactions. An adverse
11 reaction is defined in Part 1271 as a noxious and
12 unintended response to any HCT/P for which there is a
13 reasonable possibility that the HCT/P caused the
14 response. And, we leave it up to the tissue
15 manufacturer after their investigation of an adverse
16 reaction to determine whether there is a reasonable
17 possibility that it was due to the tissue and thus they
18 make a report to FDA.

19 For biological products, the term used is
20 adverse experience. And that is broader. It includes
21 any adverse event associated with the use of a

1 biological product whether or not it's related to the
2 product. Okay. So, we have requirements that HCT/P
3 manufacturers must investigate any adverse reaction
4 involving a communicable disease, again because the
5 focus of 361 is on preventing communicable disease
6 transmission. So any adverse reaction involving a
7 communicable disease related to an HCT/P that they made
8 available for distribution, they must investigate.
9 They are not required to investigate adverse reactions
10 that do not involve communicable disease but they can
11 certainly do so and voluntarily report to FDA. These
12 might include product defects such as the package was
13 opened when it was received by the surgeon, et cetera.

14 Okay. What adverse reactions are required
15 to be reported to CBER? Those that again involve a
16 communicable disease and are fatal, life threatening,
17 result in permanent impairment or damage or necessitate
18 medical or surgical intervention. The tissue
19 manufacturer must report within 15 days of receiving
20 the information from the hospital or physician. And,
21 they use MedWatch, the same type form that is used for

1 FDA's other products for reporting adverse reactions.

2 The form is FDA 3500A for a required report.

3 Again, as I mentioned, some clinicians and
4 consumers will voluntarily report an adverse reaction
5 on a different form, 3500. All of these reports can be
6 faxed in or mailed in or telephoned in. So, where does
7 the center for biologic CBER receive their adverse
8 reaction reports from? Well, as I said, the majority
9 are from tissue establishments because they are
10 required to report adverse reactions involving a
11 communicable disease. We also get reports from
12 consumers or healthcare professionals through the
13 MedWatch office. Also, some reports are received from
14 CDC because CDC is often involved in the follow-up on
15 organ recipient transmissions of infectious disease and
16 the same donor may have donated both organs and tissues
17 so CDC let's us know about that.

18 Also during some of these procedures not
19 only are tissues implanted but certain synthetic or
20 nonhuman material devices are also implanted so
21 sometimes the reports would start out at CDRH and they

1 would be, we would be informed that human tissue was
2 also transplanted. In addition, there's a program that
3 was started by CDRH called MedSun where it's a
4 voluntary program where hospitals assign a particular
5 person to be on the lookout for adverse reactions at
6 that hospital and to make sure that they are, that they
7 report to CDRH. But the tissues had a pilot program
8 which we tab onto the MedWatch device program and got
9 some of the reports through that.

10 Okay. The Tissue Safety Team is one of the
11 three safety teams in CBER. You already heard about
12 the Blood Safety Team. There's also a vaccine safety
13 team. The Tissue Safety Team was the first one
14 established in May 2004. And, the purpose was to
15 provide a coordinated, efficient approach to the
16 receipt, routing, investigation, evaluation,
17 documentation and trending of reporting adverse
18 reactions involving HCT/Ps across five different
19 offices in CBER ands also beyond CBER. So, the Tissue
20 Safety Team, as I said, includes five offices in CBER.
21 We review all MedWatch reports received even though

1 those that our not infectious disease related. We
2 conduct follow-up on infectious adverse reactions
3 related to HCT/Ps. We often seek additional
4 information from the clinician and the tissue
5 manufacturer. The cases are evaluated and discussed
6 with the entire Tissue Safety Team and we have an SOPP
7 that describes the responsibility for each office
8 involved in the Tissue Safety Team.

9 So, these five offices of course are very
10 similar to the ones that Dr. Holness presented to you,
11 the only difference being that the product office is
12 different; in other words, instead of OBRR for the
13 Blood Safety Team, our office, the office of cellular
14 tissue and gene therapies is involved but we also have
15 Office of Epidemiology, OCTMA, Office of the Director
16 and the Office of Compliance and Biologics Quality. We
17 have a point person at each of these offices. Then
18 outside of CBER but still within FDA there are points
19 of contact at CDRH, the office of regulatory affairs,
20 office of crisis management. We also have point
21 persons outside of FDA, such as at CDC, HRSA and CMS.

1 We also sometimes involve a special government employee
2 who is consulted on unusual cases.

3 The reports first come into the office of
4 biostatistics and epidemiology and they determine if
5 it's a 361 HCT/P. They're entered into a database and
6 if there's an infectious adverse reaction, we determine
7 whether they are high priority. And there are certain
8 criteria for that, that I will mention in a minute.
9 And if they are lie priority, the entire TST working
10 group would be notified and we would begin follow-up
11 immediately. For other reports that are not considered
12 high priority, we determine if follow-up is needed and
13 they are on a slightly slower timeframe.

14 Okay. What we consider high priority cases
15 are any fatality, any infection with Clostridium or
16 group A strep because of past experiences where these
17 organisms have caused either fatality or morbidity.
18 Serious viral disease or seroconversion such as HIV,
19 HBV and HCV. CJD, for instance, an individual may die
20 of CJD and then it's discovered that they received a
21 cornea several years prior to death. And, so, there's

1 always the possibility that the cornea was responsible
2 for the CJD transmission and that is investigated. We
3 have one currently that's being investigated in
4 association with CDC.

5 Another high priority case would be if two
6 or more recipients of tissue or organs from a single
7 donor develop infections with the same organism. And
8 the example I put up there is incorrect. I meant to
9 give you an example, group B, beta hemolytic strep. We
10 had a case this year of two corneas from the same donor
11 being implanted into two recipients and both recipients
12 developed group B, beta hemolytic strep infection. In
13 that case we also saw that the preimplant cultures, the
14 cultures that the surgeons do prior to implanting the
15 corneas were also positive for the group B strep, and
16 also we go back and look at the donor information and
17 the tissue processor routinely takes cultures of the
18 tissue prior to processing the tissue. So, those are
19 called preprocessing cultures. There are also cultures
20 taken post processing.

21 So, in this case the preprocessing cultures

1 show that some of them, of the tissues, were positive
2 form group B -- beta hemolytic strep. Another high
3 priority case would be the same unusual organism is
4 cultured from the recipient's wound infection as was
5 found in one or more of the recovery, preprocessing or
6 postprocessing cultures of the tissue. For instance,
7 there were two cases of Clostridium transmission or
8 Clostridium infection in 2007 where the preprocessing
9 cultures also were positive for Clostridium. That
10 doesn't mean necessarily a causal relationship but it's
11 suspicious.

12 Also, if an unusual organism is found,
13 culture from the recipient's wound infection and all
14 match an environmental culture, we had one in 2006,
15 where an unusual organization name Chryseobacterium,
16 formerly known as Flavobacterium, for some older
17 microbiology students in here, where two recipients
18 again developed infection with Chryseobacterium and in
19 retrospect the tissue bank had noticed that their post
20 processing culture, positivity, those cultures are
21 supposed to be negative post processing. Well, they

1 seemed to be increasing. They got an increasing
2 percentage of positive cultures. And they did some
3 investigation and found that Chryseobacterium, which is
4 a water-borne organism, was found in the sink drain.
5 So, it was an environmental contaminant that probably
6 caused the infections.

7 Okay. When we do clinical follow-up the
8 office of biostatistics and epidemiology does that.
9 The types of things they would ask the clinician would
10 be if they don't, if this is not already been indicated
11 on the MedWatch form, the name of the product, lot
12 number and manufacturer.

13 Also important would be time interval from
14 implantation to the onset of symptoms. The culture
15 results, as I mentioned, the clinician might do culture
16 of the transport fluid. They might do a preimplant
17 culture of the tissue. If the patient develops a wound
18 infection, they would culture that and if they go in
19 and have to take out the graft, that is also cultured
20 sometimes. We would also ask if the patient
21 immunosuppressed, did they have infection prior to the

1 graft implant, was there anything unusual about the
2 surgery, an unusual length of time, for instance, and
3 then any medical or surgical interventions, special
4 handling or preparation of the allograft prior to
5 implantation.

6 Some surgeons actually soak the allograft
7 in antibiotic solution in the OR prior to implanting
8 it. Were devices also implanted? What's the general
9 impression of the surgeon? Does the surgeon feel that
10 the tissue caused the reaction? Most often they say
11 no. And also, did a hospital infection control group
12 investigate the case and what did they find.

13 So, if additional questions need to be
14 asked of the tissue manufacturer, the office of
15 compliance does that. For instance, the tissue
16 manufacturer is required to do an investigation so we
17 want to know what were their conclusions. We sometimes
18 ask for the donor medical records, to go through them
19 again, the processing methods, were there any
20 deviations in processing. Environmental monitoring is
21 reviewed. The pre and post culture results are

1 reviewed to see if there's a match with the recipient's
2 infection, whether or not there were other complaints
3 related to the same donor or whether other tissue banks
4 or recovered tissue from the same donor received
5 complaints.

6 So, our challenges, some of them are
7 similar to the blood safety group, in that this is
8 passive surveillance so there's often under-reporting
9 and bias. For instance, we find some, one particular
10 tissue processor seems to report a lot more than
11 others. It's not that they have more adverse reactions
12 from their tissues, it's just that their threshold of
13 reporting might be lower. We don't have denominator
14 data; the same problem as the Blood Safety Team. Also,
15 with tissue transplant it's difficult to distinguish
16 whether the infection in the recipient was due to the
17 graft or, as we all know, postoperatively you commonly
18 get infections, and distinguishing those is difficult.

19 The follow-up activities are very
20 labor-intensive. We would close a case when we've done
21 all the investigation we can think of and based on the

1 available information we don't think there's any
2 additional action that the TST can take. In most cases
3 there's no conclusion reached about whether the tissue
4 caused the reaction. In a few cases each year we think
5 there could be a probable link but of course it's not
6 certain.

7 Okay. And these are some statistics on how
8 many of these adverse reactions reports we receive.
9 This is not saying that the tissue caused the reaction,
10 just the reports that are received. So in 2006 there
11 were 147 reports; in 2007, 123. Their distribution by
12 tissue parallels the frequency with which these tissues
13 are transplanted. For instance, bone is the most
14 commonly transplanted tissue and so that accounts for
15 26 percent of the reports.

16 Okay. Then as I mentioned before, tissue
17 manufacturers are required to report the infectious
18 adverse reactions but not -- they can voluntarily
19 report noninfectious ones. So, remember this reporting
20 just started in 2005, May of 2005. So, in 2006, many
21 of the tissue establishments were reporting

1 noninfectious adverse reactions but this number has
2 dropped with our outreach to the establishments and
3 often product problems that are not adverse reactions
4 in the recipients are also reported.

5 So, we have several Websites if you're
6 interested in the rules and guidance documents that
7 have been issued so far for cells and tissues and also
8 any questions are funneled through our OCTMA, at their
9 Website and you can call them also. And lastly this is
10 a picture of the seven dedicated individuals who
11 comprise the division of human tissues.

12 DR. BRACEY: Thank you, Dr. Solomon. May I
13 ask one question, and that is, in that while the
14 reporting from the manufacturers is voluntary and I
15 guess at the hospital level it's quite voluntary, I'm
16 just projecting. Are there standards-setting
17 organizations that require reporting of such adverse
18 events? You know, if I'm a plastic surgeon I'm putting
19 in something, and there's something that goes awry, are
20 there clinical standards out there that require
21 reporting of such?

1 DR. SOLOMON: Klaus Nether from the Drug
2 Commission can probably better address that.

3 MR. NETHER: Yeah, with regards to in terms
4 of the healthcare organizations, such as hospitals,
5 ambulatory settings the Drug Commission does require in
6 terms of reporting any disease transmission or any
7 infections related to the tissue back to the tissue
8 manufacturer.

9 DR. BRACEY: Okay. Great. Thank you. And
10 then one other question is that perhaps unlike blood,
11 is there an international reach of these products and,
12 if so, do we hear from, you know, AEs outside of the
13 states?

14 DR. SOLOMON: Yes. There is an
15 international reach. Approximately half of all corneas
16 are exported from this country, all corneas recovered.
17 Yes, we do have some foreign reports but they're often
18 difficult for the Eye Bank or Tissue Bank to follow-up
19 on them. So, in general the information we get from
20 those are less than a domestic report would reveal.

21 DR. BRACEY: Dr. Triulzi?

1 DR. TRIULZI: Does your group sit on the
2 AATB, American Association of Tissue Bank's standard
3 setting Committee as a liaison and do you see any gaps
4 between what you would like and what their current
5 standards require?

6 DR. SOLOMON: Yes, we do. FDA has liaisons
7 to several of their committees, the Standards
8 Committee, the Uniform Donors Questionnaire Committee.
9 There are several committees. In terms of gaps, I
10 think their standards are very closely aligned to the
11 FDA requirements. That's why we're on the committees.
12 I don't see any gaps other than what was already
13 mentioned, the reporting by the clinicians. That's the
14 first step in knowing about an adverse reaction and
15 they're sometimes not reported.

16 The tissue and eye banks do try to make an
17 effort to get information back on who received the
18 tissue. They include, for instance, they can include
19 cards when they send the tissue to the surgeon or the
20 hospital and they would like the hospital or physician
21 or nurse to fill the cards and send them back. They're

1 seeing about an, on average, 50 percent return rate and
2 they would like to increase that amount because they
3 can't really address something if they don't know about
4 it. Also, we also sit on the efforts being made by the
5 CDC through UNOS the tissue, TTSN, Tissue Transplant
6 Safety Network that's being developed to try to
7 encourage reporting.

8 DR. BRACEY: Dr. Busch has a question or
9 comment?

10 DR. BUSCH: One question on both the blood
11 and the tissue surveillance activity, kind of relates
12 to Harvey's point about hemovigilance. This is a
13 really a global environment these days and I know the
14 FDA has interfaced with international organizations but
15 I'm just wondering, a lot of the these issues and a lot
16 of the preventions that have been implemented or
17 evaluated internationally, I'm just wondering what
18 formal relationships FDA has that allows them to
19 observe and monitor data, similar data coming from
20 other countries. For example, the SHOCK program, as
21 they implemented the program they saw a trend upwards

1 in reports. It was unrelated to events. There was
2 simply better case finding and then eventually that
3 settled out and then they were able to really monitor
4 the effect of intervention such as plasma. I'm just
5 wondering if there's a formal liaison relationship in
6 an effort to capture that data and to compare and
7 communicate with the regulatory agencies.

8 DR. BRACEY: Dr. Epstein, would you like to
9 comment, or Dr. Solomon? It looks like Dr. Epstein.

10 DR. EPSTEIN: We can both comment.
11 Because, there are parallel initiatives ongoing both
12 for organ cell tissues and for blood. What I can tell
13 you is first of all with respect to other regulatory
14 authorities, the FDA has established information
15 sharing agreements with at least a dozen other key
16 regulatory agencies in the world and although we don't
17 have ongoing shared databases, we do have the ability
18 to exchange information which should arise.
19 Additionally, we are participating members of a variety
20 of working groups, many of which are under the auspices
21 of the WHO, that are seeking to organize global data,

1 acquisitioning and information dissemination.

2 All of these efforts kind of fall into two
3 bins, one of which we tend to call surveillance, which
4 is to track numerators and denominators regarding
5 things that we know about, and that's to look at
6 long-term trends and it's to assess the impact of new
7 technology innovations, policy changes et cetera. But
8 then the other we tend call central monitoring, which
9 is the idea that when an unexpected or a novel event
10 occurs to ensure that there's prompt recognition and
11 then prompt response and prompt dissemination of
12 information. So, there are international groups
13 seeking to globalize both of those activities and we
14 are participants. So, yeah, Ruth, I guess you can tell
15 the parallel story.

16 DR. SOLOMON: We also have a memorandum of
17 understanding with other countries, you know, in the
18 tissue area. We also participate with other groups
19 such as DG Sanco, the European Union. The European
20 Union is in fact starting a program called Use-Site
21 (phonetic), where they will monitor adverse reactions

1 throughout their member states. We're also asked to
2 often review and comment on various directives -- their
3 called directives in Europe -- various documents that
4 other countries are developing. Many of them are
5 modelled on the U.S. system regulation of cells and
6 tissues. So, we do have a lot of interaction with
7 foreign governments.

8 DR. BRACEY: Thank you. Additional
9 comments? Yes, Mr. Nether?

10 MR. NETHER: Yeah, I have one question with
11 regard to when we talk a lot about the reporting but
12 now the flip side of that is, you know, everything that
13 gets reported, how does that filter back down in terms
14 of communication back to organizations that could have
15 infected tissue or infected organ in that same donor?

16 DR. SOLOMON: Okay. If there's a, if it's
17 probable that a tissue is the cause of an adverse
18 reaction, the tissue manufacturer usually voluntarily
19 will do a recall, which means that they will notify
20 their, what we call their consignees, the hospitals and
21 physicians, about a situation, ask that any

1 nonimplanted tissue sitting on the shelf be returned to
2 the tissue bank and also ask that the surgeons be
3 notified and leave it up to the surgeons whether they
4 want to tell their patients.

5 As I said, the majority of these are
6 voluntary, are done voluntarily. If, for instance, a
7 tissue bank or eye bank were not willing to undertake
8 this, FDA has the authority to order them to recall,
9 retain or destroy tissue and to cease manufacturing.
10 We've done that twice so far.

11 DR. BRACEY: I had one question in terms of
12 your challenge, in terms of the denominator, which is a
13 universal challenge, it seems, and that is, is there
14 any entity that actually has those data, you know, the
15 nongrowth tissues that are trans -- does that exist
16 anywhere?

17 DR. SOLOMON: Well, AATB does surveys of
18 their membership periodically to try to gather that
19 information and they often share that information with
20 us. That's the only organization I'm aware of that
21 monitors the usage. Actually, it's not really the

1 usage, it's the distribution; in other words, the
2 tissue, how many tissues were distributed; whether
3 they're actually implanted again is difficult to get
4 at.

5 DR. BRACEY: Okay. Thank you. If there
6 are any other questions, if not, we'll move on to our
7 next speaker. Thank you, Dr. Solomon. Our next
8 speaker is Dr. Elizabeth Ortiz-Rios. We've introduced
9 her before. And, this time she will present on the
10 review of organ transplantation-related serious adverse
11 events. Dr. Ortiz-Rios, thank you.

12 DR. ORTIZ-RIOS: Hi. Good morning, again.
13 My presentation, although it says review of organ
14 transplantation-related serious adverse events will be
15 more focused on death as post transplantation as an
16 adverse event, at least the first part of the
17 presentation. I have already talked about NOTA and the
18 final rule. I will mostly focus on post-transplant
19 data by organ, focusing on kidney, liver and heart,
20 talk a little bit about OPTN policy, 4.0, and its
21 reporting responsibilities, describe the Disease

1 Transmission Advisory Group, DTAG, and present some of
2 the data from 2006, 2007 and talk about HRSA's
3 implications for the future.

4 As I mentioned, OPTN was established by
5 NOTA in 1984. It's a unified transplant network,
6 private, nonprofit organization under federal location.
7 It is part of the United Network for Organ Sharing,
8 UNOS, and it regulates the final rule 2000. The final
9 rule, the objective of the final rule is to make
10 allocation policies more strongly based on objective
11 and measurable medical criteria. And it assigns
12 responsibilities. HRSA has a regulatory oversight.
13 OPTN has the responsibility for policy formation and
14 data collection and SRTR has the responsibility of
15 statistical analyses and evaluating policy compliance.

16 UNET is a -- secure online database for the
17 collection, storage, analysis and publication of all
18 OPTN data, regarding patient waiting list, organ
19 matching and transplants. It is used by all transplant
20 programs, OPOs and histocompatibility labs. It is a
21 secure means of communication between OPTN members, is

1 a means of disseminating information to all transplant
2 programs and OPOs regarding policy changes, technology
3 changes, training events.

4 Now I'm going to present some data from the
5 OPTN database on transplant death, post
6 transplantation, focusing on kidney, liver and heart.
7 As you can see, transplant death from 2001, 2006.
8 Thank you. The number of transplants for kidneys from
9 2001, 2006 was 93,759, and post transplant deaths
10 within the first year was 3,881, that is, 4 percent of
11 the transplants died within the first year. We then
12 reviewed the data 2001, 2004, for the same for
13 transplant deaths within one year, to be able to -- and
14 I'm losing some numbers here -- to be able to look at
15 death within the first year and within the first year
16 and less than three years, post transplant. Basically,
17 for what the data here is showing is that kidneys
18 within the first year, 4 percent die and within the
19 first and three years 5 percent die of the 60,000
20 transplants that occur with kidneys. With liver there
21 is a 14 percent death during the first year and 8

1 percent death within the first year and the third year.
2 And for heart is 13 percent death within the first year
3 and 7 percent death within the first and third year.
4 And this data is as of May 2008.

5 I wanted to present to you before talking
6 about the causes of death for kidneys, post
7 transplanted kidneys, as you can see here, this is the
8 wait list which is increasing, and transplants are
9 increasing but are not of the same rate but at least we
10 show some increase here, almost 10,000 people on the
11 wait list in 2006, while there is a little bit less
12 than 20,000 transplants occurring in the same year.

13 Regarding causes of death for those during
14 the first year those 14 percent or 7 percent within the
15 first and third year, basically the majority of the
16 death is due to infection or cardiovascular problems
17 and within the first year and third year, still
18 infection is a little bit high and cardiovascular,
19 although we see other numbers here, which I'm not going
20 to go into because we need to do further analysis on
21 this, unknown there's an 18 percent death, where we

1 know that the person is dead, loss the follow-up to be
2 able to say what the cause of death was, we're not
3 quite sure yet but mostly the focus here, infection,
4 cardiovascular problems, have been the cause of death
5 within the first year and within the first and third
6 year.

7 For liver, this is the wait list, has
8 decreased a little bit and then stabilized between 16
9 to 18,000 but there has been some slight increase in
10 transplants throughout the years, which, of course, we
11 have the collaborative program, which have increased
12 donation in the U.S. These are the causes of death of
13 liver within the first year, is mostly infection,
14 cardiovascular and graft failure and within the first
15 and third year -- and we picked this 2001, 2004 to be
16 able to have data for the last three years. We see
17 that malignancy is the cause of death, the majority,
18 the causes of death within this period for liver,
19 followed by graft failure and infection but it is
20 slightly less.

21 For heart, the wait list, it is good to see

1 that is going down, between 2001, 2006 while the
2 transplant, number of transplant decreased a little
3 bit, 2003, and perhaps due to the collaboratives we see
4 that the numbers of transplants are increasing. And
5 again for primary cause of death during the first year
6 is graft failure, infection and cardiovascular and
7 within the first year and third year basically is the
8 same, infection, graft failure, infection and
9 cardiovascular. Limitations of the OPTN database is
10 that there's no data collected about serious viral,
11 bacterial, fungal, parasitic infections, and
12 donor-related malignancy data is collected but not
13 nearly inclusive, although we do have a collaboration
14 with SEER/NCI to look at cancer data and post
15 transplant plant death or causes, malignancy among post
16 transplant patients.

17 Now I want to talk a little bit about
18 OPTN/UNOS policy 4.0 and the reporting
19 responsibilities. The OPTN/UNOS policy 4.0 was
20 approved by the board of directors in November 2004 and
21 at this time is under revision. This policy created a

1 list of diseases, medical conditions that must be
2 communicated to the transplant center if known to be
3 present in the donor. And it established requirements
4 for prompt reporting of cases of potential transmission
5 of diseases or medical conditions which would be of
6 donor origin, detected by transplant center or the OPO.
7 When a transplant program is informed that a recipient
8 has or has been confirmed positive or has died from a
9 transmissible disease, they have a working day to be
10 able to notify the OPO as soon as possible, with
11 regards to the OPO, in turn, must communicate test
12 results and diagnosis to any transplant center or
13 tissue bank that received organ or tissue from that
14 donor. The OPO manages the investigation, determines
15 whether the donor was diagnosed with a potentially
16 transmissible disease and notifies OPTN as soon as
17 possible. They must submit a written report within 45
18 days.

19 So, here even though it is not for Dr.
20 Solomon, with regards to infections related to the
21 donor, that we think are related to the donor, all the

1 tissue banks that receive tissue from that donor will
2 be notified. OPTN in turn assists the procuring of OPO
3 in identifying all transplant programs and recipients
4 who is an organ from that donor or tissue from that
5 donor. OPTN will monitor the notification process,
6 request any additional diagnostic results and should
7 forward a copy of the OPO's final report to the
8 recipient transplant centers as well as to HRSA.

9 Now I would like to describe what the
10 disease transmission advisory group. It is an ad hoc
11 OPTN/UNOS Committee which was established in 2006 as a
12 subcommittee of the Operations Committee to review each
13 of these cases reported to the electronic patient
14 safety system. HRSA and CDC are ex officio members.
15 The DTAG -- the disease transmission advisory group,
16 called the DTAG, DTAG reviews current disease
17 transmission reporting policies, develops disease
18 reporting forms and reviews each case report to ensure
19 secure share-point site and makes recommendations to
20 the OPTN/UNOS Policy 4.0.

21 DTAG's workflow, there is a report made to

1 UNOS regarding an apparent donor related infection or
2 malignancy. The UNOS will prepare a summary of the
3 event, redact patient OPO and transplant center
4 identifiers, upload all this material in the share
5 point server, and alerts the DTAG members by e-mail.
6 And then the members will respond within 24 or 48 hours
7 and they will have an ongoing electronic discussion
8 regarding this case, looking at what had been done,
9 what could be done in making recommendations.

10 There is coordination with CDC. CDC is
11 alerted with regards to reportable diseases and those
12 with potential epidemiologic importance. There are
13 event-specific conference calls, like, for instance,
14 with the HIV, CDC cases or the TV cases, there are
15 specific goals for certain of these call reports. They
16 require a 45-day report and DTAG will have monthly
17 reports review the reports over the past month and
18 review outstanding queries.

19 DTAG categorizes all these events as
20 definite, probable, possible, excluded, expected or
21 unexpected, as cytomegalovirus or -- infections which

1 you have to expect. And DTAG has been collecting data
2 from 2006 to 2007 on malignancies and infections.
3 Initially the reports were not as many as we see now in
4 2007 and you will see how it has increased.

5 This is just to show you what types of
6 malignancies -- I know the numbers and letters are
7 small -- but what malignancies have been reported as
8 donor-related. And these are infections reported as
9 donor-related infections.

10 Looking only at the 2007 data that DTAG has
11 been collecting, there have been many false positive
12 testing results, reports of expected transmissions, as
13 cytomegalovirus or toxoplasmosis and death related to
14 donor-derived disease. There have been, 2007, actually
15 there have been nine deaths, but 7 are of those cases
16 that have been reported, as proven. And this is really
17 8 percent of all the reports and 35 percent of the
18 proven cases. Overall there have been 88 reports in
19 2007, and it's looking at all the donors, 14,395, that
20 is 3.6 percent but we believe there is under-reporting
21 so these might be close to .1 percent. And of the

1 transmissions we see that proven, probable, possible is
2 3.2 percent of the reports and proven is .1 percent,
3 when you do the numbers of the reports, of the donors,
4 I'm sorry, of the donors.

5 Limitations on DTAG data, this is voluntary
6 reporting. Individuals may not be recognized the donor
7 derived disease transmission. They may have limited
8 ability to detect clusters if the recipients are in
9 different hospitals or different places where they
10 cannot meet, they're not able to link these infections
11 and some may try to work up the problem on their own.
12 There's no enforcement. Many reports go without the
13 day 45 report and there is no ability to require
14 testing or follow-up. Limited follow-up, the 45 day
15 report may be insufficient, especially for malignancy.

16 And now what does HRSA see for the future?
17 To deal with the events we need to define reporting
18 expectations to OPOs, CDC and state health authorities
19 and we are presently working on that. We need to
20 strengthen DTAG's interactions for initial
21 determination of donor transmission. We need to

1 strengthen DTAG's communication to other potential
2 tissue and organ destinations and we must clarify and
3 expedite CDC involvement in the investigation as the
4 event unfolds.

5 What we see for decreasing these events, we
6 need, HRSA has asked OPTN when NAT -- test for HIV and
7 CDC can be made nationally routine? We have a
8 subcommittee, OPTN has a subcommittee in place where
9 members of DTAG and members of OPO -- OPO, right -- of
10 the OPOs. And we must continue to work with CDC to
11 study events for guidance on how to screen more
12 effectively without loss of organs to false positives
13 and we need to investigate the possibility of an
14 explicit approach relating the risk without
15 transmission versus the risk of transmission with the
16 transplant for the individual cases, and DTAG has been
17 given the charge. I believe they will be presenting on
18 this during the summer to the board this summer on how
19 to assess the risk for the individual case. And I
20 thank you.

21 DR. BRACEY: Thank you. I guess I have one

1 question and that is given the high ratio of those in
2 need to means available, there are certain differences
3 between organ transplants and other, you know,
4 biological tissues that are shared, i.e. blood. When,
5 for example, if you took the case of Chagas, for
6 example, and you note that there are individuals that
7 are sort of, well, organs that may infect the same, the
8 same donor affecting multiple individuals, I guess what
9 I'm kind of getting at is, so, how do your findings
10 affect the policies of those that are doing the
11 transplants or procuring the organs? You're surveying
12 and you're reporting back, but, how does the policy
13 change?

14 DR. ORTIZ-RIOS: Are we talking about
15 Chagas in particular or any infection diseases?

16 DR. BRACEY: Oh, no. I'm just using that
17 as an example. If you have organism X and suddenly
18 organism X is found to be transmitted a little more,
19 well, more than you would expect, you report that back
20 to the OP -- you report that back to some groups, but
21 my question is so then what happens; how is that acted

1 upon?

2 DR. ORTIZ-RIOS: Go ahead, Dr. Ison.

3 DR. BRACEY: Dr. Ison.

4 DR. ORTIZ-RIOS: So, I'm the chair of the
5 disease transmission advisory group, so this group,
6 just to clarify one issue that has changed a lot over
7 the past year from one that was a little bit more
8 passive to one that's been very active. In every
9 meeting I go to, seems like we get added
10 responsibilities. What we are really in our agency
11 working on this data, what we are doing to address that
12 issue is up to this point just looked at the data and
13 not done very much with it. We're doing several things
14 to move the issue forward. Number one, I feel very
15 strongly and the group is moving forward with making
16 sure that the transplant community is aware of these
17 transmission events because unless they're aware of it
18 they can't look at it to help us get a better sense of
19 what the numerator is in this case.

20 Secondly, we are in the process and
21 shooting for the September meeting to look at the

1 entire policy four, which and policy two which is donor
2 testing criteria to consider in, information presented
3 to the transplant center organs to see what kind of
4 things we need to change based on the data that we're
5 collecting. And this is going to have to be something
6 that is reviewed on a regular basis. But, the big
7 challenge is we can identify if something is a problem
8 like Chagas, clearly been transmission events but the
9 challenge is how do we design policy that won't affect
10 organ availability. And so that is why we're going to
11 need to do additional research related to the impact,
12 so that we don't have adverse effect on organ
13 availability while increasing safety.

14 DR. BRACEY: Dr. Rios?

15 DR. ORTIZ-RIOS: And that's why the third
16 point there for decreasing events, occurrences to
17 investigate the possibility to be able to assess what
18 the risk really is and not lose organs. So, as Dr.
19 Ison said, the policy 4.0 is under revision. And the
20 good thing is that more and more data is being
21 collected through DTAG, is more organized this year and

1 we will be able to analyze this data and make better
2 decisions.

3 DR. BRACEY: Dr. Ramsey, then Dr. Klein.
4 Dr. Ramsey?

5 DR. RAMSEY: Yeah, I just wanted to come
6 back to your table -- for as second and, I guess for a
7 second I guess point out for the verbal record here
8 that there were shown the table four cases labeled as
9 confirmed recipients of hepatitis C and HIV and zero
10 cases of hepatitis B. And, I just wanted to point out
11 of course we're backwards from what is expected in
12 terms of the blood transfusion risk, and I wanted to
13 ask whether confirmed recipients means that that was
14 confirmed as a transmission from a donor or whether
15 that was just confirmed in a recipient.

16 DR. ORTIZ-RIOS: These are confirmed --
17 we're talking about this one, right?

18 DR. RAMSEY: Yes.

19 DR. ORTIZ-RIOS: And those four cases
20 of HBc and HIV are the same patients, the same
21 recipients. They were infected with both and they were

1 confirmed to be donor-related.

2 DR. RAMSEY: Thank you.

3 DR. BRACEY: Dr. Klein?

4 DR. KLEIN: Yeah, I have two questions.

5 The first is, why do you think that the renal
6 transplant waiting list is increasing?

7 DR. ORTIZ-RIOS: Renal transplant, right
8 here. Let's go back to that.

9 DR. KLEIN: The question is why. I mean,
10 is this because the criteria for transplant are
11 increasing, are patients surviving longer end-stage
12 renal disease by the transplant? What are the reasons
13 we're seeing that increased waiting list?

14 DR. ORTIZ-RIOS: Well, I really think that
15 there is an increased number of patients in need for
16 renal transplant and although we have seen increases in
17 transplantation and these have, with the collaboratives
18 there have been increases, we need more organs, donated
19 organs.

20 DR. KLEIN: I guess, increased numbers of
21 patients with end-stage renal disease?

1 DR. ORTIZ-RIOS: Yes.

2 DR. KLEIN: Thank you. The second question
3 I had is I noticed that the major cause of death as you
4 pointed out is infection?

5 DR. ORTIZ-RIOS: Yes.

6 DR. KLEIN: And yet there are no national
7 statistics on what kinds of organisms or fungi or
8 whatever, or at least --

9 DR. ORTIZ-RIOS: Not here but I could look
10 farther into the data. I don't have it here.

11 DR. KLEIN: Yeah, that was the question,
12 whether there is a national database because that seems
13 to me to be enormously important in terms of
14 availability organs, if you're losing the organs you
15 have, you would like to know on a national basis what
16 the causes are, and maybe one could address those.
17 Again, if not, if there isn't a national database,
18 maybe that ought to be on a person's list for the
19 future.

20 DR. BRACEY: I think Dr. Ison had a comment
21 on that.

1 DR. ISON: Yeah, that is one of the major
2 limitations that we have, look at the data that is
3 collected, It's very limited and so to be able to get
4 down into detailed information is -- current database
5 -- is something that definitely needs to be looked
6 into.

7 DR. BRACEY: Dr. Triulzi?

8 DR. ORTIZ-RIOS: I wonder if we could go
9 back to the table with malignancies that are -- and I
10 can understand that if a malignancy is arising in a
11 transplanted organ, that that would make sense. But,
12 what are the criteria that would be a confirmed
13 recipient, for instance the glioblastoma multiforme or
14 the metastatic melanoma, how do you attribute those to
15 the donor?

16 DR. BRACEY: Dr. Ison again.

17 DR. ISON: So it's actually difficult to do
18 but ease once you get the answer. So basically what
19 they do is they have ways to look at markers on the
20 tumor surface to determine whether or not it is of
21 donor origin. So if you have a male donor to a female

1 you can look just at whether it's XY in tumor cells.
2 If it's a sexless match you have to look at each of the
3 markers but in the cases where we have confirmed in
4 most of the cases there's clear keratitic (phonetic)
5 changes that are suggestive of donor origin.

6 DR. BRACEY: Dr. Pomper?

7 DR. POMPER: I was just wondering, are
8 there data available on the loss of organs to false
9 positive results? Because that was alluded to, there's
10 a concern about a false positive result possibly losing
11 organs so I was wondering how often it occurred.

12 DR. BRACEY: Dr. Ison?

13 DR. ISON: Yeah, there is a good data
14 working in the process of trying to get that data with
15 the false positive rate is but we know it's a problem
16 because around the HIV, hp-C transmission we had a huge
17 spike in reporting of positive results from nucleic
18 acid testing done after organ transplantation but
19 subsequently were revolved to being truly negative and
20 that that reporting dropped off as concern for
21 reporting that dropped down so clearly we are

1 collecting that data initially.

2 DR. BRACEY: And one other question, in
3 terms of the challenge to provide a test result in such
4 a finite period of time, is there research or
5 development taking place to yield more rapid accurate
6 assay systems?

7 DR. ISON: There is although there's not a
8 lot of funding behind it. It's mostly industry
9 sponsored and as we have learned from talking with
10 industry, we're a drop in the bucket, you know, that
11 the number of organ or donors that are evaluated is
12 very small compared to blood donors, tissue donors
13 those kind of things as well as other indications for
14 these platforms. So, having a platform that's easy to
15 do in the settings that we need it is the challenge,
16 and it's one of the things that we're looking at
17 particularly with nucleic acid testing, again it's much
18 more challenging to do and a lot of these tests are
19 done in the middle of the night, you know, on one
20 single specimen and the experience in the center may be
21 highly variable and that will probably be related to

1 false positives.

2 DR. BRACEY: Thank you. Additional
3 questions? Yes, Dr. Duffell.

4 DR. DUFFELL: On your malignancy table I
5 was struck by the number for the renal cell carcinoma,
6 not only how it stands out against everything else but
7 also in comparison with the confirmed recipients. I
8 mean, is there any comments you have about that?

9 DR. ISON: So we put together the whole
10 issue of malignancy, I feel very uncomfortable with the
11 data that we have, that we have information up to day
12 45. Well, as all of us know for malignancy
13 intersection 45 days after the initial report and often
14 most of these are made at the time of procurement,
15 where a malignancy is noted. So day 45, really, we're
16 not getting good quality data to assess true
17 transmission. We've established an entire malignancy
18 risk group that's going to look at this issue very
19 carefully. The interesting thing from the organ
20 availability standpoint is what's done with these renal
21 cell carcinoma cases. Many times they're tiny, little

1 foci that are excisable. Some centers will use those
2 organs, some centers won't, so again trying to provide
3 advice to the transplant community about how best to
4 handle these cases but we also need more information on
5 the back end of what's happening with these organs when
6 they are used.

7 DR. BRACEY: Dr. Epstein?

8 DR. EPSTEIN: Actually I had a similar
9 question about marker positive organ donation because
10 use is not prohibited and to what extent does
11 transmission reflect the use of seropositive donors?

12 DR. ISON: And again that's not something,
13 we don't have a good, from a defect standpoint a good
14 handle on that because there is no requirement that if
15 you use these organs that they have any additional
16 follow-up testing. The night before guidelines that
17 were designed to reduce the transmission of HIV, for
18 example, recommended that all patients that receive
19 organs from what they define as high-risk recipients
20 get post transplant testing for HIV, we went back and
21 also suggested that information be reported back to

1 SRTR, we went back to the UNOS database and found that
2 only about 6 percent of recipients of high-risk donors
3 in the very short time period where we could look at
4 that data in the database actually have follow-up
5 testing on file so there's probably also a lot of very
6 limited follow-up testing in known patients.

7 DR. BRACEY: Thank you, Dr. Holmberg?

8 DR. HOLMBERG: Just to hopefully get the
9 last word in, let me just say that first of all, as you
10 heard, Dr. Ison is quite the authority on DTAG and this
11 is one thing that we did have is the conflict of
12 interest with the DTAG, as you, this is very beneficial
13 for you to be on the Committee because of the
14 experience that you bring with us. I'm a little
15 concerned with the evolution or I shouldn't say concern
16 is not probably the right word but where DTAG started
17 off as an ad hoc Committee, do you see this moving as a
18 more standing Committee? It sounds like it is a
19 standing Committee, under the UNOS, and, you know, I
20 think that we've heard very clearly that there's a need
21 for more data collection. Can you comment on both of

1 those, Standing Committee and data collection.

2 DR. ISON: So, we're technically an ad hoc
3 committee, not one of the formal standing committees
4 under the board so slight differences but very, very
5 similar in those regards. We have a number of
6 different areas that we've been asked to look at.
7 We're kind of -- the subgroup looking at nucleic acid
8 testing, we've been asked to assess risk of infection
9 related to the particular transplantation, and that the
10 malignancy group is going to look at the malignancy
11 data as well, to better determine how to move forward.
12 Clearly more research is going to be needed to be done.
13 We're also going to need more expertise on the group as
14 our pattern of activities has increased and so over the
15 coming years, my goal at least to increase expertise on
16 the group as well as start dealing with some of these
17 issues as the reporting groups come back.

18 There is a lot of work actually going on in
19 the background, for example, with nucleic acid testing,
20 working with the OPO Committee and the OPO to try to
21 get a better sense of what's actually being done now,

1 actually look at the UNOS database to see is the
2 presence of having nucleic acid testing impacting the
3 decision to use organs. And I think as we start
4 getting that first layer of evidence it will help us
5 better inform how to move forward including research as
6 well as policy issues. So does that answer --

7 DR. BRACEY: We've heard I think some
8 interesting reports and there seemed to be an
9 opportunity as was mentioned by Dr. Holmberg to acquire
10 more information. Specifically one consideration that
11 I would offer is that we, as a Committee would consider
12 recommending that the biannual survey that we require
13 information on tissue activity, help with deriving a
14 denominator.

15 The second consideration would be whether
16 we would have a recommendation that efforts would be
17 made to capture the type of specific infection that
18 occurred following transplant, and then finally to
19 support the developmental efforts for rapid assay
20 development for donor screening in the transplant
21 setting. Discussion, what does the Committee think of

1 those potential recommendations?

2 DR. ISON: I strongly support, especially
3 the development of testing capacity because another
4 issue that hasn't been talked about today is that there
5 are changes in availability of testing platforms that
6 are commonly used in the transplant population by some
7 of the industry and so we may be left in the very near
8 future with an absence of proof tests to do in an
9 efficient and cost efficient way for this and so again
10 you may need some support on that as well.

11 DR. BRACEY: Thank you. Additional
12 comments? If there are none, then what I will attempt
13 to do is to work on coming up with a resolution a
14 little later on to address those three points. We're
15 at the point of -- we're near lunch but we're not quite
16 there. Dr. Epstein.

17 DR. EPSTEIN: This is on the uptake but for
18 certain organs, as Dr. Klein pointed out, we have this
19 growing disparity between number of people on waiting
20 list and number of transplants accomplished and I think
21 that there's an unanswered question here whether these

1 are people who are desperately in need of their
2 transplant or people who are now able to be sustained
3 medically pending their transplant. And, so some
4 effort needs to be directed at closing that
5 gap whatever the cause --

6 DR. BRACEY: Yeah, that's a good point.
7 Okay. So we will then consider those four points. We
8 are at the point of public comment. Is there anyone in
9 the audience that wishes to -- yes, please.

10 DR. CAVANAUGH: David Cavanaugh, Committee
11 of Ten Thousand. No funding from pharmaceutical
12 companies for our organization. Certainly more of a
13 question, some of the description of DTAG reminded me,
14 the voluntary nature the lack of ability to follow-up,
15 cooperation follow-up, of the AERS and FDA, which has
16 been suffering from that problem for many years, last
17 week the Commissioner, head of CMS, Office of the
18 Secretary, jointly announced the commencement of a
19 sentinel initiative which will do data mining of the
20 health records held by corporations involved in
21 administering Part D of Medicare, specific medical

1 clearance. Now, this is very specialized compared to a
2 larger number of, drug recipients, if you will -- for
3 example, but it seems like it might offer some linkage
4 opportunities both to the work of tissue and blood, FDA
5 as well as to -- organ and I just didn't hear mention
6 yet, I was wondering if there was any comment on that.

7 DR. BRACEY: Dr. Solomon?

8 DR. SOLOMON: Actually, our Office of
9 Epidemiology has hired someone who will participate in
10 the data mining, CMS data for tissue adverse reactions.

11 DR. BRACEY: Dr. Epstein?

12 DR. EPSTEIN: Yeah, in fact there's a
13 cooperative initiative on using large health databases
14 to help clarify issues related to event surveillance
15 and FDA has engaged in a cooperative agreement with CMS
16 to try to utilize CMS databases.

17 DR. BRACEY: Dr. Klein?

18 DR. KLEIN: This is incredibly important
19 and can really give us a lot of information we don't
20 have. I would hate to think that this would overshadow
21 the need for prospective studies of these events

1 because those are so much more important than what
2 they're going to show you in any kind of data mining
3 activity.

4 DR. BRACEY: Thank you. Dr. Busch, did you
5 have a comment?

6 DR. BUSCH: Yes. Just on the issue of test
7 development for organs, tissue rapid turnaround and
8 testing, and I think you know the challenges allude to
9 do is that the big players here are NAT, Roche, and
10 Genco. They've grouped even more automated forms that
11 have better don't have stack capacity and these
12 companies, I work with these companies and their not
13 interested in these small hedge markets. We can't even
14 get them to respond to relatively important agents like
15 Dengue and stuff because there's not a developed
16 country, you know, a high yield return.

17 And, the alternative, one is, you know,
18 rapid, there are some companies developing rapid
19 nucleic acid but they're really targeting third world
20 or diagnostic applications and then there are also
21 really quite robust so-called fourth generation,

1 antigen antibody kind of tests which in many settings
2 especially in sort of the general population screening,
3 where the infections tend to be relatively more
4 symptomatic, higher viral load, they pick up the vast
5 majority of the window phase units that NAT can detect.
6 We are beginning to see some companies finally after a
7 decade of these tests really being available in Europe
8 and even in developed countries bringing some of these
9 to the FDA but they may be being reviewed at CBER but
10 they're not being reviewed with a blood safety claim
11 because NAT has embedded, has a market in it so they're
12 in the path for a blood safety claim, much more onerous
13 from a regulatory perspective.

14 So I guess the point here is, I don't think
15 you're going to see tests developed that are going to
16 get approved with blood safety screening claims that
17 are going to be appropriate for this high turnaround
18 market and I just wonder whether the FDA, is the
19 expectation, tests used for organ donor screening must
20 be approved for blood screening or is there an
21 alternative path where diagnostic assays that have

1 utility in this setting could be approved that don't
2 have a blood screening claim and employed in this
3 environment?

4 DR. BRACEY: Dr. Epstein.

5 DR. EPSTEIN: Yes, well, we do actually
6 separately regulate diagnostic claims from donor
7 screening claims, and, you know we have the ability to
8 consider different intended uses.

9 DR. BRACEY: Okay. If there are no other
10 comments, we are at the lunch break and we are
11 scheduled to resume at 1 o'clock. Thank you.

12 (There was a break in the proceedings.)

13 DR. BRACEY: Welcome back to the afternoon
14 session of day one. As mentioned before, in this
15 specific session we will address issues related to
16 bacterial contamination of platelets and also hear
17 regarding strategies to reduce risk related to pathogen
18 inactivation.

19 Our first speaker is Dr. William Murphy.
20 Dr. Murphy is the senior lecturer in medicine at the
21 University of Edinburgh and consultant natologist for

1 the Scottish National Blood Transfusion and he has vast
2 experience in the world of coagulation, including many
3 aspects of platelet therapy. He will speak to us on
4 the Irish Blood Transfusion Service study on bacterial
5 contamination, platelet concentrates. Dr. Murphy.

6 DR. MURPHY: Sure. Thank you very much.
7 It's a great honor and privilege to be asked to address
8 the Committee with this work. I will try to explain
9 why we did what we did, what we found and what we
10 ultimately made of it. In 2004 -- this is as a
11 background, to bring us up-to-date -- the Irish Blood
12 Transfusion Service brought in a hundred percent
13 testing effect of platelets for bacteria. At the time
14 we used single platelets -- Bact/ALERT system, which is
15 illustrated in the picture there. About a year later
16 we heard from our colleagues at the blood transfusion
17 service that they were seeing, using a larger sample
18 than two bottles. They were seeing most of their
19 positives were positive in one bottle only, suggesting
20 that we were below the level of sensitivity, that they
21 could achieve using a two-bottle sample.

1 So, in 2005 we changed. We now tested all
2 of our platelets after manufacturing, using two
3 bottles, two 7.5 mil samples, into both an aerobic and
4 anaerobic sample. On the basis of that -- and I'll go
5 through this in some detail in a moment -- we extended
6 the shelf life of platelets to, from day five to day
7 seven on the basis of a retest at day four.

8 What is the basis of this work, mainly what
9 is being presented today is that we had a policy for
10 several years since before 2004 testing all platelets
11 that expired using a very large amount, two 10 mil
12 samples into both aerobic and anaerobic bacteria
13 bottles. Just explain, if I may, rationale for day
14 four retesting. I think it's generally accepted that
15 bacterial testing before they're issued improves the
16 safety of platelets even if they're only stored to day
17 five. But it wasn't clear to us that this was
18 sufficient to allow platelets to be extended to 7 days
19 of storage, just on the basis of a bacterial test,
20 storage. We had shown in a paper we published in
21 Transfusion in 2000 that the preparation of platelets

1 itself can reduce the initial level of contamination
2 from perhaps a very low level of starting contamination
3 to a much lower level and that this increased the
4 chance of sampling error for the earlier bacterial
5 testing.

6 What we did in that paper is we used 19
7 different clinical isolates of coagulase negative
8 Staphylococci. Mostly Staphylococcus epidermidis, they
9 were always in there as well. We did that because we
10 didn't think that there is such a thing as a species or
11 a strain of a species that speaks for all clinical
12 isolates, that there would be differences in behavior
13 in platelets between different isolates in the same
14 species. We spiked these 19 different clinical
15 isolates into whole blood genes shortly after we
16 collected while they were still warm. We then sampled
17 them immediately after spiking and throughout the
18 manufacturing process. And we store our platelets as
19 whole blood overnight, at 22 degrees from which we then
20 isolate the buffy coat, we pool the buffy coat, make
21 the final product out of that and then you filter it.

1 This is somewhat different than the usual U.S. method.

2 What we showed was that the detectable
3 contamination even for low starting inoculata fell from
4 15 out of the 19 immediately after spiking to only
5 three detectable contaminated -- deliberately
6 contaminated after filtration. So that by the end of
7 the first test, we had to remove, upon having
8 sterilized, we removed a lot of bacteria, we had not
9 sterilized. So there was still residual infectivity of
10 contamination in the platelets after the final
11 filtration. And the same is true if we used a tenfold
12 higher inoculation.

13 So that gave us the information that in
14 fact by the end of processing you're already starting
15 low levels of contamination from the venipuncture
16 process, have been reduced even further to make it even
17 more difficult, to be confident that a bacterial or a
18 sample of bacteria contamination -- was going to be
19 sensitive enough.

20 We did publish in the following year in
21 Transfusion & Apheresis Science the rationale for

1 testing that we did. We started off with a requirement
2 for sensitivity, for a test that upon which we were
3 going to make a change based entirely on logistical
4 reasons. This was, you don't extend platelets from day
5 five to day seven for the good of the patient other
6 than to improve availability of product. So, we were
7 quite strict with our demand for sensitivity. We put
8 in a 99.5 percent sensitivity to detect a bacterium
9 that will grow from very low levels at the end of
10 manufacture.

11 So, we said one CFU per bag to 10,000 CFU
12 per bag by the end of storage, by the end of day seven.
13 That was to give us an order of magnitude of safety.
14 We thought that 10,000 CFU of bacteria in a bag is
15 unlikely to be associated with an adverse clinical
16 event. The 99.5 percent sensitivity is sort of the
17 standard European form for a new test for virus, for
18 bacteria, and we thought that one CFU per bag was a
19 realistic degree of contamination at the end of
20 manufacture based on previous observation.

21 We then wanted the test to be able to

1 detect ten bacteria per sample volume of ten mls from a
2 mean platelet volume of 300 mls. And we worked out, as
3 I'm sure people have already done in the audience, that
4 takes one to two hours of culture in a bag, before
5 sample. That's assuming log-linear growth which is a
6 big assumption for bacteria.

7 So, on that basis we worked out that two
8 times 7.5 mil sample taken on day four of shelf life
9 meets these criteria and furthermore it allows us
10 second culture running for 36 hours before the original
11 day five expired is reached. This also gives us the
12 advantage of not testing every platelet for seven-day
13 shelf life extension, so we can use platelets for a
14 particular bag -- at the time. So it is
15 cost-effective.

16 Just briefly, this, just mention, we did
17 actually try an initial pilot study using just ten mil
18 samples in BacT/ALERT per platelets we tested on days
19 two, four and seven, storage, the basis being that we
20 expected that something that was negative on day four
21 would always be negative on day seven; however, sample

1 numbers -- day four -- proved us wrong, volume, almost,
2 and that shows on that we detected a Staph capitis that
3 was present that was isolated only on day seven, had
4 been negative on day two and day four.

5 When we took that isolate and spiked it
6 back into six units after manufacture, we showed that a
7 ten to a hundred CFU per bag, we could always detect
8 that at day four but at the lower inoculation of one to
9 ten CFU per bag only one of three which was positive at
10 day four. What this shows is quantitative cultures of
11 bacteria floating in spiked platelet concentrates, and
12 we could never detect this image until after day three,
13 until day four, and after which it showed exponential
14 growth. But the two units out on the right were not
15 detectable until day six and day seven. And what this
16 showed in fact is that our initial assumption was
17 correct, that this, that we would be able to detect
18 this if it subsequently grew to greater than 10,000
19 units per bag or 10,000 CFU per bag by day seven. So,
20 as I said, used 15 mil sample at day four and we
21 continued with a hundred percent testing at outdate.

1 Under our regulatory -- this was allowed,
2 under EU Directive to store platelets to day seven with
3 a validated bacteria detection system, was ahead of the
4 state of the art at that time, and the pilot study had
5 detected all units where the isolate had grown to
6 greater than a hundred thousand CFU at day seven.

7 Just a couple of points that, on how we do
8 this. We do our bacterial sampling, platelets, using
9 Class D cleanroom, not in a laboratory. We use a
10 laminar flow hood. We use specialized technologies.
11 This is not done by blood bank technicians. As a side
12 issue, we use trained microbiology technicians to do
13 it. We also have found that if we immerse the bottles
14 head first in the bactericidal and sporicidal agent
15 before inoculation that this reduces the amount of
16 false positives insignificantly.

17 Our sampling protocol means that we test
18 our apheresis units a minimum of 14, after a minimum of
19 14-hour hold after collection, a mean of 17 hours.
20 That's pragmatic -- once the inoculations have been
21 completed. For pooled platelets we hold them for at

1 least 12 hours after final manufacture, fine
2 leukodepletion, which means about 30 hours after
3 venipuncture has been carried out.

4 This, we have a slightly, somewhat
5 different category of positives, and, I think get false
6 positives where there's a signal in the automated or
7 semiautomated culture device, Bact/ALERT, but there are
8 no bacteria in the bottle. Simply an issue of a false
9 positive. Where we detect bacteria in the bottle and
10 in the platelet unit in which it came or in
11 another component of that donation, or in the recipient
12 if there's an adverse event, then we can safely say
13 that that is a true confirmed positive.

14 Quite often we don't have the platelet
15 because it can take day or three, four days for a
16 culture to be positive by which time the platelet may
17 not have been transfused or we may not have another
18 component of donation, either not made or they've both
19 been used, in which case if we detect bacteria in the
20 bottle but we don't have the bag or if it's not present
21 in the unit or there's no component made from that from

1 that platelet collection or whole blood collection
2 which we can't test for if we don't find it, we call
3 that an unconfirmed positive.

4 So to date we've tested 43,000 platelet
5 units prior to issue. 15,000, a third of these was in
6 the initial part of the study where we used 8 mls as a
7 single bottle sample and approximately 28,000 have been
8 not related to two bottle inoculation, screening tests.
9 Over this time we detected 14 confirmed and 21
10 nonconfirmed positives on the initial test for a total
11 positive rate of .08 percent.

12 Over the period of this study, nearly
13 13,000 of the 42,000 units were from apheresis
14 platelets, 30,000 from pooled, and we found in the
15 left-hand column of the confirmed positives that there
16 were similar percentages between apheresis and pooled
17 platelets. This is not unusual for reports looking at
18 contamination rates between apheresis and pooled
19 platelets where the pools are made by the method.
20 There seems to be substantially lower levels of
21 contamination at the end where you use the overnight

1 method.

2 This line shows the rate of confirmed and
3 unconfirmed total positives on the subsequent retesting
4 of the initially screened units. The top line shows
5 the difference already, with 35 total positives out of
6 43,000. We retested 3,300 of those units and found
7 three confirmed positives. And we retested at outdate
8 8,282 of those units and found 18 total positives, 7
9 confirmed and 11 unconfirmed, for a positive rate at
10 outdate of 0.22 percent, which is approximately three
11 times the initial rate, where the totals are 0.09
12 percent, looking at just confirmed which is the same
13 reason, three times the initial positive rate.

14 Just for general, for information, this is
15 a breakdown of bacteria isolated. Most of them were
16 either coagulase-negative Staphylococci, which is what
17 you would expect. The bacteria that get into
18 platelets, come in either from the skin of the donor or
19 the, most of the time, perhaps, from contamination of
20 the skin, and very rarely from other causes during
21 manufacture. So you expect to see from skin,

1 contaminated skin of the cultures.

2 The figures in parentheses the days to
3 detection in the culture where the culture is positive.
4 These data and others, to calculate the sensitivity of
5 the assay, the initial test performed based on the fact
6 that the false negative rate of initial screening test
7 was the positive rate at outdate, 18 out of 8282
8 retested samples.

9 And I've used the combined confirmed and
10 unconfirmed rates as the total positive rate for the
11 purpose of these calculations and that is the affect of
12 changing the confidence intervals or narrowing the
13 confidence levels, we observed, but it doesn't change
14 the actual rate itself. The sensitivity was being
15 tested, total observed positive rate over the total
16 true positive rate, which was observed total positive
17 and false negative rate.

18 And that gives us a sensitivity of
19 approximately 30 percent and, as I say, using the
20 combination confirmed and unconfirmed gives us a 95
21 percent CI for that sensitivity of the initial

1 screening test of between 20 and 40 percent, which is
2 low. But it's complicated or worsens that fairly poor
3 result even worse is that by the time we detected
4 contamination, 12 of 35 contaminated units were
5 transfused. For the screening effectiveness itself,
6 which was only 30 percent sensitive, the effectiveness
7 was only two-thirds or 66 percent.

8 And we have a very comprehensive
9 hemovigilance program. Just to explain that we have
10 similar to the French system there is a number of
11 staff, nursing staff, every one of the hospitals in the
12 country, whose sole job it is to follow-up on
13 transfusion reactions in the hospital so we do have
14 good connections with individual data so that zero part
15 was probably true.

16 Finally, experiment of the amount of
17 contamination in culture positive units, so, we feel we
18 are able to estimate the number of bacteria in the
19 initial contaminating inoculum. Remember this is
20 approximately 17 hours after collection from apheresis,
21 and 30 hours after venipuncture. So of the 24

1 two-bottle positives, 11 were Propioni, only could grow
2 in one bottle anyway. Thirteen should grow in both
3 bottles, both aerobic and anaerobic, but none did.
4 Eight grew in the aerobic culture and 5 grew in the
5 anaerobic culture. And this allows us to calculate
6 that the mean number of bacteria in the platelet units
7 at sampling was about 1.386. That's overly precise but
8 nevertheless less than 2 CFU per test volume. In other
9 words, our mean volumes are less than 300. There were
10 less than 60 bacteria per CFU, there were less than 60
11 CFU per platelet unit in most instances.

12 And that, that led us on to the conclusion
13 that the low sensitivity is going to be a perpetual
14 problem due to the low numbers of bacteria in the
15 initial inoculum by the time we go into sampling and we
16 feel for you that the sampling of bacterial testing at
17 the start of the platelet storage will never reach an
18 acceptable level of detection no matter how large the
19 sample or how sensitive the test. That's not trivial,
20 although we have had no clinical adverse effects from
21 contaminated platelet samples, there have been some

1 positives that undoubtedly have led to very serious
2 transfusion reactions, having not detected them, for
3 example, that we detected in two of the three triple
4 apheresis collections, that having not detected them
5 wouldn't be what they expected, a very severe
6 transfusion reaction; nevertheless, we feel that while
7 haven't closed the door on morbidity, we do have a
8 large number of recalls because of the late detection,
9 late positive cultures and losses of product. Thank
10 you.

11 DR. BRACEY: Thank you, Dr. Murphy.
12 Questions or comments from the Committee? Dr. Epstein.

13 MR. EPSTEIN: First thank you very much,
14 Dr. Murphy. That was some very illuminating data, also
15 great concern worldwide. This is perhaps an
16 off-the-map question but since you've shown that
17 filters has so effectively lowered bacterial load has
18 anybody tried to reculture --

19 DR. MURPHY: Not to my knowledge, no. If
20 we could. Those were in spiking experiments. We never
21 tried to recover the bacteria from after that. Are you

1 suggesting that you could do it as a screen test?

2 MR. EPSTEIN: Yeah, that if the filters are
3 relatively efficient in concentrating the bacteria,
4 then maybe that's where you ought to go for the
5 culture.

6 DR. MURPHY: It's a thought. Absolutely.

7 DR. BRACEY: Additional questions or
8 comments? Could you perhaps, I think you commented on
9 it before but the nature of the low CFU count or the
10 small number of organisms was clearly a great limiting
11 factor, an issue of, the issue of the volume or the
12 content that the -- negative, clinical outcomes, could
13 you comments on that? I mean, is there some level of
14 combination that might for the immunocompetent patient
15 might not be clinically relevant?

16 DR. MURPHY: We picked a cutoff for our
17 sensitivity they amounted to our sample size really.
18 Based on the fact that we wanted to detect an
19 organization that would grow from a very low level to
20 10,000 units or 10,000 bacteria in the bag a, that was
21 based on data, not as much data was entered by Steve -

1 that I would have, and that I don't know that anyone
2 here can answer that -- is that although you might want
3 to get a clinically relevant bag reaction, fever,
4 sepsis hypertension, whether you see patients with some
5 of these bacteria, for example, on incoming lines or
6 whether you can relate infections receiving somewhere
7 else is probably unknown or possibly under-appreciated.

8 DR. MURPHY: That's absolutely true,
9 correct.

10 DR. BRACEY: Dr. Benjamin and Dr. Triulzi.

11 DR. BENJAMIN: I can answer both of those
12 questions and I'll be addressing them during my
13 presentation so I won't spend much time doing them but
14 we have a lot of data we know exactly how much
15 organisms were present in fifty days of cases so I'll
16 be showing you that data. As far as having staff
17 causes an infection in these patients, currently look
18 at staff causing infection, line infections so on,
19 multidrivers, contaminated late let users they're
20 always highly susceptible and I've never seen an
21 infection, okay anytime came from an infected bag.

1 DR. BRACEY: Thank you. Dr. Triulzi?

2 DR. TRIULZI: Yeah, as we listen to this
3 presentation I think it's pretty clear that we cannot
4 screen into sterility, that there will be no way to do
5 that and so, the question becomes -- and maybe you can
6 address this -- is clinical relevance or is sterility
7 the goal? Because if sterility is where we are
8 heading, than we need a different strategy than
9 testing. And we talked about that at our last meeting
10 so I'm not going to bring it up again. But I would be
11 interested to hear what the FDA's position on that,
12 whether it's clinical relevance or sterility and I know
13 safety, pure -- and potency so that will help us direct
14 to where we really need to spend the effort.

15 DR. BRACEY: Dr. Epstein?

16 MR. EPSTEIN: Well, I think that the
17 standards tend to be developed based on the available
18 technology. And, I would say that right now unless and
19 until we have sterilizing methods compatible with the
20 products and we're going to hear some discussion later
21 about pathogen reduction technology, testing is not

1 capable of producing sterile products. So what we're
2 talking about is what is the state of the art, in other
3 words, what is the lowest risk that's reasonably
4 achievable with available technology. And I guess
5 that's why the Secretary had framed a question to the
6 Committee about whether current levels of risk are
7 quote-unquote acceptable. I mean, you know, no
8 preventable risk is ever acceptable. The question is
9 what's achievable, that's practical.

10 So, FDA has never declared that there is a
11 sterility requirement towards transfused blood
12 component. That doesn't exist anywhere in our lexicon.
13 And what we do want is to establish a state of the art
14 as a standard. And, I think what we're debating is you
15 know, given the available technologies, where does that
16 level lie? So and I guess it comes back to you, Dr.
17 Murphy, so given this conclusion what is the Irish
18 Blood Transfusion Service now doing, and have you
19 discontinued having platelets moving to PRT; where have
20 you decided to go.

21 DR. MURPHY: We've decided to go to

1 pathogen reduction technology. We haven't removed the
2 day seven platelets because we recognize with day four
3 retest, our retest late let is probably the safest
4 platelet on the planet. So, certainly for day five the
5 shelf life, it's much safer than our initial skin
6 product, we think it's reasonable to continue storing
7 those to day six and day seven but we have more or less
8 given up on bacteria testing we still do it and we will
9 continue to do it, we'll be putting plates, pathogen
10 reduction technology that meets our needs to gives us
11 good clinical results and good in vitro results as
12 well.

13 So that's the state of the art. We're
14 evaluating both available methods, C marked in
15 Europe -- so, available for use within regulations, so
16 we're evaluating, what it does, we spend a lot of money
17 to on this bacteria, testing program, there's six staff
18 involved in testing 22,000 humans per year we have do
19 it day in day out, couple gains as well, requirements,
20 to dispose very expense interest every platelet ends up
21 being tested at least twice, once screen, day four

1 bottles, we think it won't be far off cost mutual to
2 introduce pathogen reduction technology in that
3 setting. And so that's where we're headed and I expect
4 we'll be there about this time next year.

5 DR. BRACEY: Thank you, Dr. Murphy. Our
6 next speaker is Dr. Larry Dumont. Dr. Dumont is
7 certainly well known to all of those in the field of
8 bacterial contamination, platelet physiology. He
9 received a Ph.D. in Clinical Sciences from University
10 of Colorado, spent a long amount of time more recently
11 at Dartmouth-Hitchcock Medical Center. He will talk
12 about PASSPORT and risk assessment.

13 DR. DUMONT: Mr. Chairman, ladies and
14 gentlemen of the Committee, thanks for the invitation
15 to be here and to share some data with you. First
16 there's some potential conflict of interest on this
17 topic that you might want to consider from me
18 personally. Today I'm going to cover several things.
19 First of all, I'll give an overview of the preliminary
20 results from the PASSPORT study.

21 Secondly, I'm going to go through a risk

1 assessment that was developed by a group from AABB and
2 then finally give you an outline of the proposal for
3 PASSPORT 2 study for reintroduction of 7-day platelets
4 in the United States. A few important facts I want to
5 mention. One is 7-day platelets are 510 (k) cleared as
6 a product by FDA and those 510(k)s are held by Gambro
7 and Fenwal. PASSPORT in fact is a post-marketing
8 surveillance of 7-day platelets that is to say a phase
9 four type trial. It is not an IME or IDE study as a
10 pre-req for clearance of a product. And, and PASSPORT
11 does have an explicitly stated primary hypothesis with
12 a written analysis plan which was reviewed and accepted
13 by FDA prior to the start of 7-day platelets in the
14 U.S. The plan analysis has not been conducted and the
15 primary hypothesis as stated has not been tested.

16 So back at the beginning of this century,
17 actually, some assumptions that we made going into this
18 project was that the true contamination rate in
19 apheresis platelets was somewhere between 178 and 349
20 per million, and, that's roughly one in 5,000. And
21 that was based on early testing point at 24 hours in

1 one bottle.

2 Secondly, we assumed that the release test
3 or the bacterial test would detect at least 50 percent
4 of those contaminated products; therefore, we expected
5 a residual risk of approximately 100 per million, one
6 in 10,000. This led to a sample size calculation shown
7 here where we wanted to see less than or equal to four
8 positives out of 50,000 surveillance tests. I'll show
9 you in a second what a surveillance test is.

10 And, finally, these risks are not weighted
11 for either clinical risk, that could be presented by
12 the particular organism or species or the day the
13 organism may be detected.

14 Well, today we know that the assumptions we
15 made a few years ago are incorrect, the data. So, the
16 7-day platelets has had a long history in the United
17 States. We're going to focus on the most recent
18 history that was initiated in September 2005, that
19 7-day platelets in the U.S., the PASSPORT surveillance
20 study that's being done was run by Gambro and Fenwal.
21 And then I think everybody knows that earlier there

1 year that 7-day platelets in fact were taken off the
2 market and that was effective in vivo.

3 What is a 7-day platelet, apheresis
4 platelet? Right at the beginning of this box we have
5 an apheresis platelet collection. Apheresis platelet
6 has been held for 24 to 36 hours and there's an
7 aliquot taken out of that. And for the release test,
8 this is a two bottle test, both anaerobic and aerobic
9 bottles, four mil per bottle, that is put on an
10 incubator and it's held for at least 24 hours. If at
11 the end of 24 hours we still have a negative result
12 then the product is released and labeled as a 7-day
13 platelet. So that's 7-day platelet.

14 Now, what is the post-market surveillance
15 study? That in fact is anything that goes beyond the
16 expiration date, is then recultured and our target is
17 50,000 of these. In the same manner that we tested,
18 release test, the total incubation of was dates and the
19 plan was to compare the data at the end of the day.
20 There are two types of participants in these studies,
21 one is a tier one center, and these are centered

1 because of their size and logistics. They can only
2 supply release test data. And other centers are large
3 enough, they're able to supply both release test and
4 surveillance test data. The primary hypothesis as
5 written was to compare a 7-day single donor platelet
6 that's been tested against the 5-day untested product.
7 And specific aims of the study were to evaluate the
8 performance of the system looking at specificity,
9 sensitivity, negative predicted value, positive
10 predicted value, almost standard epidemiological terms.

11 Secondly was to determine the prevalence of
12 bacterial contamination as we really didn't know what
13 that was for both untested and for the two bottle
14 tested, single donor platelets, and then finally to
15 determine the performance contribution of the anaerobic
16 bottle as that's fairly controversial in the United
17 States. Oh, I'm sorry that doesn't show up. Believe
18 it or not, that's an outline of the United States.
19 Over here is a California. This is not Hawaii. This
20 happens to be Denver. There's the northwest and I live
21 up in here, someplace in Florida, and that is Texas

1 down there. So I think you get the idea that there
2 have been several organizations and centers that have
3 participated nationwide. This excludes all American
4 Red Cross.

5 The results, as of the end of last year
6 have been over 320,000 single donor platelet
7 collections and these are collections as a unit of
8 analysis and we estimate that about 50 percent of these
9 are split into multiple products. So this represents
10 well over 450 thousand transfusions. This number of
11 collections have been interdicted because of the
12 release test.

13 This number here have been transfused. You
14 can see, for example, in this breakdown, which is
15 actually, this one is pretty similar to Dr. Murphy's,
16 where we have a true confirmed positive. There were 62
17 that gives us a rate per million of 193 million content
18 sample. False positives, of course, and
19 indeterminants, those things where we get a real
20 positive in the bottle but we can't go back either at
21 patient or a product or focal point and confirm and

1 test. So a lot of things get dumped in the
2 indeterminant category.

3 These are products that by the time the
4 positives come up with the release test, they have been
5 transfused. And we have had a few false negatives
6 reported where we never did get a positive in a release
7 test. These two, one was a CNS in a split product, one
8 of those was transfused on day six and the patient had
9 a fever; the other one was transfused on day six the
10 patient didn't have any reaction. And the other was
11 day four was Staph aureus, there were actually two
12 transfusion reactions. One was a severe septic
13 reaction.

14 The surveillance test, of course this is
15 the goal of the PASSPORT study. There have been 4369
16 tested after day 7 so these are products that have been
17 released tested on day one and then they went the full
18 7 days. There have been three true positives for a
19 rate of 686 per million. And, the first two
20 positives -- and this is important because this is all
21 that was known at the beginning of the year -- Staph

1 aureus and Staph epi, and these were confirmed. This
2 particular split donation, the staph epi came up on the
3 product that expired. Its sister product was actually
4 transfused on day four and there was no adverse
5 reaction in the clinic. These two actually came up
6 with the same center in roughly the same period of
7 time. We believe that they were true positives. And
8 then there has been one more that's come up since early
9 this year. It was a Strep veridans, and the
10 confirmatory test actually came up with only a
11 diphtheroid-like Gram positive rods but because of the
12 way the definitions are, this is counted as a true
13 positive.

14 To try to put all these rates on the same
15 page, so we're somewhat looking at the same numbers I
16 what I've shown here is a one bottle test. So this is
17 aerobic bottle only from the American Red Cross, and
18 we're going to hear more about that. This is
19 our previous publication, and the PASSPORT data, single
20 bottle. And you can see the rates, positives per
21 million collections is about the same. These over here

1 are the two bottle tests with the PASSPORT data right
2 here and then the data we just heard about from William
3 Murphy, and I laboriously went through all this data,
4 collaborating with Dr. Murphy and his colleagues to try
5 to break this out and get it in the same nomenclature.
6 You can see these rates right here and then some data
7 that I was able to get from the Welsh Transfusion
8 Service. And it's important to note that as we go from
9 the Welsh to the Irish to the PASSPORT, these aren't
10 really apples and apples you we just saw but they're
11 kind of close and you can see that the rates maybe
12 aren't that much different.

13 Now, the Irish, the Welsh and then of
14 course PASSPORT had this surveillance study and that's
15 over here so we can see the PASSPORT rates from expired
16 products. We can see the Irish, which is a composite
17 of the apheresis and buffy coat and then the Welsh. So
18 again with the caveat that these aren't perfectly
19 comparable, it looks like the rates are in there
20 somewhere, the same. And if we would, for example, add
21 this rate and that rate, that would be an estimate of

1 the true number of positives we have going into this
2 storage period. Our clinical outcomes, there have been
3 13 true positives and 202 indeterminants that were
4 transfused. We have had no deaths reported. There
5 have been 14 transfusion reactions related to bacterial
6 contamination, for a rate of 44 per million.

7 And, these are shown in detail here. These
8 are the first two false negatives that I showed you
9 previously, where one product was split against viral
10 reaction and no reaction in the second patient and this
11 one clearly have severe sepsis and then no doubt
12 another sepsis here was confirmed. These cases are a
13 situation where the hospital calls back to the, or the
14 blood transfusion, the transfusion service calls back
15 to the blood center with the information. In a
16 situation like this, we have true positives so these
17 come up in the release test so the call goes from the
18 blood center to the clinical service to find out what
19 happened.

20 Just to go through these quickly, we have a
21 lot of indeterminants that we couldn't really get the

1 information out of the clinical service primarily,
2 products were gone, we couldn't reculture, we didn't
3 have blood cultures from the patient or whatever,
4 didn't fall into the right category definition.

5 What I do want to point out on this slide
6 is platelet age from day three to day seven, this is
7 the number of reactions that have been reported.
8 Unfortunately we don't have good estimates for
9 denominators for each of those days so we can't
10 calculate rates for each day and risk.

11 So, in summary with the two-bottle release
12 test, what we have is a true positive rate of 234 per
13 million, and if we add true positives and
14 indeterminants assuming an indeterminant is really the
15 real bug in there, we're at about a thousand per
16 million and a thousand, and this seems to be generally
17 consistent with other reports. 256 collections were
18 not interdicted prior to transfusion.

19 And in our surveillance we had 686 per
20 million positive. And this also seemed to be generally
21 consistent with other reports. We had no deaths

1 reported and that's in contrast to Paul Ness's data
2 from the last century, that's 15 per million and 14
3 transfusion reactions have been reported by PASSPORT,
4 44 per million in contrast to Dr. Ness's data, and 70
5 per million for data from the nineties.

6 So what I want to do is shift gears and I
7 want two, I want to talk about a subcommittee that was
8 pulled together by the AABB because we wanted to assess
9 the risk of actually discontinuing 7-day storage of
10 platelets on recipient safety in the United States.
11 And this auspicious group of individuals who made up
12 that, I think mostly these people who know, a doctor
13 from Mayo Clinic was involved because he's an expert in
14 TRALI.

15 As a background, PASSPORT was discontinued
16 after preliminary report of two out of 2571 tested
17 positive on recultured after 7-day storage. There was
18 no formal risk assessment on overall safety performed
19 by anyone that we knew of. In April there was an ABC
20 member survey that Dr. Bianco conducted and out of 18
21 PASSPORT organizations that we contacted, 16 responded

1 and there were 40 responses out of 57 nonparticipants
2 in 7-day platelets.

3 To speak to apheresis platelet
4 availability, the centers that were using 7-day
5 platelets felt that to reach their prior distribution
6 goals where they were at the 7-day platelets, if they
7 would go back to 5-day, they felt would take three to
8 six months to obtain that in ten of the centers and
9 five of the centers felt that it would take more than
10 six months to get that availability back in their
11 inventory. Five of the larger centers reported that
12 they would need to increase their apheresis collection
13 between one and 6,000 units per year, and that was
14 primarily to compensate for the increased outdates that
15 they were anticipating, which was approximately three
16 percent, 7-day platelet going to around 10 percent
17 5-day.

18 The increased distribution of whole blood
19 derived platelets, there would be an increase in
20 distribution of whole blood derived platelets, one
21 center is going to replace losses with prepooled

1 platelets from whole blood and three others were going
2 to distribute whole blood derived platelets and they're
3 going to increase that by 20 to 30 percent.
4 Interestingly five of the 40 nonparticipants responded
5 that this discontinuation of PASSPORT would affect
6 their operations. That was curious. But to continue
7 on that, for bacterial detection, there were of course
8 with 7-day platelets there was two bottle test and
9 there were several centers that were considering going
10 to the single aerobic bottle. Changes, four out of the
11 fifteen had already changed to one bottle and two
12 planned to change in the near future and six of these
13 fifteen centers were going to reduce the incubation in
14 the incubator prior to release to less than 24 hours.
15 So that was a change in detection method for the
16 release test.

17 For TRALI mitigation, a delay in the time
18 line for TRALI mitigation for people who were trying to
19 get in place this year, there were 7 centers that felt
20 that it would delay the mitigation by about 6 months
21 and there were four centers that felt it would delay it

1 at least nine months or longer. And then four out of
2 the 40 nonparticipants felt that it delayed
3 implementation of TRALI mitigation by six months or
4 more, would affect them because of the discontinuation
5 of 7-day platelets.

6 Well, the objective of the task force was
7 to develop a sensitivity model to explore incremental
8 risk from the discontinuation of 7-day platelet
9 availability and wanted to look at the septic
10 transfusion reactions of clinical sepsis and TRALI.

11 And I'm going to paint you a picture of our
12 major assumptions on a separate transfusion risk
13 assessment. So if this is available in -- from day two
14 to day 7 for 7-day platelet we assumed that there would
15 be some number of septic transfusion reactions for a
16 product that was 5 days old and less and there would be
17 some other number for days 6 and 7. This was about 20
18 percent of the total number of transfusions given for
19 participating centers, and that this would need to be
20 replaced, this inventory would need to be released with
21 some combination of apheresis platelets, whole blood

1 derived platelets using culture screen, or whole blood
2 derived platelets using surrogate screen, surrogate
3 being a pH test or glucose or something like that.

4 And then we assumed that this inventory
5 would be distributed in a 5-day world, where we only
6 have 5-day platelets. So we only considered things to
7 the right of the line, that we're interested in
8 incremental because we assumed this inventory right
9 here would not change in the 5-day platelet world.

10 Risk was taken from data from the American
11 Red Cross. There was a range we evaluated, 7.4 to 16
12 per million for 5-day platelets. We assumed that the
13 risk of day five, day six and day 7, clinical risk is
14 the same and that ranged from 25 to 80 per million.
15 And with these numbers we were then able to get an
16 estimated number of septic transfusion reactions out of
17 this inventory. And then down here we assumed against
18 a risk-based background risk of 7.4 to 16 per million
19 and we can get a number out of that and then we can
20 compare those two.

21 So that's what I'm going to show you here,

1 model assumptions for the participating centers about
2 400,000 PASSPORT platelets per year. That was from ABC
3 survey. Replacement inventory, we touched on that,
4 septic transfusion reactions of 5-day platelets was
5 from American Red Cross data. We assumed clinical risk
6 of day five, day six, day 7 platelets would be the
7 same. The inventory estimate was based on data from
8 blood systems and from Mississippi Valley. Whole blood
9 derived platelets that are culture screened in pools of
10 five, we assumed it's five times the risk of an
11 apheresis platelet, and that's based on American Red
12 Cross data that was published in June of last year.

13 Whole blood platelets that are surrogate
14 screened, we assumed that those are 4.6 times the risk
15 of false negative of whole blood derived platelets,
16 culture screening. These numbers just aren't very good
17 and the reference for that is listed there, in
18 Transfusion. We assumed Bact/ALERT test performance
19 was unchanged for 5-day platelets and that replacement
20 platelets would be distributed without bias over the
21 shelf life.

1 So this is incremental transfusion
2 reactions for 80,000 transfusions, listed 20 percent of
3 that 400,000 and replaced in inventory. And when we
4 were with 7-day platelets, a hundred percent of that
5 inventory was single donor platelets and we estimated
6 the annual number of septic transfusion reactions was
7 somewhere between two and six based on these risk
8 assumptions.

9 Now, since we have to replace that five to
10 six to eight inventory, if we replace it with all
11 single donor platelets, then the septic transfusion
12 reaction will go from .6 to 1.3, so there's definitely
13 improvement there. If that was split between single
14 donor platelets and whole blood derived cultured, the
15 numbers are just about the same as we had with 6 and
16 7-day platelets. And then here's some more inventory
17 bases, if we go a hundred percent, with whole blood
18 culture, we can see how those numbers go up. As we
19 start to mix in surrogate, tested the numbers go up
20 even farther. And really the only way to see a
21 decrease is to replace everything with single donor

1 platelets.

2 So in conclusion from this exercise
3 replacing 7-day, single donor platelets entirely with
4 5-day single donor platelets will reduce current risk
5 by avoiding two septic transfusion reactions per year.
6 A worst-case analysis would suggest 60 septic
7 transfusion reactions a year. Replacing single donor
8 platelets with 5-day whole blood derived platelets,
9 surrogate tested, is likely three to increase septic
10 transfusion reaction risk. And that 7-day inventory,
11 day six and day 7 is replaced with 5-day whole blood
12 derived cultured products, and it seems that the risk
13 will stay about the same.

14 I want to move to TRALI. The risk of TRALI
15 from platelets has not been clearly established. We
16 made estimates based on data from Mayo, Povsky's early
17 work, and a Canadian, passive surveillance study
18 showing anywhere from one in a 1,000 to one in 23,000.
19 Risk reduction from HLA or gender screening of
20 apheresis platelets, in donors, we estimate that that
21 might have an effect of reduction 40 to 80 percent of

1 TRALI cases based on UK data and some other data.

2 TRALI risk from single donor platelets is
3 independent of storage day at transfusions. The risk
4 is the same at day two as it is in day 7. TRALI risk
5 of five unit pool of whole blood derived is equivalent
6 to that of single donor platelets, and that a six or
7 twelve month delay in optimal TRALI mitigation to
8 replace the 6 percent outdate of inventory was our
9 other assumption.

10 And so these three ranges, one in 1,000,
11 one in 5,000, 40 to 80 percent, and six or twelve month
12 delay is what we exercised in simple linear model for
13 sensitivity and that's shown here. So this shows that
14 the total number of cases that might be observed. In a
15 six month interval, and if we look at baseline risk of
16 200 per million, then we would expect 40 TRALI cases in
17 that six months. If the risk reduction is actually 40
18 percent, then we would expect the number to go down to
19 24. If it was 80 percent, go down to 8, and see a
20 similar thing, those numbers double for twelve months.

21 So, a little arithmetic and you can see

1 that the numbers are not prevented from a delay so a
2 six month delay, if the baseline risk is 200 per
3 million, there would be somewhere between 16 and 32
4 TRALI cases that would not be prevented. So that's
5 what those numbers mean. So you can pick what you
6 think is reasonable based on your experience.

7 But our conclusion is delay of TRALI
8 mitigation measures may result in 8 to 160 potentially
9 avoidable TRALI cases observed in six months, and, 16
10 to 320 in twelve months. And a delay in TRALI
11 interventions due to discontinuation of PASSPORT could
12 result in the number of TRALI cases in six months, when
13 greater than the number of septic transfusion reactions
14 reported over a twelve month period of time.

15 So suspension of 7-day platelet
16 availability, PASSPORT may avoid 2 to 6 septic
17 transfusion reactions per year while resulting in an
18 increased number of TRALI cases and further concluded
19 that a comprehensive risk assessment that considered
20 the major morbidity and mortality risks of platelet
21 transfusion conducted prior to the decision to

1 discontinuing 7-day platelet availability would have
2 allowed for a more informed debate and discussion and
3 consideration of the overall risk of discontinuation.

4 So, finally I just want to show you real
5 briefly the outline of PASSPORT 2 proposal. This was
6 put together by a second AABB ad hoc committee with the
7 participants shown right here. And this was a letter
8 to FDA on April 28th. And the major elements are as
9 far as labeling is that the platelets would be labeled
10 for a 7-day expiration. The results of the PASSPORT 1
11 study, would be made known in labeling, not in the bag
12 but in labeling, and that rapid tests for platelet
13 products are available for use, for example, Verax and
14 PGD tests -- and there may be others in the future.
15 For collection to recommend best practice, acceptable
16 venipuncture site preparation and diversion of the
17 initial blood bolus. For testing, recommend increasing
18 the sample volume because we were at four to five mls,
19 I recommend going, doubling that, eight to ten mls,
20 again using an aerobic and anaerobic bottle.

21 For post-marketing surveillance we suggest

1 primary surveillance outcome of the rate of septic
2 transfusion reactions. There would be no active
3 clinical or platelet culture surveillance and the blood
4 centers would be responsible to make estimates of
5 platelet age at transfusion so we could look at risk
6 per day. And passive reporting of transfusion
7 reactions to the blood center would occur similar to
8 what we have today. And we would work on getting an
9 enhanced process in place for follow-up with
10 transfusing physicians for clinical outcomes and that
11 we would set up an independent panel that would, number
12 one, adjudicate the reports of any septic transfusion
13 reaction and, number two, they would play a data safety
14 and monitoring role. So 7-day platelets for
15 transfusion in the United States has had a long
16 history. We don't know what's going to happen here.
17 Thank you very much.

18 DR. BRACEY: Questions or comments for Dr.
19 Dumont? Dr. Triulzi?

20 DR. TRIULZI: Larry, two questions on
21 assumptions that really drive the fact that the 7-day

1 platelets would not result in a net safety issue, have
2 to do with assumptions about the full -- goal -- of the
3 platelets. And I would like to ask about two of the
4 assumptions, one relating to bacteria, that it's clear
5 that a full platelet has a five plus five times the
6 chance of having bacteria detected but I would question
7 the data that says it's five times the risk of a septic
8 transfusion reaction. And so I would like to know what
9 data you're quoting for that. And then the second is
10 the AABB TRALI working group looked at the data on
11 risks of TRALI from pheresis versus pooled platelets,
12 whole blood platelets and determined that whole blood
13 platelets were a low risk component; yet, in your
14 assumption you have made the assumption that a pheresis
15 and a pooled had the same TRALI risk and the AABB
16 working group based that on Red Cross data. You can
17 comment.

18 MR. BENJAMIN: Before he answers that,
19 comment on that. Red Cross data dealt with fatalities,
20 and so the adult risk for fatalities, it did not
21 address just TRALI reactions.

1 DR. TRIULZI: So again I would ask, what is
2 the source of data that assumes that the risk of TRALI,
3 either fatality or case from a pool is the same as a
4 pheresis? Because those really drive --

5 DR. DUMONT: Sure.

6 DR. TRIULZI: -- the ultimate conclusion,
7 which is that there's no safety benefit by getting rid
8 of these 7-day platelets.

9 DR. DUMONT: So, I'll take them in reverse
10 order. On TRALI there are no good data to compare
11 apheresis platelets and pool platelets from whole blood
12 for TRALI. So it was only expert opinion of the panel
13 that you saw up there that drove that. We didn't have
14 a good reason to not say they were appropriate so that
15 was the -- and we recognize that may not be the truth;
16 we just don't have the data.

17 The second as far as the risk of a
18 contaminated product that would go to a patient with a
19 pool and subsequent septic transfusion reaction, the
20 assumption was made that whatever the risk is, if you
21 have a contaminated platelet product, some percentage

1 of that will result in a clinical reaction, gotten
2 bacteria -- and we assumed that that would probably be
3 the same for the two units. But the risk of having a
4 contaminated pool is higher by five times and you can
5 get that two different ways. One is that even though
6 you use screening the prior odds is five so you just
7 you multiply five times the prior odds and so they give
8 you for first -- the second source was the American Red
9 Cross data, where they actually went out and tested
10 accurately those platelets where they had done the
11 Acrodose production method, pools, screened them and
12 they found that the residual risk after that was about
13 five times higher than they saw with apheresis and I'm
14 sure Dr. Benjamin will tighten it up.

15 DR. BRACEY: Dr. Benjamin?

16 DR. BENJAMIN: If I could, there are
17 sources of data for that. The first actually is Dr.
18 Jacobs and Dr. Yomtovin's data with at issue cultures
19 which show that the cultures were positive for
20 apheresis platelets, one in 2000, and for pooled at one
21 in 400, hundred, about a fivefold difference. And

1 pooled stored data which I will show you when I
2 present, shows a 5.8-fold higher confirmed positive
3 rate for pool and stored than apheresis platelets when
4 measured with comparable tests and with diversion to
5 all sides.

6 DR. TRIULZI: The point is, I think it's
7 clear that the rate of finding bacteria is five times.
8 The question is the risk of a septic reaction fivefold
9 because you're getting 200 to 300 ML of infected
10 product versus one unit diluted in the pool of four
11 others. And I don't think there are data to show that
12 the septic transfusion reaction rate is five times
13 higher with a pool than apheresis plate.

14 DR. BENJAMIN: As you say it's less clear
15 but as Dr. Jacobs and Dr. Yomtovin have shown, the
16 correlation between septic reactions and contamination
17 is not good.

18 DR. BRACEY: To that point it appears that
19 in the proposal for PASSPORT 2, the notion of sterility
20 is relinquished but yet there's a check which would be
21 the Verax system or some alternate system which is

1 calibrated to detect clinically significant amounts of
2 bacteria, is that correct; am I thinking in terms of
3 your proposal for PASSPORT 2?

4 DR. DUMONT: Well, the initial proposal
5 which has not been processed or vetted with FDA at all,
6 is that the companies would make known that that's
7 available, make known what the residual risks are and
8 say that this test is available for use but not put
9 that in as a requirement. But, like I say, that's
10 preliminary. There's a lot of discussion yet to take
11 place on that.

12 DR. BRACEY: Thank you. Dr. Holmberg?

13 DR. HOLMBERG: So, what you're saying is
14 you put the burden back on the hospital to do the
15 testing?

16 DR. DUMONT: Yes.

17 DR. HOLMBERG: The point of release; what
18 about the reculturing on day four and five?

19 DR. DUMONT: Well, reculturing is certainly
20 another option that becomes, even logistically some of
21 these things become just extremely difficult to do

1 because you have a blood center and they're sending
2 platelets off to Timbuktu. We're not sure what they
3 have in the hospital. We're pretty sure that not every
4 hospital has BACT/ALERT. So that may be an option.
5 Somebody could certainly take a culture and evaluate
6 that -- 48 hours; 24 hours, 48 hours, and then reissue
7 it like Dr. Murphy has done. That's an option. That
8 we're trying to leave open right now.

9 DR. HOLMBERG: Would you collect, in your
10 surveillance process, would you collect this, these
11 data if the hospital did point of release testing?

12 DR. DUMONT: Well, we would love to have
13 that data. How that could be gathered, how much money
14 that's going to cost, I think that's something that the
15 study sponsor would have to evaluate if that's even
16 feasible. So, I don't know the answer to that
17 question.

18 DR. BRACEY: Question, comment from Dr.
19 Corash?

20 DR. CORASH: And a comment. The false
21 positives is a very large number, 528, fivefold, for

1 what you got for the true positives or indeterminants,
2 what were those made up of, when you say false
3 positives --

4 DR. DUMONT: The organism?

5 DR. CORASH: No. But how did you define,
6 it wasn't clear to me what, was that, because you could
7 not reculture?

8 DR. DUMONT: Those are, those are, no,
9 culture -- generally indeterminates so generally false
10 positive is clearly demonstrated as a false positive so
11 we go back to the bottle. The bottle is sterile so it
12 was a machine error, those types of things, for the
13 BACT/ALERT. So, it wasn't that we couldn't.

14 DR. CORASH: And was the bag recultured and
15 was negative, in other words?

16 DR. DUMONT: Well, in some cases.

17 DR. CORASH: But not in all?

18 DR. DUMONT: Not in all.

19 DR. CORASH: Okay. Secondly, when you talk
20 about septic transfusion reactions, I assume since no
21 defined criteria were given, that we're talking about

1 some type of febrile elevation or sign or symptoms
2 occurring within some defined period, which I'm
3 assuming is probably pretty close to the time of
4 transfusion; is there a definition that's being used
5 for this?

6 DR. DUMONT: That's, that's one of the
7 weaknesses of PASSPORT 1, is there was not a clear
8 definition. It was sensitive users, number one, and
9 number two, there wasn't an adjudication panel that
10 reviewed each case against a well-defined criteria.

11 DR. CORASH: So, you know, I think a lot of
12 people in this know that literature has many accounts
13 of infections arising from transfusions that aren't
14 recognized as septic transfusion reactions. I suspect
15 Dr. Jacobs will speak to that to some extent, and yet
16 recognized potentially one, two, three, four and even
17 further out from the actual time of the transfusion.
18 And so one question I have for PASSPORT 2 is why
19 couldn't you do active surveillance where you provide a
20 one-page case report form with every product that's
21 issued and get the transfusing clinical entity to

1 return that form to you and at least have a 24-hour
2 evaluation period and no time limit on reporting, if
3 somebody wants to report beyond that. It would seem to
4 me possible that clinicians could do that.

5 DR. DUMONT: Well, number one, we think
6 that's a great idea. We would love to have the data.
7 Some preliminary exploration into feasibility of that
8 was that we could expect -- variable -- even in my
9 hospital I mean we have forms of supposed to be filled
10 out by the transfusing service and oftentimes we'll
11 have a transfusion medicine resident there who forms
12 still in the bottle get thrown out and it's very
13 difficult to execute that. I mean, we can hardly
14 figure out how to do that on a large scale. So if you
15 have some ideas I'm sure the team will be happy to use
16 them.

17 DR. CORASH: Well, I think the French have
18 criminal penalties and it's --

19 DR. BRACEY: Dr. Epstein?

20 MR. EPSTEIN: Yeah, I just want to focus
21 back on the implication of the point that Dr. Holmberg

1 raised, which we're really battling around, which is the
2 hospital's role versus the blood collector's role. And
3 what Dr. Murphy showed us if you want to do the
4 surveillance right, you need a culture done at the
5 hospital but under meticulous conditions, you know,
6 sterile fluids, properly trained operators, et cetera,
7 et cetera, et cetera. And what's been lacking from the
8 start, you know, we knew when PASSPORT 1 was discussed
9 that it would be optimal to get a culture on day five.
10 At that time we were talking about day five, or day
11 four and the culture at day 7 but there was no way to
12 either fund or require that the hospital perform this.
13 And, I think we're dancing around the same problem,
14 when you propose, and I know it's not a formal proposal
15 at this stage but what you're proposing is, you know,
16 passive surveillance mechanism at the hospital and
17 maybe they do or maybe they don't do Verax test. And
18 so, really the bug-bear in all of this has been once
19 the product leaves the blood collection center what is
20 the medical level of control for participation
21 scientifically at the hospital level and I don't think

1 that we completely solved that problem. You know, we
2 know that's one of the gadflies in terms of the
3 effectiveness of the intervention and the gathering of
4 the data.

5 DR. DUMONT: Well, I agree with what you
6 said but I don't know if everybody agrees with what you
7 said but I do. And I think that the thing we're going
8 to have to consider is, you know, we'd love to have the
9 data, we'd all love to have all the data but to do
10 that, you know, those all associated with dollar signs
11 and complexity and can't really be executed, it isn't
12 reasonable to spend that much money and resource to get
13 that data, is it that valuable, is it really going to
14 in the end make that much of an incremental improvement
15 in public health to do that? I don't think we know the
16 answer to that.

17 DR. BRACEY: Speaking from the hospital
18 side, given the option of having no platelets, i.e., a
19 shortage or platelets that have a premium associated
20 with a longer length of utilization, I would, obviously
21 the hospitals are not looking to spend more money but

1 given the option of not having good inventories, I
2 think that they would spend a certain margin, not
3 double but a certain margin. Dr. Jacobs, do you have a
4 comment or question?

5 DR. JACOBS: In answer to Dr. Epstein's
6 question and also relevant to this presentation, what
7 we have been doing is at present at issue we do a
8 simple plate culture and detecting contamination at day
9 5, 6 and 7 is much easier than a production because
10 your numbers of organisms are much larger. So, I was
11 discussing this during my presentation but that's a
12 much easier, much cheaper way of doing it than trying
13 to use two bags, bottles at contamination after day
14 five.

15 DR. BRACEY: Dr. Benjamin, and then after
16 that we probably do need to move on so we can hear Dr.
17 Benjamin later.

18 MR. BENJAMIN: Just one comment is that
19 we're principally dealing with two conflicting issues
20 here. One, we want to do day 7 for the availability
21 that provides. Two, we know we can't have sterile

1 products by testing. Three, older the platelet is,
2 increased risk and decreased efficacy. So, how do you
3 balance those things? The PASSPORT 2 protocol, as I
4 understand it, needs to have a disincentive to prevent
5 hospitals using day 6 and day 7 platelets as a
6 mechanism for treatment, control on regular use, that
7 they need to be aware that older platelets are not as
8 good. So how do you create that disincentive? By
9 asking them to do the Verax test, it costs them money,
10 means work, that's disincentive but you could think of
11 other disincentives. We would like, American Red Cross
12 would like to have a label 7-day product out there
13 available on long weekends when platelet inventories
14 are low but we would not like to see hospitals
15 routinely using it. So, we should be discussing how do
16 you disincentivize hospitals from doing that? You
17 know, another way may be AABB standard that says you
18 should review, the hospital should have a transfusion
19 Committee that reviews the clinical outcomes of every
20 day 6 and day 7 transfusion and makes a decision about
21 when it is acceptable to use that. That could be

1 another disincentive. I think we could come up with
2 other ways. So we're advancing safety and availability
3 and I think the practitioner at the bedside is the
4 person to make that decision, not necessarily the blood
5 center.

6 DR. BRACEY: Thank you, Dr. Benjamin. I
7 think with that we will move on to our next speaker,
8 who is Dr. Benjamin. Dr. Benjamin has been introduced
9 to us earlier today. Dr. Benjamin is the Chief Medical
10 Officer of the American Red Cross National Headquarters
11 and has done extensive work in the field of transfusion
12 medicine, particularly platelet safety and TRALI as
13 risk interventionist. He will present the American
14 experience, the American Red Cross experience with
15 bacterial culture of platelets.

16 DR. BENJAMIN: I would like to thank the
17 Committee for the opportunity to address the issue of
18 bacterial contamination of platelets. I would like to
19 start by disclosing my consultancy relationships with
20 Cerus Corporation and Immunocal.

21 American Red Cross collects, processes and

1 distributes approximately 22 percent of the blood
2 supply in the U.S., with 35 blood centers and testing
3 by different national testing labs. Each year we, or
4 this year we will distribute about 6 million red cells,
5 1.7 million plasma products, about 700,000 apheresis
6 platelets, about 350,000 whole blood platelets and
7 about 40,000 aquadosed pooled platelets. We have in
8 place a single set of procedures and processes and we
9 have in place a hemovigilance system. This basically
10 allows us to process an incredible amount of data in a
11 very short time. We distribute as many platelets in a
12 month as many countries do in a year. So, I would like
13 to show you some of that data.

14 We started at the beginning, in March 2004.
15 We implemented as did 80 percent of blood centers in
16 the U cyst, the BACT/ALERT system where apheresis
17 platelets only, not whole blood derived platelets, we
18 after collection, collection volumes of 175 to 750 mls,
19 that's the size of the bag, were collected. They were
20 held for 24 hours, and after 24 hours, the total volume
21 was pooled into one bag. A formal sample was taken of,

1 taken off and inoculated into an aerobic bottle only.
2 The products were held for 12 hours before release,
3 negative to date, and we used the 5-day outdate for
4 platelets.

5 Just to comment briefly, we used aerobic
6 bottles only. That has become more of a controversy
7 recently, since package inserts strongly recommends the
8 use of both an aerobic and anaerobic bottle, and I will
9 make a statement at the end of this presentation about
10 that. But I do want to mention that we have formally
11 asked the FDA for clarification, whether a strong
12 recommendation, whether as not, following the strong
13 recommendation compromises cGMP in terms of following
14 package inserts. I think it's time to clarify that
15 situation.

16 We monitor the efficacy of the culture
17 system by looking monthly at our true positive, false
18 positive and indeterminant rates and through our
19 individual sepsis reports. We have published our data
20 after testing a million products and 1.5 million
21 distributed components. We detected true positives at

1 a rate of about 1 in 5,400, very similar to results
2 reported by others. For every confirmed positive, we
3 have two false positives, one directly due to sampling
4 contamination and one probably due to instrument error.
5 We have interdicted in this study 292 of the 293 true
6 positive components, so, eventually very effective at
7 detecting bacteria and at detecting the true positive
8 components.

9 We did in our report, though, mention that
10 we had had 20 septic transfusion reactions reported to
11 us in this 26-month time period, including three
12 fatalities and we reported that they were predominantly
13 on day five of transfusion, after collection, and all
14 three fatalities were on day five. We also reported
15 that when we looked at our data, both the true positive
16 and the septic transfusion reaction rates were higher
17 in collections done with two-arm procedures as opposed
18 to one-arm procedure. In fact, the cultures were 1.9
19 times higher with two arm and the septic rate was 4.7
20 times higher, highly statistically significant.
21 Because of this observation we moved to do two things,

1 to universal inner-line sample diversion on all of our
2 collections, both two-arm and one-arm, because we
3 identified the issue to be that the two-arm procedures
4 lacked endokine sampling diversion on the right arm.
5 In fact, we had diversion bags but they were on the
6 return line where they were useless and they should
7 have been on the -- inner -- line. So we moved to
8 implement that change.

9 We have now submitted an abstract to the
10 AABB for this year where after implementing both an 8
11 mil aerobic only culture and moving from 39 percent
12 diversion to 100 percent diversion, we have seen a
13 slight have fall in the confirmed positive rates, which
14 may be expected as doubling the volume would be an
15 expected increase in rates and diversion would decrease
16 the rates. And there in fact was a small decrease in
17 the confirmed positive rates. I will come back to the
18 other side of this slide looking at just the affected
19 volume.

20 So, what effect have these interventions
21 had on the septic transfusion matching rate? I should

1 tell you that since March 2004 we have had 31 septic
2 transfusion reactions reported to us, including four
3 fatalities. We reported the first 20 in our paper last
4 year. During the period when we were putting, placed
5 the interventions of doubling the volume and adding
6 diversion, three more septic reactions occurred. We
7 have now submitted an abstract to the AABB for the
8 12-month period after putting those interventions in
9 place. In that 12-month period we had one fatality and
10 four other septic transfusion reactions reported to us.
11 Of course this is a continually moving target and
12 instead of workout rates is, so that workout rates is
13 an issue but we will be comparing the rates that we
14 reported in the Eder, et al., paper versus the
15 abstract.

16 We need to point out since we submitted
17 this abstract we have had three more septic transfusion
18 reactions from one collection reported to us. Just to
19 mention that, the fact that these all came from one
20 collection started us to question the effect of product
21 volume on the sensitivity of our assay.

1 I'll show you an analysis later on of
2 product volume, which is something that hasn't really
3 been considered so far in the analysis of sensitivity.
4 Having said that, we have seen a progressive decline in
5 septic transfusion rates in the Red Cross, comparing
6 the estimate before we started versus the Eder, et al.,
7 paper about from 2007 versus our abstract at the AABB,
8 the rates have fallen from about 1 in 40,000 to about 1
9 in 140,000 distributed products and fatalities have
10 fallen from about 1 in 250 to about 1 in 700,000
11 distributed products.

12 So, we want to point out that what we're
13 doing has been a good thing, has been effective and has
14 been working. It's not perfect but this investment we
15 made in safety since 2004 has been worth every cent.
16 But then why are we missing some true positive samples
17 and why are we still seeing septic transfusion
18 reactions? I want to briefly go through the mechanism
19 of failure with you, as we understand it and as we
20 published in Transfusion last year. Clearly a single
21 viable bacteria is necessary and sufficient to yield

1 positive culture. BACT/ALERT, the biomorphics will
2 tell you that. We have validated the BACT/ALERT assay
3 to a sensitivity of 1 to 10 CFU per ml, equivalent of
4 300 to 3,000 CFU product. But we know and Dr. Murphy's
5 presentation emphasized that a single CFU in a product
6 may be sufficient to cause a fatal septic reaction 5
7 days later. And we believe that false negative tests
8 are due to the lack of a single viable bacterium in the
9 sample or sampling error.

10 So the model goes something like this. We
11 believe that initial concentrations of bacteria are
12 low. We waited 24 hours before we take our sample and
13 indeed that the bacteria will divide and that at the
14 time of sampling will be in the 1 to 10 CFU per ml
15 range and that we will have one or more viable bacteria
16 in our sampling. But we now know that bacteria behave
17 in other ways. They may just die. They may simply
18 assist viable but do not divide. And we believe
19 that -- does this and some publications, to show now
20 that this is the behavior.

21 What we really are concerned about are the

1 bacteria of the prolonged black phase that then divide
2 and cause septic reactions later on. And this, it's
3 our view of the mechanism of failure. And Eder and
4 Steve Wagner published a paper in Transfusion last
5 year, using Poisson probability analysis to look at
6 this circumstance where they calculated the probability
7 of there being a single viable bacteria, in this case a
8 formal sample of a 475 mil product. I'm using 475 mls
9 because that turns out that's the mean volume of the
10 American Red Cross's collections at this point in time.
11 It's not 300 mls; it's 475 mls. So if you work out the
12 probability of one or more viable bacteria in a
13 four-mil sample you get a curve that looks likes this,
14 bacteria concentration going from zero to .5 CFU per
15 ml. The probability of there being a single, one or
16 more viable bags goes up with concentration. If you
17 look at this curve at .1 CFU per ml, you've got about a
18 30 percent chance of having one or more bags in your
19 sample, and a 70 percent chance of a sterile sample.
20 So we believe that the false negative tests are because
21 we have been in this range up here.

1 You can then ask what the effect of
2 doubling your volume would be and you draw the same
3 curves of a four mil versus the eight mil sample by
4 concentration. And Eder and Steve Wagner looked at
5 these two curves, say if you subtract that curve from
6 that curve you get the other curve and what you find
7 out is that at the time of sampling doubling your
8 volume can give you a maximum absolute increase of
9 about 25 percent increase in sensitivity of an assay.

10 We have now done the experiment. We have
11 now done the doubling the volume experiment. We've
12 moved from four mls to eight mls sampling. Showed you
13 this, this graph earlier. Within the million products
14 tested in our Transfusion paper, there were 386,000
15 collected on the TREMA and the AMICUS machines with
16 single arm with a hundred percent diversion and four
17 mls testing. And this was the rate of confirmed
18 positives. With a hundred percent diversion and eight
19 mil samples -- this is on the same machines, actually,
20 also single arm -- we tested 150,000 products and we
21 have seen -- sorry -- a 68 percent increase in

1 confirmed positive cultures, odds ratio of 1.68.
2 Understand that this is a relative increase of 1.68.
3 We talked about an absolute increase of 25 percent.
4 How does that work? Well, the relative
5 increase is actually to divide this curve by that
6 curve. The relative increase is this one over that
7 one, is this green line. And what you actually see is
8 that at very low bacterial concentrations, doubling the
9 volume does double the sensitivity of the assay. But
10 as you increase concentration the net effect decreases
11 to one. So high concentration is zero the effect of
12 doubling the volume, at very low concentrations you
13 double sensitivity of the assay. Well, we can now use
14 these curves because we know have an odds ratio of
15 1.68. We can now, so the maximum relative increase is
16 twofold but we can use these curves to say that our
17 ratio was 1.68 so we must be over here on this curve
18 and our concentrations must be about .1 CFU per ml.
19 Remember it's 475 ml product .1 CFU per ml is 47 CFUs
20 in the product, which is very close to Dr. Murphy's
21 less than 60 CFU so we concur.

1 But you can then use this curve to say that
2 at a four mil sample, we were detecting about 55
3 percent of the aerobic organisms. At an eight mil
4 sample we were detecting just under 60 percent of the
5 aerobic organisms, a relative increase of almost 25
6 percent. But you can also look at that and say, well,
7 what about 16 mls or 32 mls and you can work out the
8 approximate increase in sensitivity.

9 So you can take this data now, say hold on
10 a second, products aren't all 475 mls, what is the
11 relative effect of the volume of the product, you take
12 an eight mil sample from 170 mls is very different from
13 taking an 8 mil sample from 750 mls. So, well, this
14 median may be a 60 percent detection. If you actually
15 look at our range of volumes in American Red Cross
16 collections, for singles, doubles and triples is shown
17 on these bars. For an eight million sample the median
18 is about a 60 percent detection rate but for a 750 mil
19 product it's about a 45 percent detection rate and for
20 175 mil product it's a 90 percent detection rate. So,
21 in fact, our range of sensitivity then varies from 45

1 percent to 90 percent. You can do the same curve for
2 doubling the volume and you will actually see about a
3 20 percent absolute increase again if you go to 16 mls.
4 And this is the basis of the PASSPORT 2 proposal to go
5 to a 16 mil sample is based on the fact that we have
6 calibrated effective volume on sensitivity at least for
7 aerobic organisms. So from this, an eight ml culture,
8 this is a 55 percent of aerobic organisms due to
9 limitations of sampling and 16 mil could substantially
10 increase culture sensitivity.

11 Okay. I'm going to cover two other topics
12 very briefly. We were asked in our brief to consider
13 whole blood derived platelets as well as apheresis
14 platelets. I will show you some data from the American
15 Red Cross Hemovigilance program, relating to whole
16 blood derived platelets. In the time period from
17 January 2003 to December 2006 we distributed two and a
18 half million whole blood derived platelets. These were
19 leukoreduced but had no sample diversion. Remember
20 that point of issue testing in hospitals was instituted
21 in March 2004, in the middle or to the early side of

1 this time range. However, during this time period we
2 had 20 septic transfusion reactions reported to us for
3 a rate of about 1 in 126,000 distributed products, and
4 two fatalities, one in 1.25 million products. If you
5 assume an average pool size of five whole blood
6 components, you come up with a septic rate of 39 per
7 million or 1 in 25,000 and fatality of 1 in 250,000.
8 From the 2005 nationwide report of distributions and
9 collections we know that about 18 percent of
10 distributions are probably discarded.

11 So, the actual rate of sepsis probably is
12 in the range of 1 in 20,000, which is no different to
13 the published range that was put forward from Johns
14 Hopkins, about 1 in 15,000 whole blood, pool whole
15 blood platelets causing sepsis before the AABB standard
16 was put in place. So, our data, which is mostly after
17 the standard was put in place, shows a rate of sepsis
18 which is very similar to that reported before the
19 standard was put in place. This, to my mind, really
20 draws attention to the fact that we've done very little
21 until recently at least for whole blood platelets and

1 this is an urgent issue that we are clearly addressing
2 but needs to continue to get our attention. I also
3 point out that of the 20 septic reactions, 15 were on
4 day five, in line with our apheresis data.

5 American Red Cross has gone onto validate
6 the Acrodose prestorage pool system, using the aerobic
7 only eight mil bacterial cultures and the identical
8 conditions to our apheresis culture system. What we
9 found was if this is our confirmed positive rate with
10 apheresis, with diversion in eight mil cultures,
11 initially we implemented Acrodose without identifying
12 sample diversion and we found something like a, I think
13 a 13 or 14-fold higher rate of confirmed positives.

14 We then implemented diversion and this fell
15 by 50 percent, 54 percent, I think it was, and we now
16 see a true positive rate of Acrodose cultures of
17 5.8-fold the rate we were seeing with apheresis. And
18 that's the basis for Dr. Dumont's comments about a pool
19 of five having about five-fold the rate of confirmed
20 positives those report. The risk is that false
21 negatives may be higher as well but we have no data at

1 this point in time on septic transfusion reactions with
2 Acrodose platelets.

3 I will point out, though, that Dr. Jacobs
4 in Cleveland still cultures everything that comes
5 through his hospital and he has cultured last year 574
6 of our Acrodose pooled platelets and he has found one
7 that has a staph epi at 1.4 times ten to the fourth --
8 I can't remember the concentration -- but there are
9 still false negatives getting through even with culture
10 systems.

11 Okay. My last two slides really address
12 the issue for us of anaerobic cultures. One of the
13 goals of the PASSPORT study was to address the issue of
14 the performance of -- characteristics of the Bact/ALERT
15 test and whether the anaerobic culture as strongly
16 recommended in the package insert was really necessary.
17 And looking at the data that Dr. Dumont has presented,
18 I will, I do believe now that it's for 7-day platelets,
19 indeed anaerobic testing is probably an appropriate
20 thing to do with their aerobic testing. But I would
21 like to suggest that the same data shows that for 5-day

1 platelets anaerobic testing has little utility and in
2 fact may be harmful.

3 Why do I say this? Well, let's look at the
4 data. In the PASSPORT study they demonstrated no
5 increase in detection or decrease in the rate of
6 reported septic reactions compared to the data I have
7 shown you with the Red Cross. Anaerobic vitals have a
8 possible role in detecting obligate anaerobes but these
9 are slow-growing and so most are transfused by the time
10 of detection. In fact, in the PASSPORT study, looking
11 at the just at the true positive and indeterminants,
12 i.e., the potentially dangerous products that prove
13 only in the anaerobic bottle, 72 percent of those have
14 been transfused at the time the cultures went positive.
15 So you only detected 28 percent with a 7-day product.
16 I'll wage -- and I haven't got the data to look at but
17 on a 5-day cutoff you will have a false or -- will
18 actually be detected in time. We know that it takes
19 five and a half days to the median time from collection
20 to actually go to culture positive. So I would suggest
21 that for 5 days storage, that anaerobic cultures have

1 little utility.

2 We also have seen no material increase in
3 the PASSPORT study in sensitivity or decrease in the
4 time to positive cultures for facultative anaerobes in
5 the PASSPORT study. And I'll show you a slide that
6 reinforces this conclusion. For this we see the
7 potential loss of sensitivity to obligate aerobes, the
8 Pseudomonas and salmonella bacillus species won't grow
9 in an anaerobic bottle and if you split your product
10 you'll sample between two bottles, you'll actually
11 decrease sensitivity to obligate aerobes.

12 I'm showing you that 68 percent factor in
13 the volume difference. What worries me the most is an
14 excessive loss of platelets given the high false
15 positive rates. In the Red Cross system if we were
16 doing the PASSPORT protocol, we would have lost another
17 1500 platelets a year due to false positive cultures.
18 For every confirmed positive they had 11 indeterminate
19 or false positives that they threw away. So we would
20 suggest that in fact the Red Cross protocol
21 aerobic-only cultures should be considered as a release

1 test for 5-day platelets. I would agree that for 7-day
2 platelets I would like to have anaerobic testing. It
3 has some efficacy. But the teeter-totter, as someone
4 has said, for 5 days tends to favor the Red Cross
5 protocol. And I believe actually now, after PASSPORT
6 has passed, that probably the majority of blood centers
7 in this country are probably doing aerobic only but I
8 would have to confirm that.

9 One other piece of data I would like to
10 show you is, these false negatives we've seen, it has
11 been suggested that perhaps they are products that are
12 being contaminated after testing; maybe there are
13 pinholes in the bags, maybe they are pinholes in the
14 lines and these aren't actually cross negatives, they
15 are true negatives and you have later contamination of
16 the products.

17 What I've done here is look at the
18 bacterial species that we detect in our aerobic-only
19 cultures and compared them with the bacterial species
20 we've detected in 31 septic transfusion reactions in
21 the Red Cross and 6 other reactions reported by the

1 German, Canadian and our Dutch colleagues. What you
2 can see is that our confirmed positive cultures, about
3 85 percent Gram positives, 15 percent Gram negatives,
4 and you see pretty much the same range of organisms on
5 your septic transfusion reactions, suggesting that it's
6 not environmental organisms that are causing these
7 septic reactions, it's actually coming from the same
8 source.

9 So I think that reinforces our idea that we
10 are seeing false negative cultures. There is one
11 notable exception and that is and that is that we have
12 yet to see a septic transfusion reaction caused by
13 streptococcus although our cultures are about 20
14 percent positive. It has been suggested that one
15 advantage of an anaerobic culture volume was that
16 streptococcus grows a little faster in the anaerobic
17 bottle than the aerobic bottle. And the PASSPORT data
18 show that not to be true for half of the streptococcal
19 species but the other half was an hour or two
20 difference. Our septic transfusion reaction data would
21 suggest that it's immaterial, that streptococcus is not

1 a major public health hazard when it comes to septic
2 transfusion reactions in the system that we are using.

3 So, in conclusion then we do believe that
4 culture has substantially reduced the risk of bacterial
5 sepsis for platelets. We do believe that there remains
6 a small risk due to the limitation of sampling and that
7 that risk increases with storage duration. In our
8 hands we saw a 10 to 55 percent failure, predicted
9 failure to miss organisms using our current protocol.
10 Increasing sample volume would have a dramatic effect
11 on the sensitivity of the assay, for aerobes, at least.
12 I can only speak for aerobes. And I would like to
13 conclude by saying that in our view anaerobic culture
14 really has little utility for 5-day platelet storage
15 and threatens platelet availability due to the high
16 false positive rate. Thank you, Mr. Chairman.

17 DR. BRACEY: Thank you. Questions or
18 comments for Dr. Benjamin? Dr. Ramsey?

19 DR. RAMSEY: Thanks very much. I have a
20 question about when you collect double products, are
21 both products being cultured or just one, is there just

1 one culture being taken?

2 DR. BENJAMIN: There's one culture being
3 taken. What happens is they come in two bags connected
4 by a tube. You even connect to the 24 hours and after
5 24 hours you empty into one bag and mix it up, take a
6 sample off. The most expensive part of the whole
7 BACT/ALERT system is not the bottle, it's actually the
8 little syringe collection system that we sterile-dock
9 onto the bag and to take our eight mil sample. The
10 cost of that sterile-dock plus the sampling system is
11 almost twice the cost of a bottle, so.

12 DR. RAMSEY: So is there a -- if the
13 variable here is the relative percentage of the product
14 that's being cultured, is there a difference in the
15 culture, in the culture rates or the reaction rates of
16 double products that have been cultured once versus
17 single products that have been cultured once?

18 DR. BENJAMIN: And that's the analysis that
19 we are doing, based on that triple septic reaction that
20 we just recently saw, which I noted to us, in fact that
21 there's danger, we have going back and looking at our

1 trying to get all the volume data that we can on the
2 septic reactions we've had. Our problem is that I
3 don't have historic volume data at hand on every, on
4 all the two and a half million collections that we have
5 tested for.

6 DR. RAMSEY: Whether they're double
7 products or single products could be --

8 DR. BENJAMIN: Well, it turns out that
9 volume variation is greatest for single products. What
10 happens is you try for a double, you try for a triple
11 and you miss. You have failure because of bad lines or
12 bad access. And so if you look at the volume range of
13 single products, if it goes from 170 to 650 mls it's
14 the full range, whereas doubles may be, you know, more
15 constrained and triples are pretty constrained, say
16 pretty much 550 to 750 mls of total volume. Single
17 collections have a massive variation in volume.

18 DR. BRACEY: We have a question or comment
19 from Dr. Klein.

20 MR. KLEIN: Yes, Richard, thank you very
21 much. That was an enormous amount of information and

1 very illuminating. And clearly volume is an important
2 variable that you're now analyzing but I wonder if
3 you've looked at not volume but platelet concentration
4 as a variable, since we know that things stick to
5 platelets and platelets can act as -- bacteria, your
6 triple makes me wonder whether there's an issue there.

7 DR. BENJAMIN: You know, clearly we haven't
8 looked at that. I mean, I would have to look at this
9 more carefully they but I think the manufacturer's
10 specifications for concentration are quite constrained.
11 You tend to collect larger volumes on triples than
12 singles if you can. But, no, we haven't looked at
13 that, and it's an interesting idea.

14 DR. BRACEY: Okay. One last comment from
15 Dr. Bianco.

16 DR. BIANCO: It's just a question, Richard.
17 Will you consider joining PASSPORT 2 --

18 DR. BENJAMIN: Dr. Bianco, I'm not sitting
19 on this Committee to waste my time. I'm referring to
20 the PASSPORT 2 Committee, subcommittee that designed
21 the study. I am very definitely wanting the Red Cross

1 to participate in that study but the devil is in the
2 details and we need to go and work out a protocol that
3 blood centers can do that has the right safety for
4 patients and doesn't add additional cost for little
5 additional safety.

6 DR. BRACEY: Actually, Dr. Benjamin, one
7 more question from Dr. Lessa.

8 DR. LESSA: I just want to comment, we have
9 a paper in press, Transfusion, it's a fatal case of six
10 practice following conclusion of platelet, and, in that
11 paper, and the donor was a healthy, young donor and we
12 don't have -- rates of group G strep in the U.S., from
13 Canada and, in Europe has been shown that incidence of
14 group G strep is increasing. So in our paper like one
15 of our recommendations is the use of the anaerobic
16 bottle because of the reasons you mentioned regarding
17 the strep is being that faster, in anaerobic media.

18 DR. BENJAMIN: Would you clarify, are you
19 using bacteria, eight mil cultures anaerobic only?

20 DR. LESSA: Yeah, actually, the blood
21 center, they use one bottle of aerobic.

1 DR. BENJAMIN: And what volume are they
2 testing?

3 DR. LESSA: Eight ml.

4 DR. BENJAMIN: Okay.

5 DR. LESSA: But it was pooled platelet
6 culture so it's like 2 cc from each, so from each
7 platelet whole blood -- so it's like two cc segments so
8 they pool that and culture them out in one aerobic
9 bottle.

10 DR, BENJAMIN: I look forward to adding
11 your publication to my list of publications. The
12 expected rate of 20 percent of streptococcus would have
13 predicted that we should have seen 6 out of the 31 that
14 we've documented. So, to find one that, I don't think
15 streptococcus is immune from causing sepsis. What I
16 was trying to point out, that it's less than expected.
17 It's actually, even with one, it would still be
18 statistically less than expected. I'm aware of one
19 other case from Belgium of a strep G causing sepsis
20 after bacteria testing. Also with a pooled buffy coat
21 platelet that's not published and, but they sample --

1 apheresis platelet -- they sample almost within 12
2 hours of collection and I think that has a critical
3 influence on the outcome. So, with the protocol that
4 we use and the more sensitive protocols that the
5 Germans and the Dutch are using, I would have expected
6 streptococcus as a public health menace that we'd have
7 seen more than we have seen even including your case.

8 DR. BRACEY: We just have one more burning
9 question or comment from Ms. Finley.

10 MS. FINLEY: Thank you. It's all been very
11 interesting information but I have a couple of, just a
12 general question. A lot of these issues, whether or
13 not we should use the Verax test, whether there's a
14 labeling deviation from cGMP requirements, whether
15 it's, the sample size should be 8 mls or 16 mls,
16 whether one fatality or 250 in 80,000, you know, is too
17 much or too little, whether we should be sampling
18 anaerobic versus aerobic cultures, these are not really
19 questions for the advisory committee.
20 And I know that if I have questions about what is
21 expected by the department that there are other people

1 on the Committee who do as well. These issues go to
2 the robustness of the science behind application. They
3 go to conditions of use, things that are not
4 appropriately evaluated by us. I mean, this is a
5 regulator's job.

6 And I'm just concerned that as we head
7 further into the afternoon and into tomorrow, as the
8 department is clearly looking for something that the
9 issues that I'm raising here is that our objectives
10 here and what's in our charter is to evaluate broad
11 public health parameters of safety and availability.
12 The kinds of questions we should be looking at is, do
13 we have enough platelets out there to meet hospital
14 needs? Are there regional shortages? If there are,
15 what can we identify and how do we make recommendations
16 to the department to address that? Making trades
17 between, you know, various kinds of product
18 availability, those are issues that should really be
19 reviewed by the regulators first, possibly reviewed by
20 the BPAC and then later on coming to us. But I just
21 wanted to register that because I have very strong

1 feelings about this going --

2 DR. BRACEY: Oh, no. This is definitely
3 recognized in the sense that the context of this
4 discussion really is not necessarily that we would end
5 up recommending whether one would use four mls or eight
6 mls or 16 mls but really looking at the broader issue,
7 availability, is there anything such as a risk-free
8 product. I mean the questions that have been posed to
9 us by the Secretary are to comment on a current state
10 of testing and as whether or not we feel that those,
11 the limitations are reasonable or whether we should
12 recommend more investigation. So, again, the issue is,
13 it's a broad issue and we're not really talking about
14 the details. That is best left for the regulatory
15 agency.

16 MS. FINLEY: Thank you.

17 DR. BRACEY: Dr. Epstein?

18 DR. EPSTEIN: Just to come full circle, it
19 is FDA's intention to bring a question of redesign of
20 PASSPORT, which is really the question of conditions
21 for acceptable use of 7-day platelets back to the Blood

1 Products Advisory Committee. And just so everybody
2 understands, the discussion that has been going on
3 publicly hear today is really a very preliminary stage,
4 that these options really have not been presented
5 formally or reviewed by the FDA. And all of the things
6 that our colleague, Ms. Finley, is pointing out are on
7 the table and in flux. Can it be an anaerobic bottle
8 alone? Is it eight mls versus 16 mls, you know, what's
9 the relevant Verax test, et cetera, et cetera, et
10 cetera, et cetera.

11 So, I think the original intent here was an
12 informational update and if there's a question to be
13 addressed by the ACBSA, it's really some broad public
14 health question and nothing that is so highly specific
15 to product approvals, product labels, you know,
16 conditions of use, et cetera.

17 DR. BRACEY: Yes, Dr. Benjamin?

18 DR. BENJAMIN: If I could -- I assume that
19 was a question. In the view of many blood center
20 personnel and I assume hospitals, too, the 7-day
21 platelet is an availability issue. The analysis you

1 saw from the AABB committees is about the availability.
2 The loss of the PASSPORT protocol increased outdates, I
3 believe -- by 5 to 10 percent, which is a pure
4 availability issue. So we may be lost in the science
5 but I think the motivation here is availability.

6 DR. BRACEY: That's it. All right. Can we
7 continue then with the next presenter? We've heard
8 from some comments from Dr. Jacobs earlier today.
9 We'll hear his full presentation. Dr. Jacobs is a
10 Professor of Pathology at the Case Western Reserve
11 University and Director of Clinical Microbiology at the
12 Case Medical Center. He's done extensive work on
13 assessing platelets for bacterial contamination along
14 with a colleague known to many of us, Dr. Yomtovian.
15 And he will present the effect of recent changes and
16 practices on the risk of bacterial contamination of
17 platelet products.

18 DR. JACOBS: Thank you, Mr. Chairman,
19 Committee members, ladies and gentlemen. I'm honored
20 to be asked to address this Committee and I would like
21 to first off be starting by acknowledging Dr.

1 Yomtovian, who as director of our transfusion service
2 for 18 years first brought this problem to my attention
3 and got me working on the subject and since then we
4 have been collaborating very closely. My disclosures
5 are shown over here. I received funding as an
6 investigator to investigate and do studies on many of
7 the products we have been discussing and I have also
8 provided consultations services.

9 Now, as far as bacterial contamination of
10 platelet products is concerned, I mean to address five
11 questions. What is the incidence of bacterial
12 contamination? What are the effects on patients of
13 transfusing these products? Because I think that's the
14 key issue and it's been addressed and I want to show
15 you our data in comparison with the literature. What
16 has been done to decrease the risk of bacterial
17 contamination? Again that's been discussed and I'm
18 going to try and compare the different studies. How
19 effective have these measures been? And, finally, what
20 additional steps can be taken to further reduce the
21 risk?

1 My interest in this first started in 1991,
2 where we had two cases within a very short period of
3 time. We were concerned that there was a major
4 breakdown in sterile procedures, and we had two cases
5 within a very short period of time, and they instituted
6 100 percent surveillance by culturing all our platelet
7 units at issue. And we found, much to our surprise,
8 that we had two more cases and within just over a
9 one-month period we had four cases, two were sort of
10 serious, one, *Pseudomonas aeruginosa* and one
11 *Staphylococcus epidermidis*. The *Staph epidermidis*
12 didn't cause a reaction but we had severe reactions and
13 one death from the other three. This was reported to
14 FDA and recorded in CDC. They did an investigation and
15 could find no breakdown; however, we did surveillance
16 following that and I'll be presenting the results that
17 we found since then.

18 Now, just, Dr. Benjamin alluded to this to
19 some extent but one of the issues here is you start off
20 with low numbers of organisms and you can start off,
21 this is the lowest number of organisms you can, this is

1 one organism in a 400 ml bag, that I did this
2 calculation on, and if it grows within an eight-hour
3 generation time you can see that you don't get terribly
4 many organisms by 7 days, roughly ten to the three.
5 However, if an organism grows in a four-hour generation
6 time you get some high numbers and if it grows within a
7 one-hour generation time which is based on the data, of
8 the studies I've done is about the fastest an organism
9 will grow in platelets, you'll get your very high
10 numbers. And this brings up a question of how far
11 ahead of time can you test a platelet and what level of
12 sensitivity do you need and what length of time would
13 that affected unit be safe or have some numbers after
14 testing.

15 And again you see an extensive evidence on
16 what testing early does but you also have to bear this
17 in mind that even when you test near or at issue or if
18 you want to try and test 24 hours before issue on day
19 four, as Dr. Murphy's data has shown, you have to bear
20 these additional changes in mind. In addition this is
21 starting with one organism per bag, you can end up with

1 more organisms per bag. Some of the data you have been
2 presented shows that you probably are starting off with
3 40 to 60 organisms per bag.

4 Now, one of the other things that can
5 happen is that you can have your organism, it can grow
6 and in the war that goes on between the host defense
7 mechanisms you have and the bacteria that are present
8 in the bag, the host defenses can win and the bacteria
9 or the bag water-sterilized. And in fact with many
10 strands of organisms this happens and in fact when we
11 try and experimentally contaminate platelets we often
12 get water sterilization. And there are some strands,
13 for example, of E. coli., which water sterilize very
14 rarely, the same as Pseudomonas, coag-negative Staph as
15 well, and there are major variations between different
16 units. So that makes it very difficult to study these
17 organisms in the lab because you have to do so many
18 experiments to get one organism to successfully grow.

19 Now, the other thing that can happen and
20 we've probably got some good evidence this happens is
21 that the organism doesn't start growing immediately and

1 you can have a lag phase one day versus a three day lag
2 phase and they can grow at different rates. And this
3 lag phase could last several days. We have seen
4 organisms that have lag phases as long as six, 7 days
5 in experimentally contaminated platelets. So again you
6 have to bear these in mind when you're looking for the
7 most sensitive detection system and when you're going
8 to apply the test.

9 Now, going to which organisms are the most
10 important ones, and clearly ones that kill patients are
11 our most important ones; second-most important are
12 those that cause septic reactions. And you've seen
13 this data being updated, roughly six organisms or six
14 cases a year occur with platelets, and I see that for
15 2005, 2006, those numbers are similar for 2007, that
16 number went down to three. So this may reflect changes
17 in practice of lacking more extensive use of virgin
18 cultures.

19 As far as organisms are concerned, there
20 have been very few cases of strict anaerobes causing
21 death. And here's one instance of frastrilian fringes

1 (phonetic). I always take this kind of data with a
2 grain of salt because I'm not sure how well-confirmed
3 all of these cases were. There's no information on the
4 numbers of organisms in the units that were transferred
5 and there's no information on whether the culture was a
6 confirmed or an unconfirmed culture.

7 And when you find odd organisms, this
8 information becomes vital and unfortunately it's not
9 available in this kind of data. Also as far as
10 Streptococcus is concerned, you can see there are two
11 venohemolytic streps there and one of the points I'm
12 going to make in response to Dr. Benjamin's comments
13 about streps is that a microbiologist calling organisms
14 streps is like calling all blood products, products.
15 There are multiple different kinds of streps differing
16 incredibly in virulence, and I think what you probably
17 are referring to are the veridans streps which are of
18 relatively little clinical significance. The
19 venohemolytic group and Strep bovis are probably much
20 more virulent and when you do find cases they're
21 usually those Streptococci. Also as you can see here

1 the Gram negatives predominate and it's a variety of
2 the Enterobacter cloacae and the Pseudomonas aeruginosa
3 that are major pathogens.

4 And again I'm showing Dr. Benjamin's data.
5 One of the points about many studies -- and I'm using
6 this as an example -- is that most of the reactions
7 occur with day five platelets and this was certainly
8 the case in our series as well, and there are many
9 other series that show this.

10 Now, the experience I referred to earlier
11 is that starting in 1991, our experience from middle of
12 1991 when we started surveillance to date, except for a
13 three-year period where we stopped surveillance we have
14 been culturing some or all of our platelet units at
15 time of issue. When you've been culturing some of them
16 it's been day four and five only, that was
17 predominantly from about '96 to 2000. When we
18 restarted in 2004, we cultured platelets of all ages
19 although most of our use is day four and day five. And
20 you can see here, based on active versus passive
21 surveillance, when we stopped surveillance we didn't

1 detect a single case of bacterial contamination. When
2 we were doing surveillance we were finding between one
3 and seven cases per year. And, only two of this entire
4 -- series was picked up entirely by passive
5 surveillance. The others were picked up entirely by
6 active surveillance. And I'll be showing you a
7 clinical correlation of the series.

8 Now, one hopeful point that I'm seeing is
9 that in 2007 and so far to date in 2008 we have had no
10 contaminants, only one in 2007, and the two major
11 changes that have occurred in our platelet supply is
12 increasing use of diversion patches and more recently
13 the use of precooling of pool units and culturing
14 those. And I'm going to try and tease out our blood
15 supplies to see whether we can show which of those two
16 factors is more important. But just to show the point
17 here that has been alluded to many times today, is that
18 as you look for contamination, as you look for
19 reactions, many of them are missed.

20 This has been our experience over a 15-year
21 period. We found 52 bacterially contaminated

1 platelets, 50 by active surveillance, two by passive
2 surveillance, odds ratio of 32-fold higher by active
3 surveillance. Of these that were transfused we found
4 about the same number, difference between the two. Of
5 septic transfusion reactions it wasn't as much of a
6 difference. There was a tenfold difference, 16 versus
7 two. As far as septic reactions with bacteremia and
8 one of the points I make about bacteremia is some of
9 the literature only included bacteremic cases. You can
10 see that relatively few of the cases where we have
11 proven septic reactions, proven contaminated
12 transfusions, that you could actually demonstrate
13 bacteria, sorry, bacteremia in a recipient because
14 either the organisms are killed very rapidly in blood
15 or those patients are on antibiotics.

16 As far as fatalities are concerned, we only
17 had one in each group and on a red basis this was no
18 different. But, you can see at least on septic
19 transfusion reactions we picked ten-fold more by active
20 surveillance than were reported to us by passive
21 surveillance.

1 Now, what I have done here is showing you a
2 comparison, some of the studies that have been referred
3 to where you see data from today, the Ness study, which
4 was conducted between '87 and '98, septic reactions per
5 million was 65, sorry, 67 and 75 random versus
6 apheresis units. And this is all based on units so if
7 depending on the pool size, the rate per transfusion is
8 going to be five or six-fold higher for the random
9 units given as pools.

10 Perez study showed they had two kinds of
11 random units, those given as pools and those given as
12 single units. And their rates for pools were 14 given
13 as pools, 9 given as single units per million and 32
14 for apheresis units. In the U.S. study, authored by
15 Dr. Kuehnert, this required bacteremia and here the
16 contaminants, septic reaction rates were 10 to 11 per
17 million with two fatalities per million. But again a
18 lot of cases were excluded including many of the cases
19 in our series because patients did not have bacteremia.
20 And then for comparison I've shown our data again.
21 When we did active surveillance, sorry, when we did

1 passive surveillance our results were very similar to
2 other experiences maybe but lower, certainly comparable
3 to the Kuehnert study and the Perez study but when we
4 did active surveillance we found much higher rates and
5 aggregate-wise septic reactions per million units was
6 tenfold higher, for active surveillance versus passive
7 surveillance, as I showed you in the previous slide.

8 We also showed that fatality rate was
9 higher because our numerators were low. We didn't have
10 any cases. Our data is not as good but I just wanted
11 to point out one point about the data that we
12 generated. Our institution uses approximately .5
13 percent, one half a percent of the country's platelet
14 supplies but we're one of the few institutions, in fact
15 the only one that I'm aware of that's done active
16 surveillance. So a lot of this data -- and we've been
17 doing there for a fairly long period of time, 15 to 18
18 years, so even using a small amount of the country's
19 blood supply I think we have been able to come up with
20 very useful information.

21 Now, we look at contamination per million

1 units, though, that as I showed you earlier we found
2 the contamination rates were roughly 500 per million
3 units. And I'm very interested to see that in fact
4 when later cultures are done and some of the data from
5 the PASSPORT study and also Dr. Murphy's data from
6 Ireland are showing even higher rates of contamination
7 per million units because everyone who has seen this
8 data in the past says that these rates can't possibly
9 be that high and unfortunately they are and again you
10 can see the difference between active versus passive
11 surveillance.

12 So what I have done is put all this data
13 together, to estimate based on usage of platelet pools,
14 between .25 and .38 million pools per year based on
15 about one and a half million random units being
16 produced and about 1.4 million apheresis units being
17 produced. And there are some differences in numbers
18 depending on whether you use units affected or the way
19 they're split and used so then these numbers are not
20 entirely 100 percent comparable. But just to put some
21 ballpark figures on fatalities, which as are probably

1 recognized most of the time that the number of case we
2 see is between five and eight per year on a theoretical
3 basis, based on information we have and based on the
4 number of cases reported to the FDA.

5 Based on passive reporting septic
6 reactions, the data that we have shows us to be
7 anywhere from 24 to 255 per year. Based on our data
8 from active surveillance this looks like more like 400
9 and if you base this based on culture at issue based on
10 our data this comes up to about 1400 for the U.S.
11 total.

12 Now, again just to put this risk in
13 perspective for other transfusion transmitted
14 infections, you can see that there have been decreases
15 in many of the viral infections and at the current rate
16 of 1 in 2000, which was prior to introduction of
17 diversion and BACT/ALERT culturing, and probably 1500
18 contaminated platelets a year were occurring, and this
19 has probably gone down and I think we probably have
20 enough data now to show that this curve is going down
21 and to add this curve to the curve of these viral

1 infections.

2 The second question is, what are the
3 effects on platelets in transfusing these products?
4 Now, one of the things I was surprised to find out was
5 that there is no definition of a septic transfusion
6 reaction. There are definitions of infection, there
7 are definitions of febrile transfusion reactions and
8 there are other definitions available in NCI databases,
9 for example, for classifying cancer patients and so on.
10 So, what we did when we published this data this year
11 is we tried to come up with a transfusion reaction
12 rating system.

13 And we came up with a scale from zero to
14 five, no reaction, mild reaction, which is a febrile
15 reaction, one to two degree centigrade increase in
16 temperature, or an asymptomatic clinical case, with a
17 positive blood culture -- leukocytosis, moderate
18 reactions, a transient change in vital signs resolving
19 within 24 hours with minimal or no intervention, severe
20 change in vital signs requiring intervention such as
21 intravenous fluids, antibiotics, vasopressors, and with

1 resolution without sequelae, life-threatening severe
2 reaction -- vital organ function and fatal reaction is
3 obvious. But, before this and with many of the other
4 presentations I've seen today, there's no standardized
5 definition of a transfusion reaction. I don't know
6 that this is the best one to use but I think someone
7 needs to get together and put together a good
8 definition of sepsis and what the definition of that is
9 in relation to a transfusion.

10 I also looked at the organisms of what we
11 know. Again the biggest gap in our knowledge is how
12 many organisms were present to correlate that with the
13 reaction that occurred in a patient. And we had a lot
14 of information about the organisms. We had a fair
15 amount of information about what happened to patients.
16 We had very little information on how many organisms
17 there were. This paper by Ness had some information at
18 least that the gram stain was positive and we know what
19 the sensitivity of a gram stain is and at least we know
20 there were high numbers of these organisms. But for
21 example here with a negative gram stain, Staph

1 epidermidis with the sensitivity, or it's just one
2 organism, we don't know. Also, I've highlighted the
3 previous series in green the number of anaerobes. And
4 you can see here there was one anaerobe in the series.
5 And anaerobes in general are not something that we need
6 to concentrate on.

7 This is a series from the French series and
8 again the fatal cases I've outlined in red, anaerobes
9 in green, and you can see here again no information on
10 number of organisms, good information or reasonable
11 information on what happened to patients. But again
12 one of the concerns about patients with chills and
13 fevers is the vast majority of those, over 95 percent
14 are not caused by transfusion of contaminated platelet
15 or bacteria of contaminated platelets. And many of our
16 patients in our series routinely had febrile reactions
17 to every platelet reaction and only every now and then
18 was one due to a contaminated platelet.

19 Here's the U.S. data from the U.S. study.
20 This data shows red cell transfusion and platelets and
21 there's no breakdown of which ones were red cells and

1 platelets but these were the platelet fatalities. And
2 again these streps, *Strep agalactiae*, so, please don't
3 lump that in with the word streps, it's an important
4 pathogen -- Gram negatives, *E. Coli*, *Serratia*,
5 *Enterobacter* -- all providential in this case. So
6 again most of the organisms we're dealing with are the
7 Gram negatives.

8 This was our series. We published this in
9 2006, cases where death occurred shown in red, and
10 again here for the first time we do have quantitation
11 of organisms. And you can't read this but I'll be
12 showing you this graphic many times. But just to make
13 the case here that the only limitation in our case
14 series was that's for surveillance we only did aerobic
15 cultures and we this very crudely by planting 100
16 microliters onto a -- plate -- incubating this for 48
17 hours. If it became positive we went back to the
18 product, recultured. We kept the product in a
19 refrigerator, and only accepted that as a positive if
20 it was confirmed and also in the vast majority of cases
21 went back to the original platelet bag or the source

1 units and cultured the same organism at approximately
2 the same numbers to confirm that it was positive.

3 This shows you the data in a more useful
4 form, here when we looked at bacterial load greater
5 than equal to ten to the five versus less than ten to
6 five, the odds ratio of any reaction was four-fold when
7 it was greater than ten to the five and a severe
8 reaction was greater than 34-fold so we didn't have any
9 severe reactions of less than ten to the five. So just
10 numbers of bacteria per se are important, but other
11 analyses which I'll show you.

12 No significant difference between
13 contamination rates and bacterial loads of apheresis
14 versus random units. Some of these were apheresis
15 units; so far the rest of them were random pools or
16 units. As far as virulence of the organism, that
17 definitely made a difference. This is a limited
18 dataset, this all we had but you can see a Staph
19 aureus, very clear relationship between number of
20 organisms and transfusion reactions. And the virulent
21 organisms included two Streptococcus bovis. So we

1 concluded that any reaction odds ratio with a more
2 virulent organism was 3.5-fold higher and a severe
3 reaction was 8.5-fold higher than were the less
4 virulent species.

5 Now, what's been done to date to decrease
6 the risk of contamination? This started off in 2002,
7 the College of American Pathologists recommended that a
8 method for bacterial detection be put in place. In
9 2004 AABB standard 5.1.5.1 was that a blood bank or
10 transfusion service shall have methods to limit and
11 detect bacterial contamination in all platelet
12 components. And this was required to be met by March
13 the 1st, 2004. And in 2003 the AABB issued a bulletin
14 saying, use a method to detect contaminants that remain
15 and grow during storage. The more sensitive the
16 detection method, the better the assurance that the
17 majority of significant isolates will be detected.
18 Procedures that are currently available and that will
19 meet the standard include culture, which the Pall BDS
20 and IE BDS, BACT/ALERT methods, microscopy, Gram,
21 Acridine Orange and Wright stains and pH and glucose

1 were mentioned as acceptable methods.

2 And in a survey done in 2004, this showed
3 what users, hospitals were doing to detect
4 contamination. You can see dipstick pH and glucose
5 were used simultaneously by about 50 percent of
6 institutions. Remainder of institutions used a variety
7 of techniques. Other methods available, pH, swirling,
8 culture microscopy, other or none.

9 What methods do we have decreasing the
10 risk? As we discussed extensively, prevention,
11 disinfection of the venipuncture site, diversion of
12 initial blood flow, pathogen inactivation, and one
13 thing which needs to be stressed is to use your
14 platelets as early as possible. Then detection at time
15 of production versus at time of use, and that's been
16 discussed extensively but I'll be trying to summarize
17 some of that data.

18 Dr. Benjamin has already shown this data
19 showing that there's a big difference in the two-arm
20 procedure versus the one-arm procedure, mainly based on
21 the diversion culture placement, has a much lower rate

1 of contamination, bacterial contamination of apheresis
2 units. And his data showed that based on a collection
3 that this was 4.7 fold higher with a two-arm procedure
4 versus a one-arm procedure with diversion and on a unit
5 basis based on units being issued was 3.3-fold higher.

6 So, what I've done is add this data to this
7 previous slide that I've shown you -- everything up to
8 here is the previous slide -- and I've compared this,
9 and you can see that with the two-arm collection the
10 rates are pretty similar except for when we have done
11 active surveillance but it's pretty similar in the same
12 kind of ballpark as the passive surveillance data
13 previously published. But to me this is the big
14 breakthrough. This is the first convincing evidence
15 I've seen that diversion culture technology really does
16 have a major effect on decreasing the septic
17 transfusion rate here. And you can see here this went
18 from 24 down to 5, and that fatal reactions went from 5
19 to less than 3. There were no fatal reactions out in
20 this series here.

21 So, I think this demonstrates the

1 importance, at least with range of passive
2 surveillance, diversion technology is extremely
3 important. Pathogen inactivation, there's going to be
4 a presentation on this later on. I'm not going to
5 spend a lot of time on it but one of the points I want
6 to make about pathogen inactivation is that we need to
7 make sure that we have a large enough series of units
8 that have been issued to patients that have been
9 cultured at time of issue to make sure that this
10 technology is safe. The main advantage of this
11 technique is that -- sorry -- the main disadvantage is
12 that no method is equally effective for all organisms
13 and these methods may be ineffective against
14 spore-forming organisms, which Bacillus and Clostridium
15 would fall into that group.

16 In Europe the INTERCEPT system is
17 available, uses amotosalen and is currently in clinical
18 use in several European countries. And use of pathogen
19 inactivation may obviate the need for a bacterial
20 detection system. As far as detection methods are
21 concerned, we discussed culture early and late and the

1 definitive way of doing culture is to do a culture at
2 time of issue. And I think we need to spend more of
3 our efforts on doing this as we have been doing at our
4 institution and not putting as much effort into the
5 early culture. And certainly Dr. Benjamin made a
6 convincing case that there's relatively little benefit
7 to using an anaerobic culture model.

8 Microscopy, I'll be showing our experience.
9 We're one of the few institutions that tried to use
10 microscopy for prevention. Biochemical markers have
11 been shown to be very poor. In all of our series after
12 2003, we had several cases where pH was measured and
13 all of these came out normal despite bacterial
14 contamination. Conversely, approximately 2 percent
15 failed pH without bacterial contamination and were
16 discarded.

17 This is an area where we need to be
18 spending a lot more of our effort, is rapid tests for
19 use near or at time of issue. One test is available,
20 has been FDA approved, that's been referred to earlier.
21 That's bacterial lipotechoic acid and

1 lipopolysaccharide detection by lateral flow
2 immunoprecipitation. Many other systems have been
3 developed or are being investigated. There are
4 probably many others that can be used. Just simple
5 antitoxin detection by the limulus lysate test will be
6 extremely useful because this would pick up only Gram
7 negatives but those are the organisms that cause the
8 most harm.

9 This is our experience with gram stain.
10 This is both conducted prospectively and
11 retrospectively. We looked at 39 by gram stain and you
12 can see that as in the literature the detection limit
13 is approximately 10 to the 5 organisms per ml. When we
14 did this prospectively we did this for seven and a half
15 years. This was extremely time-consuming, extremely
16 labor-intensive, extremely expensive and what we found
17 was we interdicted six cases with coag-negative staph.
18 All the datapoints that have a circle around them were
19 coag-negative staph. We failed to detect one
20 coag-negative staph because the pool was not adequately
21 mixed and the sample we got actually did not have

1 organisms under the gram stain, that when we went back
2 to the product it was positive. But during this period
3 we missed two organisms. One was a Serratia and one
4 was a Viradans strep. And we also missed a Staph
5 aureus, which had a very low count. So you can see
6 here despite the gram stain performing fairly well, was
7 very labor-intensive and based on this experience we
8 abandoned doing gram stains in 1999.

9 As far as early detection systems are
10 concerned, three are on the market. Bact/ALERT, which
11 has been discussed extensively, requires bottles and an
12 instrument to do the incubation in and one of the
13 problems you've seen is that the instrument gives false
14 signals a lot of the time and detection rate depends
15 entirely on the volume. One of the concerns I have
16 about the BACT/ALERT system is that you can overwhelm
17 the bacterial medium with product, and studies that
18 were done to validate the system were only done with
19 four mls to a bottle. And I'm concerned when people
20 are sticking in eight and ten mls per bottle that your
21 yield may be somewhat lower than splitting this into

1 multiple bottles. From the data Dr. Benjamin showed, I
2 don't think this is a major concern but it is something
3 we need to be aware of.

4 The eBDS is an alternative culture system
5 using a pouch and that's read by detecting the oxygen
6 content falling in the pouch 24 hours after incubation
7 as opposed to the 5 to 7-day incubation, of the
8 BACT/ALERT bottles. And Hemosystem also developed the
9 ScanSystem which is a fluorescent staining system of
10 bacteria, has a very complex, very sophisticated
11 system, very expensive and labor-intensive and done at
12 the same time that a BACT/ALERT culture would be done,
13 worked very well experimentally but I believe the
14 system is no longer being marketed.

15 And again, as has been referred to several
16 times here, a prepooling system is FDA approved. The
17 Acrodose System includes leukocyte filtration, and Dr.
18 Benjamin presented some data on this which shows that
19 this brings pooled apheresis platelets at least up to
20 the standard of what we have been doing for apheresis
21 platelets.

1 Of the multiple at issue tests that I
2 showed you earlier, the only one that's been FDA
3 approved is the PGD test made by Verax Biomedical. It
4 has received 510 clearance as an adjunct quality
5 control test following testing with a bacterial
6 detection device cleared by the FDA for quality control
7 of leukocyte reduced apheresis platelets. The test is
8 done within 20 minutes, approximately, sorry. Within
9 approximately 20 minutes of sample addition, a pink
10 color bar will appear in one of the two reading windows
11 of the test cartridge and picks up Gram positives on
12 one side and Gram negatives on the other side. About
13 the cutoff assay, the system which differs for
14 different organisms and for optimal performance it's
15 recommended that this system be used from 72 hours
16 through the end of day five and storage.

17 How effective have these measures been?
18 Again we've alluded to these many times during this
19 presentation. This is Dr. Murphy's data. I have taken
20 the liberty of analyzing it in a slightly different
21 fashion to the way he has, based on only his confirmed

1 positives. Based on that initially he showed 324 per
2 million. If you add the ones on day four he found
3 another 300 per million, bringing the cumulative to 600
4 and if you took an outdated 7 days he found another 845
5 per million, bringing the total to 1471 per million.
6 And if you look at the cumulative sensitivity, day one
7 was only picking up 22 percent. And interestingly
8 enough I calculated the cumulative sensitivity -- data
9 of the PASSPORT study and that comes up as 25 percent.
10 So I think this is a very representative number and I
11 think it puts into perspective how sensitive the AA
12 culture is. It's missing a lot.

13 And again when you compare our rates in
14 comparison to the PASSPORT study, Dr. Murphy's study
15 shows that when you are taking platelets out to
16 expiration, our results even though they were fairly
17 unexpected are now being confirmed by the studies and
18 in fact with anaerobic culture these results are even
19 higher in comparison to the early culture again
20 differences between the one-arm and the two-arm
21 procedures.

1 Now, what additional steps can be taken to
2 further reduce the risk? And here this brings into the
3 issue of we need to concentrate on the organisms that
4 are causing harm to patients, those causing septic
5 reactions, those causing fatalities, and look at the
6 data we have on numbers of organisms and species of
7 organisms. While we would like a test to pick up
8 everything that I've shown in the green box, these are
9 the organisms we need to concentrate on, the highly
10 virulent organisms and organisms in high numbers. And
11 I showed you our data showing detecting greater than 10
12 to the 5 is much more deleterious to patients than
13 under 10 to the 5 organisms per ml. Bacterial data
14 again, any reaction four-fold higher, severe reaction
15 greater than 34-fold higher.

16 As you get to 10 to the 4 you can see you
17 pick up very little additional yield, 10 to the 3, very
18 little additional yield. So, when you look at
19 detection sensitivity based on transfusion reaction all
20 cases are shown in red but the ones we need to
21 concentrate on are the severe -- fatal reactions and

1 here you can pick up even 10 to the 6 organisms per ml,
2 would have picked up all of these cases. So from a
3 practical point of view it would be good if we had a
4 test that picked up 10 to the 4 organisms per ml but we
5 would be very happy and would have saved a lot of
6 severe, life-threatening or fatal infections if we
7 could detect even 10 to the 6 organisms per ml.

8 So my conclusions are that whole blood
9 derived platelets should be cultured early to bring
10 their levels of testing up to that of apheresis
11 platelets; however, there are practical issues that
12 need to be addressed such as culturing pools and not be
13 as sensitive as culturing individual units. And Dr.
14 Benjamin has presented you with a lot of data on
15 numbers, and numbers of organisms and detection levels.

16 The optimal volume and conditions needed to
17 provide the most cost-effective method for detection of
18 contamination by early culture needs to be studied
19 further. The value of anaerobic culture needs to be
20 clarified. And I think based on several of the
21 presentations, including Dr. Benjamin's, I think we

1 probably have some clarification and answers to this
2 question.

3 The real incidence of bacterial
4 contamination needs to be studied by quantitative
5 culture at time of issue and other than our series,
6 which again I want to stress represents .5 percent of
7 blood platelets used in the U.S., other studies need to
8 look at quantitative culture at time of issue to assess
9 the value of prevention and detection methods because
10 again the numbers of organisms as well as the species
11 as well as correlating this with clinical reactions
12 that in most cases these were expired units that were
13 not transfused so numbers of organisms are extremely
14 important to know what that data means.

15 And quantitative cultures need to be
16 performed on units with positive early broth cultures.
17 Again, so, that we can get some idea of what's happened
18 to those organisms in the interval between the culture
19 being done and the culture becoming positive in the
20 BACT/ALERT or the PDS system. And without that
21 information we've got the materials sitting there,

1 we're not taking advantage of them.

2 And finally the clinical efficacy and the
3 cost-effectiveness of point-of-issue assays by hospital
4 transfusion services, either as a stand-alone test or
5 in addition to early culturing, need to be determined.
6 And the safety, efficacy and cost-effectiveness of
7 pathogen inactivation in the eradication of bacterial
8 contamination needs to be determined. Thank you.

9 DR. BRACEY: Thank you, Dr. Jacobs. In the
10 interest of time we can have one or two questions or
11 comments. Then we're going to have to move to a break.
12 Dr. Pomper?

13 DR. POMPER: Directly regarding Ms.
14 Finley's comments on availability, when I heard the
15 20-minute timeframe to bring the point of issue assay,
16 there are instances when that would be a, too long of a
17 time to wait. So that is there any information
18 available on, I guess I was imagining this as a window
19 period between point of issue testing and then when it
20 would be okay to issue the product, if that makes
21 sense? So how long would be a reasonable time, say,

1 between testing and when the product would be okay to
2 give? Because I conceive of this being done at a
3 particular time of day, and then hopefully that window
4 would last at least 12 to 24 hours we with, where we
5 should test essentially the entire inventory so that it
6 would be available at a moment's notice for issue so is
7 there an estimate as to --

8 DR. JACOBS: In addition to the 20-minute
9 reading time, or the prep time there are several steps
10 including a -- step and adding several reagents before
11 you get to the step of adding the material to those
12 test strips. So the total turnaround time is probably
13 nearer to 40 to 45 minutes, and that's on a single
14 test. When you're doing them in batches, depends on
15 batch size, so there is considerable time. And I don't
16 think this was addressed very clearly in the product's
17 approval other than the fact that after issue you have
18 four hours to use the product. And I know when we used
19 to do gram stains we used to turn around in
20 microbiology lab within 30 minutes and that was very
21 tough to do so that we wouldn't go beyond the four-hour

1 outdate.

2 DR. BRACEY: But as a matter of
3 practicality when platelets are issued from your center
4 that when you did testing of point of release you did
5 some advanced testing some time before release?

6 DR. JACOBS: Yes. At the time we were
7 doing gram stains, when the microbiology lab is only
8 operated for two shifts so at the end of the second
9 shift they were gram-stained prospectively at two or
10 three units so those would be available during their
11 shift.

12 DR. BRACEY: Dr. Klein?

13 MR. KLEIN: Two quick questions. One, you
14 mentioned spore-forming in pathogen inactivation.
15 Could you tell us what kind of morbidity a spore-form
16 is caused from a transfusion --

17 DR. JACOBS: Yeah. The two spore-forming
18 genera are Bacillus and Clostridium and Bacillus, as
19 you've seen there have been several cases, there have
20 been two cases of Clostridium infections. So,
21 relatively rare but again it just depends on how

1 comprehensive you want to be.

2 DR. BRACEY: Last comment from Dr. Corash,
3 then we'll need to take a break and reconvene.

4 DR. CORASH: Just a point of clarification.
5 The spore-forming organisms in the vegetative phase are
6 sensitive to inactivation. It's the spores which
7 cannot be inactivated.

8 DR. JACOBS: Yeah.

9 DR. CORASH: But in blood components the
10 spores are in a rich nutrient environment and go into
11 the vegetative phase and so they become sensitive.

12 DR. BRACEY: Can -- okay. We'll take one
13 more comment and then that's it. We'll have to --
14 otherwise the floor may be wet.

15 MR. FITZPATRICK: Mike FitzPatrick, I'm the
16 president of company called Cellfire and people on the
17 on the Committee and in true disclosure our company is
18 involved in producing lyophilized platelet for
19 transfusions but my comments I hope are not
20 self-serving. One of the things brought up in by the
21 Committee is what the Committee should address and

1 availability and safety are issues that need to be
2 addressed. Supply is an issue and I applaud the work
3 that's been done to look at hemovigilance and look at
4 what's happening with bacterial testing and what the
5 impact is only supply and effectiveness.

6 But my question is, what's the clinical
7 outcome? You're saving supplies for fatalities but
8 where is the correlation to, as Dr. Benjamin suggested,
9 that six and 7-day old platelets are not as efficacious
10 as three and four day old platelets; are there
11 increased transfusions? Are there increased use, are
12 there increased outdate? And there is the assumption
13 that we can't do anything to control that -- I would
14 suggest that there's a method available -- platelets to
15 help control inventory for actively feeding patients
16 and allowing time for culturing once you have frozen
17 platelet in the first few days of -- you now can
18 stockpile platelets, liquid inventory for -- oncology
19 patients with tested and reduce the risk of patients,
20 you can take plenty of time to test and culture the
21 platelets that are frozen and then in a somewhat

1 self-serving context the next step from frozen to
2 platelets would be a lyophilized platelet -- thank you.

3 DR. BRACEY: Thank you. Let's take a
4 break.

5 (There was a break in the proceedings.)

6 DR. BRACEY: We would like to reconvene the
7 session. Our next speaker is Dr. Lawrence Corash. Dr.
8 Lawrence Corash is vice president of medical affairs
9 and chief medical officer for Cerus Corporation. Dr.
10 Corash has been very active in the field of pathogen
11 inactivation for the last decade and has been a solid
12 contributor. He will speak to us on Cerus update on
13 pathogen reduction. Dr. Corash?

14 DR. CORASH: Mr. Chairman, members of the
15 Committee, thank you very much for the opportunity to
16 provide some commentary and an update on pathogen
17 inactivation in platelet components. Just to be clear,
18 shifting gears a little bit from testing and detection
19 to the realm of pathogen inactivation, and on the prior
20 meeting of this Committee, we actually presented the
21 technology and so I'm not going to review that in great

1 detail today except to say that it is a technology
2 aimed at inactivating bacteria, viruses, protozoans and
3 leukocytes in liquid components and it's designed to be
4 used in a blood center, in the immediate 24-hour
5 post-period after collection and preparation of the
6 component. And it's compatible with both apheresis and
7 whole blood derived platelet components.

8 What I am going to talk about today is the
9 use of safety data to assess a risk-benefit profile,
10 and this has to be done on a per patient basis because
11 the clinical trial data regarding safety are developed
12 on a per patient basis. And so in looking at this type
13 of technology, obviously a risk-benefit assessment is
14 very important.

15 I'm going to talk about some additional
16 post-marketing hemovigilance data that we have
17 collected to characterize the safety profile for this
18 technology, clinical trial data that's been developed
19 in a large phase three clinical trial conducted here in
20 the United States called SPRINT, and then conclude with
21 a risk-benefit analysis looking at two common pathogens

1 and an emerging pathogen. And I would also add that
2 while we've been speaking about bacteria today, this is
3 a technology, as I said earlier, that of course goes
4 way beyond bacteria.

5 The regulatory status of this technology is
6 that in Europe it has a CE marked registration as a
7 class three drug device combination. So that means
8 with a competent authority medicinal review, the
9 INTERCEPT blood system for platelets is approved for
10 clinical indications, the similar and the same as for
11 untreated platelet components with no patient
12 population exclusions and in certain geographies it's
13 licensed for 7-day platelet storage. It's also
14 undergone national registrations, that is not just the
15 device but the "treated biologic," which in many
16 countries is treated as a drug. Platelets and plasma
17 have been approved in France by the French medicinal
18 agency AFSSAPS. In Germany the platelets have received
19 a marketing authorization from the Paul Erlich
20 Institute, and we are in discussions with FDA to define
21 the risk-benefit profile and define a pathway hopefully

1 for approval in the United States.

2 Now, in Europe we have been able to gather
3 experience. More than 150,000 doses have been
4 transfused, coming from 60 centers in 20 countries.
5 This technology has replaced bacteria detection in
6 these blood centers because it's highly effective
7 against leukocytes, particularly T-cells. It has
8 replaced gamma irradiation and has specific licensure
9 claims in Germany for that purpose, and it has also
10 replaced CMV serology. So, centers that have to do CMV
11 serology to find seronegative donors are now using this
12 in place to have a unified platelet supply. So there
13 are some availability and economic benefits that flow
14 from the technology.

15 The methods that we've used to extend and
16 establish the safety profile have included
17 post-marketing active hemovigilance programs, and we
18 have an ongoing commitment in Europe with the
19 regulatory authorities to extend the safety profile and
20 define the risk-benefit profile for the product. For
21 our European hemovigilance program we developed an

1 active hemovigilance program which requires obligatory
2 reporting for all transfusions. This is using a
3 Web-based electronic data collection system. Depending
4 upon the type of reaction observed in the patient it
5 can be between a one and three page form.

6 And, we have published data that are online
7 now in Transfusion looking at more than 15,000
8 components transfused to slightly more than 3,000
9 patients. In addition, in blood centers that have
10 universally adopted the technology where they have
11 databases for collection of information on all the
12 transfused components prior to the adoption of the
13 technology, we have been able to do specific outcome
14 surveillance. And so in Mont Godinne, Belgium, we have
15 data now on 795 patients during a three-year follow-up
16 period in the department of Alsace, this is a regional
17 blood center that supports all the blood components for
18 two million inhabitants, we have data for a two-year
19 follow-up period now on 4,000 patients. And these
20 programs have shown us a favorable safety profile with
21 a reduction in acute transfusion reactions, and, I

1 would add, no reported cases of transfusion-transmitted
2 sepsis.

3 We have a single case of TRALI from an
4 apheresis component that came from a multiporous donor
5 with high-titer HLA antibodies. The type of data that
6 one can generate can be shown here. As an example from
7 the blood center in Alsace, where for hematology
8 patients, which are heavy users of platelet components,
9 we can look in the period before and after
10 implementation of the technology and look at the
11 duration of support, both mean and median, and the
12 platelet dose per patient and not see an impact on
13 utilization of platelet components after the adoption
14 of this technology.

15 Now, the SPRINT study was a randomized,
16 controlled double-blinded clinical trial with a
17 one-sided noninferiority design conducted in the United
18 States. The primary endpoint was hemostatic efficacy
19 defined as grade two bleeding and it also was designed
20 to assess safety. It enrolled 645 patients. Many of
21 them had repeated platelet transfusions. The mean was

1 between 6 and 8 components per patient. It was
2 composed of hematology-oncology patients, 78 percent of
3 which were undergoing stem cell transplants, one-third
4 allo, and two-thirds autologous. And I believe it is
5 the largest randomized clinical trial in platelet
6 transfusion to date.

7 And the safety surveillance period in the
8 study was up to 35 days. When we look by system organ
9 class, which is a synthesis across systems for grade
10 three and grade four adverse events, we see, of course,
11 a very high level of events because these are very sick
12 patients and an analysis that was built on almost 900
13 individual specific preferred terms but we detected no
14 statistically significant differences between organ
15 system classes between the treatment groups. However,
16 we did detect nine individual preferred terms that were
17 statistically significantly different and they were all
18 in favor of control. One of these terms which was of
19 interest to us was for acute respiratory distress
20 syndrome as a preferred term.

21 And the incidence of the larger entity,

1 acute lung injury with which ARDS falls as coded by our
2 SPRINT investigators was unexpectedly low. It was 5
3 out of 645 patients per 0.8 percent. Our analysis was
4 supported by the fact that we saw differences in the
5 study arms and use of preferred terms and we felt it
6 was due to marked specificity of MeDRA coding, the fact
7 that there was no code for acute lung injury, which is
8 the predominant form of this entity, that investigators
9 were using alternative MeDRA codes and that specific
10 criteria for the diagnosis of acute lung injury or ARDS
11 were not followed or given to investigators because it
12 was not part of the basic design of this trial.

13 And we initiated a primary data review to
14 characterize the incidence and the outcome of this
15 clinically serious pulmonary adverse event syndrome in
16 a heavily transfused population and we had a very
17 specific reason for this because SPRINT offers a very
18 valuable database. It's known from other studies,
19 primarily the seminal study by Rumenfeld in the New
20 England Journal of Medicine, that blood transfusion is
21 a significant risk factor for acute lung injury. And

1 the incidence of acute lung injury among allogeneic
2 stem cell transplant patients is particularly high, 25
3 to 55 percent; yet, acute lung injury is underdiagnosed
4 in clinical practice. The diagnosis is only made 30 to
5 40 percent of the time in studies that have gone back
6 to look at this but the mortality of acute lung injury
7 and ARDS is very high and there's no difference in
8 mortality between the syndrome of acute lung injury and
9 the subset syndrome of ARDS.

10 When we looked in the SPRINT database at
11 our patients that were all coded initially with
12 suspected serious pulmonary adverse events, we saw no
13 difference in mortality. When we focused on patients
14 with the defined pulmonary adverse events, we again saw
15 no difference in mortality and in the patients who met
16 the specific criteria for acute lung injury and the
17 adult, the acute respiratory distress syndrome, no
18 difference in mortality.

19 So, our conclusions or summary of these
20 data were that acute lung injury is a leading
21 contributor to mortality in heavily transfused

1 transplant patients but the incidence was not
2 different. Between the two treatment groups in this
3 study, the platelet exposure was actually comparable in
4 these groups. The morbidity -- and I'm not showing you
5 these data but they'll be presented next month at the
6 ISBT -- if one looks at ventilation and intubation and
7 mechanical assist was not different and INTERCEPT
8 platelets in our opinion did not cause excess morbidity
9 or mortality.

10 Now, on the other side of the coin --
11 you've heard a lot about this today -- we wanted to
12 look at the risk of transfusion-transmitted infections
13 on a per patient basis. A lot of the data that you
14 have seen today is on a per unit basis and patients are
15 repeatedly transfused. So if one looks at the PASSPORT
16 and other datasets that were presented today in terms
17 of residual contamination risk, which is approximately
18 1 per 1,000 units of platelet components that have
19 undergone bacterial testing with a diversion and
20 appropriate skin disinfection and we assume based on
21 the SPRINT data that patients with acute leukemia will

1 see on average six units of platelets, then that leaves
2 us with a risk for a patient to have a bacterially
3 contaminated unit of 0.6 percent.

4 Now, we are not looking here at sepsis or
5 death in that patient group because the septic rates
6 are very poorly determined. We don't actually know
7 that from the literature which has been published and
8 so it's better, I think, just to look at the rates of
9 contamination and start from the assumption that in a
10 neutropenic acute leukemic patient, transfusion of a
11 contaminated platelet component is intrinsically not a
12 positive event. We then went on to look at CMV risk
13 because many of these patients are sensitive to CMV
14 transmitted infections. And looking at the recent data
15 by Ziemann, we see a risk which ranges from published
16 studies all the way from 0.3 to 22.2 percent, that a
17 patient could receive a leukodepleted product that
18 would contain the CMV DNA. So, that's a reasonable
19 assessment of risk from two common pathogens.

20 Then we looked at data from an emerging
21 pathogen because we think another virtue of this

1 technology, because it is broad spectrum in terms of
2 its inactivation capacity, is to deal with unrecognized
3 or emerging pathogens. And we had an experience
4 actually with the chikungunya virus epidemic in the
5 South Indian Ocean where this technology in fact was
6 implemented to make platelet components available.
7 When we started using our technology on the Island of
8 La Reunion it was the peak of the epidemic and the per
9 patient risk, again assuming 6 platelet components per
10 patient, was 15 per 1,000 units or 9 -- I'm sorry. The
11 total, the actual risk per unit was 15 per 1,000. The
12 risk for a patient getting 6 units would have been 9
13 percent. Likewise, we went back and looked at the West
14 Nile Virus data, and again using data from the bigger
15 staff study, showed that the risk for a patient would
16 have been 1 in 724 patients receiving a platelet
17 component contaminated with West Nile Virus.

18 So, in conclusion the INTERCEPT pathogen
19 inactivation technology for platelets inactivates a
20 broad spectrum of pathogens and platelet components.
21 It has been successfully implemented in many European

1 blood centers. It has a favorable safety profile based
2 on active hemovigilance, no excess treatment emergent,
3 acute lung injury or excess treatment morbidity and
4 mortality based on our analysis of the clinical data
5 from the United States and our active hemovigilance
6 data. And we believe that there is still a substantial
7 residual risk from both common pathogens and emerging
8 pathogens and we think this technology offers the
9 potential to mitigate these risks and in doing that
10 improve platelet component availability, which has
11 certainly been the case for CMV, reduce acute
12 transfusion reactions and actually replace older
13 technologies. So thank you for your attention.

14 DR. BRACEY: Thank you, Dr. Corash. In the
15 interest of time, we can have one or two questions or
16 comments because we would like to reserve as much time
17 as possible for discussion, general discussion later.
18 Questions, comments from the Committee? Thank you.

19 DR. CORASH: Thank you.

20 DR. BRACEY: Very good. Our next speaker
21 is Teresa Ayres. Teresa Ayres is President and CEO of

1 Navigant and she will also give us an update on
2 Navigant's perspective on pathogen reduction.

3 MS. AYRES: Thank you. Thank you for the
4 opportunity to speak to the Committee today. Dr.
5 Holmberg asked us to do a couple of things very quickly
6 and that is to update the Committee on where Mirasol is
7 in terms of introduction in the U.S, talk about
8 barriers or challenges for PRT in the U.S. market and
9 talk about how Health and Human Services can help us
10 with those issues. As compared to all the
11 presentations this afternoon, this is not a data-rich
12 presentation. This is not about the data. This is
13 about the business of PRT. I'm here to talk about how
14 we can get PRT into the United States.

15 I'm going to give a very brief overview of
16 the PRT system for Mirasol and when I talk about PRT
17 that means pathogen reduction technologies as a
18 category of products. Mirasol is our product's name so
19 I'm going to give you a brief overview. For those of
20 you who attended a January Committee meeting, you had
21 the opportunity to here Dr. Goodrich give a more

1 detailed update on the product, a lot of information
2 about pathogen reduction. I'll give you a brief update
3 on where we are in our clinical trial in Europe, which
4 was recently completed, share a little bit of data with
5 you and then have maybe more of a dialogue type of
6 review of why we don't have PRT in the United States
7 yet and what we can do about that, how you might be
8 able to help.

9 As a quick overview of the Mirasol PRT
10 system, it's a very simple system, uses Riboflavin,
11 which is vitamin B2 and UV light to inactivate
12 pathogens, prevents pathogens from replicating
13 themselves. It's effective against a very broad range
14 of pathogens. There are numerous peer-reviewed
15 articles that I'm not going to list and I'm not going
16 to going into. We also have a monograph that describes
17 in detail how effective the technology is. There are
18 two things that are really unique about the technology.
19 One is that the Riboflavin itself, which is the active
20 chemistry in the products, and its photo-byproducts do
21 not have to be removed after the pathogen reduction

1 process takes place. And that's because the process
2 does not introduce any new or unknown compounds into
3 the blood supply. Riboflavin is in your blood today.
4 It's in a normal diet.

5 The second thing that's really unique is
6 that this single technology of Riboflavin and light is
7 effective in pathogen reduction in all three blood
8 components. We have a platelets product that's being
9 sold in the European market right now, CE marked in
10 2007. We have a plasma product which is substantially
11 similar to the platelets product which we hope to have
12 on the market in 2008, and, interestingly, with family
13 technology, works effectively in the whole blood, which
14 gives us the opportunity to pathogen reduce whole blood
15 and from that extract red cells so that you have
16 pathogen reduction of all three blood components.

17 The process is very simple. You take
18 apheresis or manually collected platelets. You put
19 them in the illumination and storage bag. You add 35
20 milliliters of Riboflavin. You illuminate for 6 to 8
21 minutes and you put in it inventory. The product is

1 ready to use right away. This product that you're
2 looking at is optimized for use with platelets stored
3 in plasma. We also have products in development with
4 platelets stored -- but as you can see this product,
5 safe, simple effective, platelets stored in plasma is
6 an ideal product for the U.S. market.

7 In terms of our clinical study, we
8 completed our clinical study in December. The study
9 was conducted in six sites in France. It involved a
10 blood center where the product was produced, an
11 unrelated hospital, where the product was transfused.
12 We compared the Mirasol platelets to untreated
13 platelets.

14 The conclusion from the Data Safety
15 Monitoring Board, which is an independent group
16 assembled strictly for this study was what there were
17 no adverse events related to the use of the Mirasol
18 system. And despite my representation that I wasn't
19 going to talk to you about data, this is not meant to
20 be a data slide, it's meant to be a big-picture slide.
21 Essentially the study showed us that as compared to

1 untreated platelets, one hour CCI showed a decrement of
2 24 percent but 24 hour CCI, which may be the more
3 relevant factor to look at, was only 13 percent. That
4 combined with all the other metrics that were measured
5 and reported upon indicate to us that the product was
6 both safe and effective and it does not change the way
7 transfusion medicine is practiced.

8 So, if our product is so ideal for the U.S.
9 market and it seems to meet many of the needs we've
10 been talking about today, and if we really have
11 concluded that bacterial detection may not be a final
12 solution, it may be part of the solution, why don't we
13 have PRT products in the United States today? There
14 are at least four companies who are selling PRT
15 products in Europe. Why are they in Europe and not in
16 the U.S.? Are we serving our U.S. citizens as
17 effectively as we should be? Remember, I'm going to
18 talk about business. I'm not here to talk about data.
19 One of the reasons that people in the PRT industry go
20 to Europe first or go to other geography first is that
21 there's a willingness to consider an openness to the

1 use of PRT. In fact, there has been PRT for plasma in
2 the European arena for many years. It's been very
3 successful. It's been proven to be very safe. And
4 when you have a business, especially a small business
5 or start-up business you want to go where there's
6 interest. You want to go where you know there's a
7 market for your products. This gives you an
8 opportunity to determine whether there is broad-scale
9 market adoption likely for your product.

10 Another reason that we went to the European
11 arena first is it's not an all-or-nothing proposition.
12 You can do clinical trials at different levels. You
13 can do subsequent national validation work. You can
14 work with the regulatory bodies in these countries and
15 meet their needs as well as our needs to conduct and
16 collect the data that they need. So, in the U.S. it's
17 an all-or-nothing proposition but you can go to a
18 geographic region that has many different types of PRT
19 methods and you can try and test and learn and adjust
20 your methods by going to those areas.

21 And finally you have to be honest. You

1 have to say the cost of obtaining regulatory approval
2 in the U.S. is prohibitive at least for a company like
3 ours. We're privately owned. We don't have access to
4 capital markets. All of our research and development
5 is funded from corporate profits. So, we have
6 limitations on what we can do and to be realistic we
7 had to go where we could start generating revenue
8 first, even though Europe doesn't have a country which
9 is the largest life-consuming market in the world and
10 our product is really optimized for U.S. location.

11 So what are we going to do about getting
12 our product -- this is about Mirasol -- what are we
13 going to do about getting Mirasol into the U.S.? Well,
14 first we learn from people who are trying to teach us
15 how to do that. At the January meeting Dr. Vassal made
16 it very clear as to how the FDA looks at the
17 risk-benefit profile of PRT as it considers the U.S.
18 market. We tried our best to recreate the slide that
19 Dr. Vossel had used but he gave us a road map of how
20 the FDA may be looking at the PRT adoption in the U.S.
21 He also made it clear that there was only one product

1 in front of the FDA right now for PRT, and that's
2 correct, we have not applied yet to the FDA for
3 approval of our platelets product. But what we're
4 going to have to do to be successful is change the
5 balance in the teeter-totter.

6 So how do we think we're going to do that?
7 First, we're going to be very direct and we're going to
8 address the risks and benefits that the FDA has
9 identified, not try to ovoid them but to address them
10 directly. We do agree with the benefits. We do agree
11 with the risks. We also believe that our technology
12 does not have all the risks of all PRT methods. We'll
13 perhaps be persuasive but we intend to do that. We
14 also believe that there are benefits that our
15 technology may provide. So, our goal is to adjust the
16 balance of the teeter-totter and that's how we hope to
17 get our products to the U.S. market.

18 So when Dr. Holmberg said what would help,
19 certainly industry willingness to consider a new
20 approach to blood safety. These meetings for the
21 Committee are very encouraging for us. They're very

1 positive. They say that there is a willingness to
2 consider alternatives. There is an open mind to
3 determine about how to increase the availability of the
4 blood supply and safety of the blood supply. Dr.
5 Goodrich, I mean Dr. Goodman, Jesse (phonetic) also has
6 been encouraging people in the industry to do this as
7 recently as the National Blood Foundation meeting. So
8 we think that's a very positive sign. We really want
9 to encourage you and others to continue to do that.

10 Second, it would be helpful if the
11 regulatory processes take into account each technology.
12 Each technology is going to be unique. It's going to
13 have special benefits. It's going to have certain
14 risks but it's going to have certain benefits. These
15 need to be assessed on a technology-by-technology
16 basis.

17 Use of appropriate post-marketing
18 surveillance data, this is so common now and so
19 generally expected, it has to be designed well, it has
20 to be organized well, it has to be executed well, that
21 we believe that post-market surveillance data can

1 provide additional information that gives us assurances
2 about blood supply while at the same time we can
3 increase the availability through implementation of
4 PRT.

5 And, finally, I would not be a good
6 business person if I did not say we would also have to
7 have financial support. So, how specifically can HHS
8 help? Well, certainly helping find funding for large
9 studies but this was what you recommended during the
10 January meeting. This is part of the recommendation
11 that went to the Secretary. Really investigate PRT,
12 really look at it and really start putting our money
13 than where our mouths are. And we absolutely endorse
14 that recommendation. One way might be using NIH to
15 sponsor or actually lead some of the clinical studies
16 that will be required.

17 Another way is to help us find ways to
18 increase patient accruals in clinical studies. The
19 biovigilance network that I understand was mentioned
20 this morning is could be a wonderful tool for
21 identifying where to perform clinical studies and how

1 to collect data on clinical studies successfully.
2 Other ways, another way is to consider how to increase
3 the value propositioned for blood producers. There has
4 to be an interest in the customers for PRT in the U.S.
5 to implement this technology.

6 The second thing Dr. Murphy mentioned when
7 he was talking about adopting PRT in the center, the
8 first thing he talked about was safety; the second
9 thing he said was -- and I can be cost neutral, I can
10 figure out how to be cost neutral. Truly if you listen
11 to the presenters today, those who are thinking about
12 implementing PRT have to be good business people and
13 they have to think about how they're going to pay for
14 this.

15 So one of the serious recommendations we
16 would like you to consider is perhaps sponsoring
17 something that is similar to the Canadian Consensus
18 Conference that happened not too long ago. You could
19 look at what other countries are doing related to
20 pathogen reduction, where are we as the U.S., in
21 relation to those other countries, and to be very

1 specific, what kind of testing, what kind of work might
2 be discontinued in the U.S. to make adoption of PRT
3 viable and attractive to those who want to adopt PRT,
4 of all the things that we might be able to do to
5 encourage and industry willingness and encourage
6 industry excitement about this, to help them understand
7 that there is an openness to replace more traditional,
8 perhaps less effective methods with PRT.

9 Another thing we really should consider is
10 military applications, finding ways to make this
11 technology, make PRT technologies available in military
12 applications. The truth is both of the PRT companies
13 represented today here sell their products in the
14 Middle East so people who live in the Middle East have
15 access to PRT; our soldiers don't. We think that
16 should change. So, anything you could do to help get
17 this product out into military applications we think
18 would be a big step forward. So I appreciate the time.
19 I'll answer any questions.

20 DR. BRACEY: Thank you. Again comments or
21 questions from the Committee? We have time for one or

1 two. Dr. Bianco?

2 DR. BIANCO: I have one quick question.
3 How much would a clinical trial cost in the United
4 States?

5 MS. AYRES: Well, that's, how long is a
6 piece of string? If you take what we believe the FDA
7 has -- and what our predecessor company did, you have
8 to assume you you're going to have about 600 to 650
9 patients involved, empowered for safety. Most
10 companies, and certainly a company our size does not
11 have the resources to conduct a clinical trial of that
12 size with internal resources, so you would have to use
13 clinical resources. Our estimates, depending on how
14 fast you want done it, which means how many sites you
15 want to conduct it, is somewhere between 15 and \$25
16 million and between three and five years. That's
17 prohibitive for our company, at least.

18 DR. BRACEY: Ms. Finley?

19 MS. FINLEY: Thank you. I wonder -- and
20 you don't have to answer this. Have you had any
21 meetings directly with the FDA?

1 MS. AYRES: Actually, I'm really glad you
2 asked. We've requested one in the next few weeks. We
3 think we'll be meeting with FDA to talk about
4 strategies and capabilities and how we might pursue the
5 U.S. market. This is where we want to be, this is
6 where our business is, and we want to find ways to do
7 that. So, our first conversation will hopefully be
8 within the next six to eight' weeks.

9 MS. FINLEY: Okay. That's also a positive
10 step. There's also an Office of Small Business
11 Assistance and that would certainly be a good place for
12 you to start.

13 MS. AYRES: Okay.

14 MS. FINLEY: And I was reminded that Dr.
15 Nemo (phonetic) mentioned that you're eligible for SBIR
16 grants to pursue this technology, and he's sitting
17 right over there, so, that might be something you can
18 follow-up on.

19 DR. BRACEY: Okay. In the interests of
20 time I would like to then move onto the general
21 discussion and I'm going to ask the Executive Secretary

1 to pose the questions. What we have to consider, we've
2 heard lots and lots of data but there are two questions
3 and the two questions are the questions that the
4 Assistant Secretary has forwarded on to us.
5 Specifically on the topic of bacterial contamination of
6 platelets. Number one, is the risk associated with
7 bacterial contamination of platelet concentrates and
8 subsequent detection of bacterial contamination
9 acceptable for both apheresis and whole blood derived
10 platelets?

11 Now, again, this is I think a question of
12 policy and I think that in the field there are many of
13 us who feel that we have a two-tiered system, and the
14 data that we've seen presented actually supports that
15 and that the methods that are currently in use for
16 screening whole blood derived platelets today are in
17 essence window dressing, in essence ineffective. And
18 so my take -- but I want to hear the Committee's take
19 on this -- is in fact we do have a clearly recognizable
20 difference in safety between the two current platelet
21 products that are available and the problem that exists

1 specifically, the most easily is pointed towards the
2 whole blood derived platelet and the methods that we
3 use to detect bacteria in them. So discussion,
4 comments? Dr. Epstein?

5 DR. EPSTEIN: Well, it should be pointed
6 out that culture-based systems are available for whole
7 blood derived platelets. They're just not widely used,
8 particularly the Acrodose system doesn't permit
9 prestorage pooling and culture. And I think those who
10 are knowledgeable of the operations may wish to comment
11 why that is the case. Because when, you know, I agree
12 with the statement that you made, I embrace it but it's
13 because of the fact that the users are preferring to
14 use dipsticks in that environment rather than the
15 cultures and the I'm sure it has to do with cost and
16 logistics and so forth but I think we need to hear
17 that.

18 DR. BRACEY: Dr. Klein?

19 DR. KLEIN: I agree with that but I think
20 from what I heard today at least what we've considered
21 the gold standard, which is culture, is really not very

1 sensitive, the way we use it today. And, in fact, it's
2 not even very sensitive were we to go to the next step
3 and culture closer to the time of release. So, I think
4 the question is, if this is the best we have, is this
5 really good enough? I think part of that, that depends
6 upon whether you consider the risk of what we think are
7 clinically significant reactions and morbidity and
8 mortality versus the risk of giving people bacteria
9 that may or may not hurt them. I think that's a
10 difficult question because we don't have all of the
11 data but clearly the gold standard in terms of either
12 reducing our eliminating the risk of transfusion of
13 bacteria is not much of a standard.

14 DR. BRACEY: Additional comments from the
15 Committee? So then in terms of asking the question --
16 let me rephrase the question. So, we understand that
17 the culture method has limitations but given the system
18 that we have available today, is it the Committee's
19 feeling that this is an acceptable intervention or
20 method or we should recommend the use of more robust
21 techniques? Dr. Benjamin?

1 DR. BENJAMIN: I don't think the Committee
2 could ever state that the current situation is
3 acceptable with the variation between different
4 products and the proven limitations on the system we
5 have and where our colleagues in Europe are today
6 already implementing systems that may be safer. So, to
7 my mind the answer to the question is a simple, no. We
8 can get into a long paragraph that follows the "no" but
9 the answer is no.

10 DR. BRACEY: Okay. Dr. Triulzi?

11 DR. TRIULZI: I agree. I think the answer
12 is no and that's why you're speaking up front for -- or
13 up front for Verax or these other issues and we won't
14 know the impact until those are implemented for a
15 while. But just to address your whole blood platelet
16 question, I think as a large whole blood platelet user
17 the licensure of Verax gave a practical alternative to
18 the logistic issues that surround trying to culture, we
19 use 500 whole blood platelets a day, the problems with
20 doing that, so, I think that's going to be a transition
21 now.

1 And I know CAP, and I expect AABB is likely
2 to follow, in the next version of the standards of
3 those organizations are not going to allow the duty to
4 consider these inferior methods like glucose, pH,
5 swirling or any of these other methods. And so part of
6 the reason that I think those have persisted is because
7 of the lack of an alternative other than culture and
8 licensure of Verax gives an alternative. We're in a
9 transition period.

10 DR. BRACEY: Yeah, as an alternative and
11 it's the path of least resistance as people are silent
12 on. Ms. Finley, do you have a comment?

13 MS. FINLEY: I think there's some way you
14 could we could rephrase that, thank you, those two
15 questions, and just capture the concept of recognizing
16 -- we're twenty minutes from adjournment -- that we've
17 heard a wide variety of potential technologies that
18 could be implemented here and that we believe all, you
19 know, we would direct the parties involved to address
20 the FDA to fully explore those with an eye towards
21 increasing the safety of the components.

1 DR. BRACEY: So perhaps we could just, the
2 answer I think is fairly straightforward in terms of
3 no. The current level is not acceptable and then
4 programs the issue is struggling with the next portion
5 of this. More sensitive methods are needed or more
6 effective methods are needed to minimize the risk of
7 bacteria contamination. End of story.

8 MS. FINLEY: Yeah.

9 DR. BRACEY: I mean, it's a broad
10 statement. There are lots of alternatives out there.
11 We're not saying we want you to use culture. Use a
12 method that's more effective.

13 MS. FINLEY: Right.

14 DR. BRACEY: Dr. Bianco?

15 DR. BIANCO: Yes, I would like to see, Dr.
16 Bracey, separate the two questions. I think you have
17 to ask whether the apheresis platelets, using the
18 technology that is available now, is, falls into this
19 category of either safe or being acceptable and then
20 the whole blood derived platelets is another category
21 and that requires more than what you need to do for the

1 apheresis platelet. And the other thing that we need
2 to remind is that Verax is approved for apheresis
3 platelets that have been previously cultured and found
4 to be negative. So, it's not a method that will
5 resolve the issue of the buffy coat platelet, or, not
6 the buffy, the whole blood derived platelet, at this
7 point.

8 DR. BRACEY: So the statement, would you
9 consider the apheresis components is separately from
10 the whole blood derived components; does the Committee
11 have any thoughts on that? Dr. Epstein?

12 DR. EPSTEIN: Yeah. Well, I think that,
13 you know, my comments and Dr. Klein's comments reflect
14 the fact that the question is compounding two
15 completely different issues. You know, one is whether
16 we can continue to tolerate two safety levels for
17 platelet products and the other is whether we think
18 that the further efforts are needed to improve
19 bacteriological safety of platelets in general. So in
20 my personal -- I don't vote -- we're making every
21 effort we can to address both of those concerns. I

1 mean, FDA is not happy with the current status of
2 bacteriological safety of platelets. We recognize that
3 it's one of the current leading risks of
4 transfusion-related complications, fatality, and it
5 does disturb us greatly that there is not even at the
6 current level equal safety of different platelet
7 products. So I think that part we would all agree on.

8 What troubles me beyond that, though, is
9 what we could all agree that current safety is
10 disquieting, the level is disquieting. I don't know
11 that anyone would be prepared to articulate a level of
12 safety that we would accept and, you know, from the
13 FDA's standpoint, if we say that it's unacceptable, it
14 begs the question of what would be acceptable. And
15 there is no standard in place. So, I think another way
16 of getting at this is what level of safety do we think
17 is currently achievable and are there steps that could
18 be taken now to move in that direction.

19 DR. BRACEY: Right. While we can't, while
20 we may not be able to take steps tomorrow, I think the
21 Committee is on record as saying that other strategies

1 such as pathogen inactivation should be implemented to
2 make these components as safe as possible.

3 DR. BENJAMIN: I think we're just getting
4 back to the risk-benefit side of it, that that's a risk
5 statement and risk in itself is unacceptable unless
6 balanced by a benefit. And the benefit I guess is
7 availability, I think is an important benefit, that has
8 to be, and a 7-day platelet to my mind is an
9 availability issue. So you're balancing the two. So
10 as written no risk is acceptable by itself unless there
11 is a benefit that goes with it, so.

12 DR. BRACEY: Ms. Finley?

13 MS. FINLEY: My understanding of the 7-day
14 platelets is that they have to be, you know, in order
15 to use them they had to be used in a center that was in
16 the, in the --

17 DR. BRACEY: PASSPORT study.

18 MS. FINLEY: -- PASSPORT study. I was
19 going to say "Platform." PASSPORT study. Okay. So
20 that's a regulatory issue. I'm really not comfortable
21 going down that path for recommendations but I think

1 it's fair to express concern of the Committee that we
2 are in fact uncomfortable with two separate safety
3 standards, that's a very clear policy matter and that
4 we should take all available steps to eliminate that
5 disparity.

6 DR. BRACEY: Dr. Klein?

7 DR. KLEIN: Just to add to that, that's
8 absolutely true and I think we have heard today that
9 there are strategies that we can employ in a variety of
10 ways that will, if not equalize those, at least lessen
11 the difference, so, we shouldn't be doing pH testing.
12 As I've said before, that's great for swimming pools
13 but it's not great for platelets. And I'll include
14 those testing, swirling. So we clearly can address
15 that but I don't think we should be satisfied having
16 done that as the current state and I agree with Jay,
17 it's very hard to know precisely where you go from
18 that. I would also emphasize that platelet
19 availability is an issue.

20 It's an issue that even with 7-day
21 platelets we're not wealthy in terms of availability so

1 I think we need to look at that very carefully as to
2 what our strategy is going to be and what the
3 elimination perhaps, using testing, maybe less, more
4 false positives or additional testing that's going to
5 give us more false positives and eliminate apheresis or
6 pools of platelets from our platelet availability will
7 do to the supply and patient care in the United States.

8 MS. FINLEY: Could I add to that? I don't
9 disagree at all with Dr. Klein's suggestion. What I am
10 concerned about is looking at this whole concept as a
11 safety versus availability issue. There are other ways
12 to increase availability. We have had discussions in
13 the hallway in the last four meetings about platelet
14 availability in the U.S. So, you know, I don't think
15 it's unreasonable to believe that that question be
16 asked in conjunction with discussion about risk. Have
17 we taken all possible steps to increase platelet
18 donation? Are there things we have not thought of? Is
19 the Department looking at this with the appropriate
20 level of oversight relative to platelets? And I think
21 the answer to that is that we could do a better job.

1 DR. BRACEY: So, what if -- again we get
2 back to several issues within the one question but the
3 answer that's pretty clear is that no, we don't feel
4 that the current level of risk is acceptable. We
5 continue on to say, more effective methods are needed
6 for screening platelets for bacterial contamination or
7 eliminating the risk of bacterial contamination or
8 needed toward eliminating the risk of bacterial --
9 yeah -- are needed for the, eliminating the risk of
10 bacterial contamination. The current status with two
11 levels of safety for platelet products is unacceptable.
12 Is that, does the Committee feel comfortable with that?

13 MS. FINLEY: Yes, very.

14 DR. BRACEY: Okay. Interventions -- yes.

15 DR. EPSTEIN: See, I would rather see it
16 called highly problematic than unacceptable.
17 Unacceptable means that there's a liability attached to
18 issuing a unit and, you know, it's not better to die of
19 bleeding. And, you know, there are practical
20 limitations that surround everything that's being done.
21 This is what's bothering me about the whole term

1 acceptable. From a regulatory standpoint acceptable is
2 black and white. If something is unacceptable it's
3 violated, right? So I don't think that's really the
4 right word here. I think we all are concurring with
5 the concept that we should be striving to do something
6 better because the current situation is unsatisfactory
7 but that shouldn't be equated with calling products
8 unacceptable.

9 DR. BRACEY: Okay. Agreed. So basically
10 we would then say, so, the answer is no, that more
11 effective methods are needed to limit the risk of
12 bacterial contamination of platelets. The current
13 status of two levels of platelet safety is highly
14 problematic. And, leave it at that as a general
15 statement.

16 DR. KLEIN: But I think that we've heard
17 that there are strategies to at least narrow that gap.
18 Maybe that's question two, I don't know.

19 DR. BRACEY: Oh, oh, well, yes, that's a
20 good point. Let's go down to question two. If the
21 risk is associated with bacterial contamination of

1 platelet concentration and the sensitivity of the
2 currently available detection systems is unacceptable,
3 what does the Committee recommend for the next steps?
4 So, what we could say is the Committee endorses the
5 uses of available, currently available methods. Well,
6 that's not --

7 DR. RAMSEY: I've been thinking about this
8 as I'm sitting here, it is heartening to see Dr.
9 Benjamin's data on at least some reduction in septic
10 reactions with the measures that you have taken and
11 it's heartening to hear Dr. Jacobs' data on reduction,
12 at least in the recent history but I think to me it's
13 safe to say we don't quite know where we're at, at this
14 point. We're a moving target as far as measures being
15 put in place and getting the data in retrospect to see
16 where we are, how good we could be in the current, at
17 least some of the current technology. So, I'm not
18 arguing with the fact it can be safer and there are
19 things we should be thinking about to do that but it
20 seems like we're on the right track, so to speak, at
21 the present time and some things are being done.

1 DR. BRACEY: Yes, Dr. Benjamin.

2 DR. BENJAMIN: Dr. Bracey, could I have one
3 comment?

4 DR. BRACEY: Yes.

5 DR. BENJAMIN: We should recall we have to
6 no license for these tests for bacteria. We have a QC
7 test. We have an AABB mandate to do something but we
8 don't have any other mandate to do anything from -- and
9 we're in a bit of a mess and we should sort this mess
10 out. I mean we should move to a point where we have
11 testing where it's robust enough to order these tests.

12 DR. BRACEY: Dr. Epstein.

13 DR. EPSTEIN: Yes. I would like to try to
14 clarify this point, why did FDA clear -- we didn't
15 actually license -- the bacteria detection tests as
16 quality control tests rather than release tests? The
17 reason is that the data that were available to the
18 agency were based on spiking experiments, that the
19 actual levels of contamination in products were unknown
20 and that although there was a presumption that they
21 would do some benefit, the level of clinical benefit

1 translating into clinical sensitivity was unknown. So,
2 FDA took the point of view, well, we don't know what
3 percent contamination we're detecting but you can use
4 these tests to monitor your process. That's a quality
5 control.

6 Now, FDA does not have resistance to
7 relabeling certain of these quality control tests as
8 release tests based on a stated level of sensitivity
9 and specificity. And you know, Red Cross independently
10 and the PASSPORT study as a collaboration have now
11 generated data that potentially would enable us to do
12 just that. On the other hand, the flip side is the
13 results are very disquieting. There was an utterly
14 naive view that these tests would be 90-plus percent
15 sensitive and the problem is going to go away and, you
16 know, fortunately the studies have been done which are
17 telling us the true answer, which is that they're far
18 less sensitive than had been naively expected. So I
19 think that the muddy situation that we're in has less
20 to do with the fact that they're not labeled release as
21 it has to do with the fact they're far less clinically

1 sensitive than was hoped and naively expected and
2 that's the model for them.

3 DR. BRACEY: What if the statement is to
4 the effect that the Committee recommends the adoption
5 of culture-based methods for all platelet products, as
6 one step. You accept there is a method, it's not being
7 used, and then finally that the Committee further
8 recommends moving toward platelet pathogen reduction as
9 the optimum solution. I mean, on the one hand you say
10 why not use culture-based methods for all platelet
11 products because we're silent on that and do we want to
12 remain silent on that or do you want to speak to that?

13 DR. TRIULZI: I don't know that I would be
14 that proscriptive.

15 DR. BRACEY: Okay.

16 DR. TRIULZI: I have written a general
17 statement, that, and partly because I think the point,
18 we've heard about four actually that are up front,
19 culture method is performing, that a point-of-care
20 test, one point-of-care test may be better than one
21 culture and I don't think we know so I don't think we

1 need to be that proscriptive. But the wording I come
2 up with is that the Committee recommends that
3 additional measures be adopted to reduce the difference
4 in safety profile between whole blood and apheresis
5 platelets and that additional measures be adopted to
6 reduce the overall contamination. So, specifically
7 address the difference in products but also say that
8 even the baseline of pheresis as they exist today
9 requires additional measures and that could be another
10 culture, day four, that could be adding a point-of-care
11 test, that could be pathogen inactivation.

12 DR. BRACEY: All right. I like your
13 general statement.

14 DR. RAMSEY: So both detection and
15 reduction.

16 DR. TRIULZI: Yes.

17 DR. BRACEY: So I think that we are about
18 ready to get close to closure on these two questions
19 and so Dr. Holmberg is going to flash them up on the
20 screen. Okay. So what we have on the screen is the --
21 first I'll get to the mike. What's on the screen is

1 the first, answer to the first question, which is,
2 again, is the risk associated with bacterial
3 contamination, platelet concentrates, detection of
4 bacterial contamination, acceptable for both -- and
5 whole blood derived platelets and so we say no, more
6 effective methods are needed to limit the risk of
7 bacterial contamination, platelets, current status of
8 two levels of safety is highly problematic. Second --
9 Dr. Klein?

10 DR. KLEIN: Could I propose that after "no"
11 the Committee might wish to indicate that it
12 appreciates that the strategies that have been
13 undertaken such as culture and removal of diversion
14 have been effective in reducing the risk of both
15 contamination and sepsis; however --

16 DR. BRACEY: Right. Okay. So the
17 Committee appreciate that interventions such as
18 bacterial culture and diversion have been effective in
19 reducing risk; however -- sorry. However,
20 interventions --

21 DR. HOLMBERG: Interventions of what?

1 DR. BRACEY: Well, appreciates that
2 interventions including culture and diversion have --
3 we'll have too many "effective."

4 DR. KLEIN: Have reduced the risk of
5 bacterial transmission.

6 DR. BRACEY: Yeah, have reduced the risk of
7 bacterial transmission; however -- there you go,
8 right -- however, more effective methods are needed to
9 limit the risk of bacterial contamination of platelets.
10 Well, we can just say more effective, can we just say
11 more effective methods are needed? Can we stop at
12 needed and scratch the rest; what do you think?

13 DR. HOLMBERG: I'm sorry.

14 DR. BRACEY: What does the Committee think?

15 DR. HOLMBERG: I'm sorry. You said to
16 go --

17 DR. BRACEY: I'm just looking for editorial
18 comments. Dr. Epstein?

19 DR. EPSTEIN: I think it should say to
20 further limit the risk of bacterial contamination.

21 DR. BRACEY: Ah, yes.

1 DR. EPSTEIN: Line five.

2 DR. BRACEY: Yes, to further limit.

3 DR. EPSTEIN: Then I would say additionally
4 current status.

5 DR. HOLMBERG: And what was your second
6 comment?

7 DR. BRACEY: Additionally.

8 DR. HOLMBERG: Where?

9 DR. BRACEY: The last sentence, right
10 there. Additionally, the current status of two levels
11 of safety is highly problematic. All right.

12 DR. BENJAMIN: Could we add, to limit the
13 risk of contamination sort of suggests the -- diversion
14 thing was to detection or elimination, pathogen
15 inactivation -- you want to say to further limit or
16 eliminate the risk of bacterial contamination.

17 DR. BRACEY: To limit or eliminate, yeah.
18 So, put.

19 DR. BENJAMIN: We really would like to
20 eliminate it, wouldn't we?

21 DR. BRACEY: Yeah, to limit or eliminate.

1 DR. HOLMBERG: I'm sorry. Where?

2 DR. BRACEY: Further, after "are needed to
3 further," to further limit --

4 DR. HOLMBERG: The risk okay.

5 DR. BRACEY: After, after limit or
6 eliminate, after limit -- after limit.

7 DR. HOLMBERG: To further, or limit?

8 DR. BRACEY: Further limit or eliminate.
9 All right.

10 DR. POMPER: Take out the "or."

11 DR. BRACEY: Take out the "or." Lovely.
12 Okay. Doctor Epstein.

13 DR. EPSTEIN: I'm just wondering whether we
14 should be saying two levels of safety or disparate
15 levels of safety for different platelet products
16 because if you look at apheresis platelets they're
17 probably predominantly being cultured but not all in
18 the same way and if you look at whole blood platelets,
19 some are being cultured and some are just, you know,
20 have dipsticks. So I think there's actually a range
21 going on and it's really not just two levels of safety,

1 it's disparate levels of various, safety of various
2 platelet product.

3 DR. BRACEY: Good, disparate levels of
4 safety for platelet products -- for platelet products,
5 yeah, is highly particular. All right. So the one
6 thing that we have not done, sorry, is to talk about
7 availability. Should we say something about
8 availability?

9 MS. FINLEY: I have again a concern about
10 -- acceptance of the fact we have to have lesser safety
11 for availability. We haven't established that and we
12 haven't heard that in terms of information, so I would
13 leave it the way it is.

14 DR. BRACEY: Okay. You're saying you
15 really would need to see more information --

16 MS. FINLEY: Yeah, definitely.

17 DR. BRACEY: -- in terms of that -- Dr.
18 Triulzi?

19 DR. TRIULZI: I think you're absolutely
20 right because with the availability of pooled or whole
21 blood platelet that's bacterial screened we throw out

1 probably two-thirds of the whole blood platelets
2 culture this country and with that product available,
3 you flow, with a safety profile that's going to be
4 approximately apheresis.

5 MR. BENJAMIN: We don't know that, though.
6 We've only transfused 20,000 of the things and we need
7 to transfuse a couple of hundred thousand.

8 DR. TRIULZI: Well, I mean, let's say it's
9 the same method used for bacterial screening that's
10 currently used for pheresis.

11 DR. BENJAMIN: I mean, it's the same
12 position we were in four years ago.

13 DR. TRIULZI: And as Jay said, if the issue
14 is a shortage, it's better to have that.

15 DR. BENJAMIN: Okay.

16 DR. TRIULZI: Than nothing, so, I would
17 agree.

18 DR. BRACEY: Okay. So then this is, is
19 there a consensus among the Committee members that our
20 statement addresses our feeling, the Committee's
21 feelings regarding the questions at hand? Dr. Duffell?

1 DR. DUFFELL: We're limiting comments to
2 bullet one, right, or are you asking about the whole?

3 DR. BRACEY: When you say --

4 DR. DUFFELL: Because I have comments on
5 bullet two but I didn't know if you were trying to wrap
6 it up.

7 DR. BRACEY: Oh, you can -- no, no. Yeah,
8 you can comment on bullet two, sure.

9 DR. DUFFELL: Okay. I mean, my comments on
10 bullet two is just I think the term measures is rather
11 vague and I think Dr. Ramsey said before I think what
12 we're talking about measures are, it's detection or
13 pathogen reduction technology. Rather than being vague
14 I would use those terms. I don't know what else there
15 is. You're either going to detect it or you're going
16 to limit it. So, I would be specific rather than just
17 saying additional measures.

18 DR. BRACEY: Well, what if we kept it broad
19 and did an "e.g."?

20 DR. DUFFELL: As an example?

21 DR. BRACEY: "E.g.," yes.

1 DR. DUFFELL: Yeah, you could. I would be
2 okay with that.

3 DR. BRACEY: So measures, e.g., pathogen
4 inactivation and --

5 DR. DUFFELL: Detection.

6 DR. BENJAMIN: Prevention detection and
7 pathogen inactivation.

8 DR. HOLMBERG: You want to say inactivation
9 or you want to say reduction?

10 DR. BRACEY: Pathogen inactivation,
11 detection.

12 DR. DUFFELL: And prevention.

13 DR. BENJAMIN: Prevention, detection and
14 pathogen inactivation.

15 DR. BRACEY: Okay. Prevention, detection
16 and pathogen inactivation. So -- sorry about that.

17 DR. HOLMBERG: What was the event again,
18 prevention --

19 DR. BRACEY: Yes, detection, pathogen
20 inactivation, yeah. I guess what with the e.g., you
21 use a comma. Okay.

1 DR. RAMSEY: It seems to me that you got
2 two clauses here that probably could be merged. We're
3 sort of taking the same measures, both reduction of the
4 differences between the two and also the overall risks
5 so I don't know at that there's a difference between
6 the measures in the first part of the clause and the
7 measures in the second clause. Why don't we say
8 something like these measures should not be limited --
9 that should reduce the risk.

10 DR. HOLMBERG: Dr. Triulzi, could you speak
11 into the microphone?

12 DR. TRIULZI: Yeah. This is getting at
13 Celso's point about having a statement that addresses
14 the issue of whole blood platelets versus pheresis and
15 that even pheresis itself should have some measures
16 taken.

17 DR. BRACEY: Yeah, that's a good point,
18 good point. So the Committee recommends that
19 additional measures, e.g., prevention, detection,
20 pathogen inactivation be adopted -- you can scratch the
21 "and" -- to reduce the difference in safety profile

1 between whole blood and apheresis platelets. Then you
2 can say, period, how about a period after that,
3 additionally -- no --

4 DR. KLEIN: And reduce the overall risk of
5 bacterial contamination. Just eliminate the middle
6 part.

7 DR. BRACEY: Okay. So, and reduce the
8 overall risk of -- yeah, eliminate the middle part,
9 you're right. So you can eliminate all the way to "and
10 reduce the risk."

11 DR. HOLMBERG: Where are we?

12 DR. BRACEY: Oh, keep going to -- keep
13 going and -- and --

14 DR. POMPER: Take out the period, put an
15 "and."

16 DR. BRACEY: And reduce the risk, the
17 overall risk of bacterial contamination. So, then it
18 would read, the Committee recommends that additional
19 measures, e.g., prevention, detection, pathogen
20 inactivation be adopted to reduce the difference in
21 safety profile between whole blood and apheresis

1 platelets and reduce the overall risk of bacterial
2 contamination of platelets.

3 DR. HOLMBERG: Should differences be,
4 should it be "differences" or "difference"?

5 DR. BRACEY: I think it's "difference."
6 Editors?

7 MS. FINLEY: I agree.

8 DR. BRACEY: Yeah. Okay. So, we have a
9 statement, a response to the queries from the
10 Secretary. You have a motion?

11 MS. FINLEY: No. I was just going to add
12 one more thing.

13 DR. BRACEY: Oh, one more thing.

14 MS. FINLEY: And if you don't want to take
15 it, I understand. But to get to the heart of the
16 availability there have been repeated questions about
17 platelet shortages and there are questions about the
18 balance between what's risk and benefit and
19 availability and safety. So, can we get a sentence in
20 there that addresses both that says the Committee
21 recommends the Department more carefully investigate

1 the -- or carefully investigate the current status and
2 projected status of platelet availability in the U.S.

3 --

4 DR. BRACEY: Well, perhaps to the effect
5 that the Committee recommends that the Department
6 investigate the impact of these strategies on --

7 MS. FINLEY: No, it's bigger than that.

8 DR. BRACEY: Bigger than that.

9 MS. FINLEY: I think right now, you know,
10 based on what was said by our representative and other
11 things that we don't have a good feel for exactly how
12 short we might be running in terms of platelets and we
13 don't have a good feel for where we might be five years
14 and ten years from now. So I think that's the question
15 that we need to answer and we need that information to
16 evaluate the impact. So I would say get that
17 information with an eye towards in the future, once we
18 have all of these techniques that have been evaluated
19 by the FDA, we can then make up a --

20 DR. BRACEY: So what if at the very end
21 right there after platelets you have information

1 regarding platelet availability --

2 MS. FINLEY: Is short.

3 DR. BRACEY: No, information regarding the
4 platelet availability is needed to --

5 MS. FINLEY: To evaluate.

6 DR. DUFFELL: You're wanting him to modify
7 it, aren't you?

8 MS. FINLEY: Yeah.

9 DR. DUFFELL: You want him to take the
10 subjectivity out of shortage, saying, now, here is a
11 number.

12 MS. FINLEY: Yeah.

13 DR. BRACEY: To determine the best method
14 for providing safe --

15 MS. FINLEY: It's more broad than that.

16 DR. BRACEY: It's more broad than that.

17 MS. FINLEY: I think we've got a shortage
18 or we're running pretty darn close to a shortage on a
19 fairly regular basis. All I'm saying is we don't seem
20 to have that information. Let's get it now and with an
21 idea to what we're going to need in the future and then

1 move forward.

2 MR. KLEIN: The other part of that is we
3 really don't know what the potential is because many
4 people say if you put more money into getting more
5 platelets, might outdate a few more but there would be
6 plenty of platelets available. I don't think we know.
7 The other issue is this issue of whole blood derived
8 platelets, that we turn back toward those. Maybe there
9 will be plenty of platelets. We just don't know.

10 DR. BRACEY: Why don't we just say the
11 impact of these interventions on platelet availability
12 needs to be determined.

13 MS. FINLEY: Well, I don't have any
14 problems with that but I think first we need to find
15 out what our current situation is. I don't think we
16 have a good feel for that.

17 DR. BRACEY: Right. But, I mean, if we're
18 going to take those steps, we will still --

19 MS. FINLEY: I don't have any problems with
20 evaluating that. I want us to get a number so --

21 DR. BRACEY: Sure. So if we say the impact

1 of these measures on platelet availability --

2 MS. FINLEY: No.

3 DR. POMPER: There's insufficient evidence
4 to know if these measures are adopted what the impact
5 on platelet availability would be. We don't have
6 information on platelet availability to know whether it
7 has more restrictions put in place, it's going to have
8 an effect on --

9 MS. FINLEY: I have a monitor -- the
10 department should monitor or, you know, develop a
11 strategy, the current status of platelet availability
12 in the U.S., that gives us.

13 DR. KLEIN: And the potential for meeting
14 future needs.

15 MS. FINLEY: Yes. Thank you.

16 DR. BRACEY: Okay.

17 DR. HOLMBERG: And what was the last --

18 DR. BRACEY: And the potential for meeting
19 future needs. Dr. Busch, you had a comments.

20 DR. BUSCH: Just to say that this is a real
21 issue. In my organization, Blood Systems, we have

1 looked at the issue with lots of 7-day platelets. We
2 are not going to be able to implement what we had
3 intended to in terms of TRALI risk reduction
4 strategies. Our fill rates of platelet orders, numbers
5 went from, you know, something like 94 percent to close
6 to 100 percent when we had 7-day waiting. Now we've
7 lost that. So there is data. We just, I think, don't
8 have the right people here and the right numbers in
9 front of you to tell you how frequently the hospitals
10 need platelets, the blood centers can't supply. And to
11 retool the whole -- much of the country has moved to
12 apheresis -- to retool blood centers to begin to build
13 whole blood derived platelets is a huge investment and
14 if it's necessary it would make -- the availability
15 issue is a big problem.

16 DR. BRACEY: Okay. So we will include --

17 DR. BUSCH: The one comment is, I don't
18 think you addressed it -- maybe this isn't the forum --
19 the issue of PASSPORT 2 and the comfort level with
20 considering ongoing availability of a 7-day daily
21 platelet vis-a-vis bacterial safety --

1 DR. BRACEY: But I'm just saying in terms
2 of the general discussion, strategies, that's it's
3 covered under that and then the specifics go down here.
4 Dr. Epstein?

5 DR. EPSTEIN: Yeah, I was going to go where
6 Mike just went, which is that we ought to say something
7 about support should be provided to efforts that could
8 reestablish a safety and efficacy of longer-dated
9 platelets. And that's a whole unmet need in its own
10 right. We've heard concerns about, I mean, FDA has
11 decided the 7-day platelet stored in a particular way
12 is acceptable but we all realize it would be better if
13 quality were further improved. And in fact there's no
14 magic about 7. There were once 11 day platelets there
15 were at one point in time thought acceptable. You
16 know, we know they're not but, you know, better storage
17 solutions or alternatives. We heard about lyophilized
18 platelets, they're a different beast, you know, frozen
19 platelets, but there's a whole issue here about efforts
20 to further improve storage and extended dating of
21 platelets.

1 DR. BRACEY: So support should be
2 established to --

3 DR. EPSTEIN: Initiatives.

4 DR. BRACEY: -- initiatives directed to
5 support further --

6 DR. EPSTEIN: Extending platelet storage
7 life.

8 DR. BRACEY: So support should be
9 established for initiatives.

10 DR. HOLMBERG: Should be for initiatives to
11 extend --

12 DR. BRACEY: To extend platelet storage
13 life should be established. All right, I think --
14 we're behind 20 minutes but I think we have a product,
15 close to a product. And I thank you for extending the
16 time. Comments?

17 DR. EPSTEIN: Well, again, just to link the
18 idea, it's to extend the platelet storage life as a
19 strategy to improve platelet availability. Because
20 that's why we want to do it -- in our inventory.

21 DR. HOLMBERG: Strategy to improve?

1 DR. BRACEY: To improve platelet
2 availability. Okay. A motion?

3 DR. DUFFELL: Motion.

4 DR. BRACEY: Second? Motion by Dr.
5 Duffell.

6 MS. FINLEY: Seconded.

7 DR. BRACEY: Seconded by Ms. Finley. Okay.
8 We have had plenty of discussion. I think we're ready
9 to take a vote by all except those who can't, nonvoting
10 members. All in favor of the response to Secretary
11 that we have posted, raise your hands. You guys got it
12 recorded?

13 DR. HOLMBERG: Twelve. Okay. Thanks.

14 DR. BRACEY: All opposed? Any abstentions?
15 It's unanimous. Thank you. Motion to adjourn and we
16 will reconvene tomorrow at 8 o'clock and I promise, I
17 will promise to get you out of here --

18 MS. FINLEY: 8:30.

19 DR. BRACEY: Oh, it's 8:30 tomorrow, 8:30.

20 (Meeting adjourned for the day at 5:19
21 p.m.)

1 State of Maryland.

2 Baltimore County, to wit:

3 I, ROBERT A. SHOCKET, a Notary Public of
4 the State of Maryland, County of Baltimore, do hereby
5 certify that the within-named proceedings personally
6 appeared before me at the time and place herein set
7 out, and after having been duly sworn by me.

8 I further certify that the proceedings were
9 recorded stenographically by me and this transcript is
10 a true record of the proceedings.

11 I further certify that I am not of counsel
12 to any of the parties, nor in any way interested in the
13 outcome of this action.

14 As witness my hand and notarial seal this
15 18th day of June, 2008.

16

17

18 Robert A. Shocket

19 Notary Public

20 My Commission Expires:

21 November 1, 2010

