1 VOLUME II

2

3 DEPARTMENT OF HEALTH AND HUMAN SERVICES

4

5 U.S. PUBLIC HEALTH SERVICE

6

7 ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

8

9 THIRTY-THIRD MEETING

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12 The continuation of the above-mentioned meeting

13 was held on Thursday, January 10, 2008, commencing at

14 9:00 a.m., at the The Westin Washington, D.C. City Center,

15 1400 M Street, NW, Washington, D.C. 20005, before Robert A.

16 Shocket, a Notary Public.

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21 REPORTED BY: Robert A. Shocket

1 COMMITTEE/PANEL:

2 ARTHUR W. BRACEY, M.D., Chair

3 RICHARD BENJAMIN, M.B.

4 ANNE MARIE BENZINGER

5 JULIE BIRKOFER

6 JAMES BOWMAN, III, M.D.

7 JAMES BURDICK, M.D.

8 WILLIAM DUFFELL, JR. Ph.D.

9 JAY S. EPSTEIN, M.D.

10 ANNE MARIE FINLEY

11 JERRY A. HOLMBERG, Ph.D.

12 HARVEY KLEIN, M.D.

13 PETER KOUIDES, M.D.

14 MATTHEW J. KUEHNERT, M.D.

15 CDR. MICHAEL LIBBY

16 ILEANA LOPEZ-PLAZA, M.D.

17 DAVID MATYAS, J.D.

18 GLENN RAMSEY, M.D.

19 S. GERALD SANDLER, M.D.

20 RUTH SOLOMON, M.D.

21 LAURA ST. MARTIN, M.D., M.P.H

1 COMMITTEE/PANEL (cont.):

2 DARRELL J. TRIULZI, M.D.

3 JENNIFER J. LUNNEY, M.H.S, DHHS Staff/Facilitator

4

5 PRESENTERS:

6 LAURENCE CORASH, M.D., Cerus Corp.

7 BRIAN CUSTER, Ph.D. M.P.H.

8 RAY GOODRICH, M.D. Navigant

9 MARGARETHE HEIDEN, Ph.D., P. Ehrlich Institute, Germany

10 HARVEY KLEIN, M.D., NIH

11 MARC MALTAS, Octapharma

12 MARIE SCULLY, M.D., University College London Hospitals

13 JAROSLAV VOSTAL, M.D., Ph.D OBRR, CBER, FDA

14

15 PARTICIPANT: JENNIFER J. LUNNEY, M.H.S.

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

2 DR. BRACEY: Welcome to the second day of

3 the Thirty-Third Meeting of the Advisory Committee on

4 Blood Safety Availability. Mr. Chairman, are you ready

5 to take the roll call?

6 DR. HOLMBERG: Yes, good morning. Dr.

7 Bracey?

8 DR. BRACEY: Present.

9 DR. HOLMBERG: Also I would like to remind

10 those individuals as I call your name out if there is a

11 conflict of interest, if you could please mention any

12 conflict of interest or maybe a perceived conflict of

interest that you would like to disclose at this time. Dr. Bracey, is there any disclosure that you would like to make?

DR. BRACEY: None.

DR. HOLMBERG: Dr. Benjamin?

DR. BENJAMIN: Present. To disclose that I have been involved with clinical trials and sit on the Scientific Advisory Board for Cerus Corporation.

DR. HOLMBERG: Thank you. Ann Marie

Benzinger?

MS. BENZINGER: Here. Present. No conflict.

DR. HOLMBERG: Julie Birkofer?

MS. BIRKOFER: Present. Conflicts would be that Octapharma is a member of the Plasma Protein Therapeutics Association, as is Baxter, which has a relationship with Cerus. Both of those companies are members of the association of which I'm employed.

DR. HOLMBERG: Thank you. Dr. Bloche is not here. Dr. Duffell?

DR. DUFFELL: Present. And I'll acknowledge a potential for a perceived conflict of interest for my employment with BCT but I'll also highlight that I haven't had any engagement with the Navigant organization in about four years.

DR. HOLMBERG: So noted. Thank you. Ms. Finley?

MS. FINLEY: Present, and I'm employed by Celgene Corporation, which has a small stem cell business.

DR. HOLMBERG: So noted. Thank you. Dr. Kouides?

DR. KOUIDES: Present. I serve on the medical advisory boards for CSL Behring and Baxter though the Baxter relationship is only with human platelet product, not with any association with Cerus.

DR. HOLMBERG: Thank you. Dr. Lopez-Plaza?

DR. LOPEZ-PLAZA: Present. No conflict.

DR. HOLMBERG: Mr. Matyas?

MR. MATYAS: Present, no conflicts.

DR. HOLMBERG: Dr. Pierce is absent. Dr. Ramsey?

DR. RAMSEY: Present. Good morning. As I mentioned yesterday, colleagues of my institution are working on clinical trial with a product from Octapharma and the blood bank is receiving some logistical support for that project.

DR. HOLMBERG: But you are not directly involved?

DR. RAMSEY: I'm not directly supported by that, no.

DR. HOLMBERG: Thank you. Dr. Roseff, absent. Dr. Sandler?

DR. SANDLER: Present. Like Dr. Ramsey, my

4 blood bank participates in an Octapharma study. I have
5 no financial interest or conflict of interest.
6 DR. HOLMBERG: Thank you. Ms. Thomas-Wade
7 is absent. Dr. Triulzi?
8 DR. TRIULZI: Present, and a participant on
9 the medical advisory board for Cerus and a participant
10 in the Cerus SPRINT trial.
11 DR. HOLMBERG: Thank you. Let me just go
12 back, as you mentioned the SPRINT trial. Dr. Lopez, I
13 think there was a conflict there. Would you like to
14 mention that?
15 DR. LOPEZ-PLAZA: Yes. I also was a
16 participant for the SPRINT trial.
17 DR. HOLMBERG: Only reason I remember that,
18 is she's a coauthor on one of the articles.
19 DR. LOPEZ-PLAZA: Yes. Sorry. I didn't
20 know that meant --
21 DR. HOLMBERG: Thank you. Dr. Kuehnert?

DR. KUEHNERT: Here.

DR. HOLMBERG: Dr. Epstein?

DR. EPSTEIN: Present.

DR. HOLMBERG: Dr. Klein?

DR. KLEIN: Here.

DR. HOLMBERG: Commander Libby is absent today. Dr. Bowman I am sure is on his way, probably battling traffic. And sitting in for Dr. St. Martin is --

DR. SOLOMON: Ruth Solomon, no conflict.

DR. HOLMBERG: Dr. Solomon, thank you. And, also for HRSA is Dr. Burdick.

DR. BURDICK: Present.

DR. HOLMBERG: Okay. Thank you, sir. I would also again like to remind individuals as they speak today to declare any potential conflict of interest so that the Committee has a good understanding of your point of view. And not disclosing that will not inhibit you from speaking but we would like to know that so that we can have a clear evaluation of the comments that you make. I'll turn it back over to Dr.

Bracey.

DR. BRACEY: Thank you. Yesterday we heard extensive presentations regarding existing threats, emerging threats, and potential threats as well as information regarding the capabilities of our diagnostic system and we heard some very interesting presentations in terms of the ethical considerations in terms of decision-making.

Today we will hear from more individuals regarding current systems for pathogen reduction. As a matter of administrative business, I would like to ask the Committee to consider, we have two drafts, proposals for consideration and obviously we have other information to hear but there is the opportunity for us to have a working lunch. If a small group of individuals would be interested in working on further refinement of the draft during lunch so that we can make the afternoon's business more efficient, would that be acceptable to the Committee?

PARTICIPANTS: Yes.

DR. BRACEY: So then we will plan to do

1 that. Moving ahead --

2 DR. HOLMBERG: If I can just make a comment

3 concerning that, just as trying to keep us in

4 compliance with the FACA rules, is that any discussions

5 that take place in the subgroup have to be fully

6 disclosed to the open forum, to the entire Committee.

7 DR. BRACEY: We will do that. In the

8 interest of time, I would like for the speakers to

9 stick closely to the allotted time to allow us to have

10 the time for discussion and development of the

11 recommendations so that I don't intend be rude but when

12 we reach five minutes over I'll indicate that by

13 flashing the marker here.

14 Our first speaker today is Dr. Klein,

15 Harvey Klein. Dr. Klein is the Chief of the Department

16 of Transfusion Medicine and he's the Special Assistant

17 to the Director of Science for Clinical Center for NIH.

18 He's a graduate of Harvard and Johns Hopkins and he is

19 Adjunct Professor of Medicine at Johns Hopkins. He's

20 coauthored more than 200 publications and is the
21 co-editor of Mollison's Transfusion Medicine. He has

1 done a tremendous amount of work in the field
2 recognized by various awards. He will present to us
3 today on the review of the Canadian Consensus
4 Conference on Pathogen Inactivation.
5 DR. KLEIN: Thank you very much, Mr.
6 Chairman. In the interest of full disclosure, I would
7 like to disclose first that I'm not a Canadian. That's
8 a politically neutral statement. And my second
9 disclosure is that I've worked for 35 years with Dr.
10 Harvey Alter, who presented yesterday, so if my
11 opinions and biases seem similar to his, they're
12 probably not random.
13 Thank you. All right. Well, as we heard
14 yesterday, there are a variety of ways that we avoid
15 risk in transfusion medicine, all the way from the
16 donor history and examination to testing, which is the

17 bulwark to limiting exposures by using the appropriate
18 indications for transfusion. We haven't talked much
19 about that but it is a very important one. And yet
20 despite these various ways of limiting the risk, the
21 infectious risk of transfusion, we saw just several

1 years ago as you heard yesterday the introduction of a
2 new agent into the United States, an epidemic which
3 resulted in morbidity and mortality, as the result of
4 West Nile virus and certainly we could expect that this
5 would happen and will happen again because of the way
6 that we deal with infectious agents today.
7 Now, this is the paradigm that you heard
8 about yesterday, and I put this on a scale of when
9 tests appeared to safeguard the U.S. blood supply. You
10 can see that syphilis went back to 1938. Then there
11 was a large interval until around the early seventies
12 when hepatitis B surface antigen came into use and
13 since then we have added numerous tests to safeguard

14 the blood supply and despite this there are numerous
15 agents either here or on the horizon for which we could
16 make an argument for test. Now, Dr. Steve Wagner
17 pointed out to me yesterday that if I were actually to
18 use cost instead of test, the curve would be a great
19 deal steeper.
20 Now, on the other side, the pharmaceutical
21 industry for plasma fractions has a different strategy,

1 that is, using methods to inactivate agents in the
2 plasma fractions. And using that particular strategy,
3 looking at pooled plasma fractions, there hasn't been a
4 transmission that I know of, of HIV, HBV or HCV since
5 1987, and in fact when the West Nile epidemic came to
6 the United States, there were no transmissions that we
7 know of, of West Nile virus.
8 So, we learned a number of lessons I think
9 from viral inactivation of plasma fractions, first that
10 the efficacy of the plasma fractions have been very

11 well-maintained; second, that we haven't seen toxicity
12 now for many years; third, that immunogenicity is an
13 issue but it's seldom encountered; and that viral
14 safety could be achieved with methods that kill
15 somewhere between six and seven logs.
16 The goal of pathogen inactivation in blood
17 components initially was to eliminate the transmission
18 of viruses, particularly following the AIDS epidemic,
19 but there are secondary drivers such as bacteria and
20 parasites, as we heard yesterday, and there's also
21 added value perhaps in eliminating the risk

1 of graft-versus-host disease and possibly even TRALI,
2 depending upon what technology is used.
3 There are additional considerations for
4 single components compared to fractions. There's a
5 higher viral concentration in a single component that's
6 infected than the large pool, perhaps. There are more
7 proteins to consider in fresh frozen plasma than saying

8 just Factor 8 or Factor 9. There's a limited ability
9 to purify. Cells are more fragile in general than
10 proteins, and bags for inactivation are not tanks.
11 Now, there are a variety of methods that
12 you're going to hear about later today and I want to
13 emphasize that in the Canadian Consensus Conference we
14 did not consider any particular company's technology.
15 What's the reason for slow acceptance of inactivation
16 in the United States? There are probably several. As
17 you heard yesterday, the safety of the volunteer blood
18 supply is terrific in the U.S. today. There isn't any
19 inactivation method for all components. Our
20 surveillance and screening tests have really dealt very
21 well with emerging pathogens. We got a test for West

1 Nile virus, as you heard, in a year, bearing in mind
2 that there was already an existing test for West Nile
3 virus when it was introduced into the United States,
4 although it was a research test.

5 Current technologies don't inactivate all
6 agents, for example, small, nonencapsulated viruses,
7 spores, high-titer viruses, prions, so there isn't any
8 technology on the horizon that does it all. There's a
9 potential risk, as we heard, from residual chemical
10 agents, and I think we're convinced that that's
11 relatively small. And then the big issue, of course,
12 has been cost.
13 So, last March 29th and 30th, the Canadian
14 governments, Canada, Hema-Quebec, put together a
15 consensus development conference using the NIH
16 consensus guideline. And we can put together a
17 consensus development conference when there's a lot of
18 data available but not enough data to make an absolute
19 decision based on the data, so you ask for consensus.
20 For example, you wouldn't need a consensus conference
21 to use insulin for type one diabetes but if you wanted

1 to talk about beta cell transplant, you probably need a

consensus conference.

So, the topic was identified and background materials were supplied. A steering committee crafted six questions, which I will show you, identified speakers to provide background and appointed the consensus panel, of which I was the Chair. The speakers much like yesterday and today outline the issues and that took a day in Canada. The panel then deliberated late into the night and produced a draft statement answering the six questions. That statement was then presented to the public on the following day and comments were gathered from the audience and comments were solicited from those who weren't present.

Over the next month or so the panel revised and refined the consensus statement which has now been published. And this is the consensus panel. I was the chairman, as I said. Dr. Anderson is a hematologist, who deals with hemophilia and other hematologic disorders. Marie-Josee Bernard is a lawyer by training but an ethicist and a medical ethicist by practice.

1 Dr. Richard Cable, another American, has a long history
2 of running regional blood centers, so he's a
3 transfusion consultant. Bill Carey is a patient who
4 received multiple transfusions over many years for
5 chronic anemia. Jeff Hotch is an economist who looked
6 at cost-benefit issues; Nancy Robitaille, a pediatric
7 hematologist who also does transfusion. Marco
8 Sivilotti is an intensivist who also has credentials in
9 toxicology, and, finally, Fiona Smaill is a
10 microbiologist. So, it was an interesting group of
11 individuals with differing expertise and differing
12 perspectives.
13 Now, getting to the questions, the first
14 question was whether the current risk of
15 transfusion-transmitted diseases in Canada is
16 acceptable in relation to the other risks of
17 transfusion. And the panel heard a lot of testimony
18 and clearly recognized the dramatic advances in
19 transfusion safety over the last two decades. And
20 these are similar to data that you saw yesterday.
21 These happen to be the Canadian data but I would

1 suggest to you that the difference between 1 in 7
2 million and maybe 1 in 3 million in the United States
3 for HIV is really not an important difference. By and
4 large the agents that we're so concerned about have a
5 very low risk in Canada as in the U.S.
6 The risk of bacterial contamination was
7 considered. And again, you saw these data yesterday,
8 prior to the implementation of bacterial testing and
9 subsequent to the implementation of bacterial testing.
10 These might not be the exact data you heard yesterday
11 because this was in March of last year, and we've had
12 subsequent data but this is ballpark. This is the
13 ballpark risk for bacterial contamination.
14 And, finally, the Committee heard that the
15 hemovigilance data around the world suggests that the
16 aggregate infectious risks are far, far smaller than
17 the current noninfectious risks of transfusion, that
18 is, the risk of acute hemolysis, delayed hemolysis and
19 TRALI. And so the Committee felt that based on those
20 data alone we could not recommend introduction of

21 pathogen inactivation with its attendant unknown risks.

1 However, active surveillance can't account for the risk
2 of an emerging transfusion-transmitted pathogen, and
3 emerging agents, as I have shown you, have been
4 detected in blood at an increasing rate since the HIV
5 epidemic and are certain to continue to do so. Any
6 virologist or microbiologist will tell you that.
7 The reactive strategy of surveillance and
8 then identification and then test development not only
9 permits an agent to get into the blood supply but
10 frequently by secondary spread, as was the case with
11 HIV, to spread widely and, like HIV, before the disease
12 is ever recognized.
13 Now, in addition to the morbidity and
14 mortality of these new agents that are introduced into
15 the blood supply, every time this happens, it
16 undermines the public confidence in the blood supply.
17 And so the consensus panel recognized that really such

18 a risk requires a proactive approach in accordance with
19 the precautionary principle as contrasted with a
20 reactive approach.
21 Part A of this question of how safe is the

1 blood and whether pathogen inactivation ought to be
2 introduced was, if so, if it was a good thing to do,
3 under what new circumstances should pathogen
4 inactivation be implemented? The panel felt that given
5 the recognition of transfusion-transmitted agents that
6 are entering the blood supply, that pathogen
7 inactivation should be implemented as soon as a
8 feasible and safe method to inactivate a broad spectrum
9 of infectious agents is available. The panel
10 acknowledged that noninfectious hazards of transfusion
11 can entail serious safety issues, which deserves
12 specific attention, and emphasized that introducing
13 pathogen inactivation technology should not preclude
14 efforts to reduce the noninfectious risks.

15 And this was, I put together some data that
16 Sunny Dzik presented at that particular conference
17 looking at some of these methods of reducing the risk
18 of transfusion that don't deal with infectious risks.
19 And if you actually look at the costs of doing this,
20 the incremental cost, for example, of putting in a
21 barcode is 10 to $20 per unit. These are Dr. Dzik's

1 data. Of getting a unified online database so that
2 each hospital could call another hospital or use the
3 Internet to find out whether a patient had had
4 transfusion reactions or hemolysis in the past, that's
5 being done in Canada, in Quebec, that would cost 3 to
6 $6 a unit, and excluding donors by testing, for
7 example, with HLA testing for antibodies would cost 1
8 to $2 a unit.
9 So, you could introduce all three of these
10 for 14 to $28 a unit. It's not an enormous cost and
11 really shouldn't stop the introduction of some other

12 technology for infectious agents. The cost per event
13 avoided is probably about a million and a half dollars
14 by Dr. Dzik's estimates but again that's for all three
15 of these.
16 The B part to this question is if you
17 introduce pathogen inactivation should the criteria be
18 the same for red cells, for platelets and for fresh
19 frozen plasma or should you have different criteria,
20 and the panel felt that the same criteria of safety,
21 feasibility and efficacy should be applied to all blood

1 components.
2 It recognized that a single method to
3 inactive pathogens in all components would be ideal;
4 however, the absence of an integrated system shouldn't
5 imply that pathogen inactivation of any one component
6 should be delayed until a method is proven satisfactory
7 for all components. In other words, don't let the
8 excellent be the enemy of the good.

9 Should different criteria be used for
10 certain patient populations? And this has been a hot
11 issue. And the panel felt that there should be
12 universal applications to these products.
13 Traditionally premature infants, children, pregnant
14 women have been considered vulnerable populations;
15 however, these patients may also be at particular risk
16 for the infectious agents and they might arguably
17 derive special benefit from pathogen inactivated
18 components.
19 There are few data available on which to
20 individualize the risk-benefit assessment for these
21 so-called special vulnerable populations. So, that if

1 new information became available that identified groups
2 of patient who shouldn't receive pathogen inactivated
3 products, then one would deal with that but at the
4 present the panel felt that treatment should be
5 universal, all blood components for all patients.

6 The second question was, what would be the
7 minimally acceptable safety and efficacy criteria for
8 the preapproval assessment for pathogen inactivated
9 products and specifically what criteria should govern
10 acceptable toxicology standards and how should they be
11 assessed?
12 And as we heard yesterday, this is really
13 the purview of the regulatory agencies, and we know
14 that around the world different regulatory agencies
15 have established their own standard approaches. Each
16 agency has specific protocols and criteria. They look
17 at things such as genotoxicity and mutagenicity and
18 other things that we heard about yesterday. And the
19 panel certainly endorsed rigorous application of these
20 standards but strongly recommended that we use
21 well-designed, randomized clinical trials with relevant

1 endpoints for safety and efficacy. They also
2 encouraged harmonization of approaches in sharing of

3 data among the various regulatory agencies around the
4 world, recognizing that sometimes this isn't easy
5 because of proprietary restraints but if there are data
6 in one country on safety, they really ought to be
7 shared with the regulatory agency in another country.
8 And that's a public health issue.
9 Question arose as to what type of
10 postmarketing surveillance should be required, if any,
11 with the implementation of pathogen reduction. And the
12 panel recognizes the difficulty in carrying out
13 postmarketing surveillance but felt that specific
14 studies should be mandated by the regulatory
15 authorities and they ought to be supported either by
16 the manufacturers or the blood suppliers or both and
17 that postmarketing surveillance for adverse reactions
18 to these products should be linked to the national
19 hemovigilance systems and annual reports on adverse
20 reactions to specific products ought not only to be
21 performed but also analyzed and comparisons of these

1 reactions ought to be made to historical rates of
2 adverse reactions with non-PI products as is done with
3 hemovigilance in some countries around the world. And
4 the panel recommended sharing of those hemovigilance
5 data across national jurisdictions.
6 And this is just to point out why it's so
7 important, the panel saw data like this, to do
8 postmarketing surveillance. If you had an adverse
9 event of 1 in 33, you would only need a study of 100
10 patients but if you had an adverse event rate of 1 in
11 3,000, which is not a rare event, you need a phase
12 three study of 10,000 people and no one is going to do
13 those studies. So, we really do need postmarketing
14 surveillance to pick up what might even be fairly
15 common adverse events. And that's just a statistical
16 fact. There's nothing particularly deep about that.
17 Question number three was, for pathogen
18 inactivation technologies that have been approved by
19 the regulatory authorities, what implications should be
20 considered prior to adopting them widely? And there
21 are a number of implications for blood services as well

1 as for others as well as probably unintended
2 consequences.
3 So, the suppliers would have to select the
4 most appropriate technology among those available.
5 There are certainly logistical issues. The process
6 would require a detailed review of safety and efficacy
7 data, along with a determination of how adopting a new
8 technology would impact the processes of the blood
9 collectors and processors as well as the hospitals and
10 then cost-effectiveness data would need to be
11 conducted. And we'll talk a little bit more about that
12 and we're going to have a presentation about that later
13 on.
14 Consultation with patient-physician
15 stakeholders, hospital physicians and transfusion
16 groups is mandatory. Inventory management,
17 particularly at the time that you cross over from
18 noninactivated to inactivated components needs to be
19 addressed, a detailed educational program, for blood
20 centers, hospitals, healthcare providers and patients
21 prior to introducing new products. And as is currently

1 being done in France -- it probably shouldn't be
2 introduced nationwide -- there ought to be pilot
3 projects and France is going site by site, before, to
4 look at things like logistics, environmental and
5 occupational health issues.
6 And should the PI component differ in
7 function -- maybe the platelets aren't quite as good --
8 from non-PI products, that information has to be
9 disseminated to physicians, to healthcare providers and
10 to patients through an informed consent process. Now,
11 this is really the responsibility in Canada of the
12 supplier, the manufacturer and the provincial
13 departments of health.
14 Question number four is if pathogen
15 inactivation were to be implemented for all components,
16 what criteria would allow changes in donor deferral
17 testing, specifically relaxation of current donor
18 deferral exclusion policies? And the panel felt that

19 the regulatory agencies should start from zero and
20 review all of the donor screening questions and
21 eliminate or modify those that are thought to be of

1 marginal value, such as tattooing and certain travel
2 deferrals that we heard about yesterday.
3 What criteria would allow the cessation of
4 currently undertaken screening tests? Well, screening
5 tests for agents that are not readily transmissible by
6 transfusion but could be inactivated, for example, as
7 we heard yesterday, T. pallidum, the agent that causes
8 syphilis. Screening tests for agents of low infectious
9 titer and high log kill by PI, for example, West Nile
10 virus, screening tests for agents that are sensitive to
11 PI and for which there are redundant safety measures
12 such as cytomegalovirus, HTLV and anti-core screening
13 tests for agents that are exquisitely sensitive to PI
14 and for which current tests have poor specificity and
15 sensitivity, such as our current tests for bacteria.

16 And although it's not a screening test, gamma
17 irradiation of cellular blood components would probably
18 be eliminated if nucleic acid-targeted pathogen
19 inactivation technology were introduced.
20 What criteria would allow a decision not to
21 implement a new screening test? Well, a candidate

1 agent would be shown to be adequately inactivated by
2 the PI technology to do a new method. We would not
3 have to test for that unless there was an unusually
4 high titer. Then the question arose, well, should
5 there be multiple inventories for each component,
6 inactivated and nonactivated, and, if so, how should
7 you decide who gets what? And the panel recommended
8 universal implementation. They recommended strongly
9 against multiple inventories.
10 Question number five is, how should the
11 costs and benefits of pathogen inactivation be
12 assessed? And we heard a great deal about this before

13 the panel's deliberations and actually Dr. Brian
14 Custer, who will be speaking later today, was one of
15 the presenters at the meeting. And the panel felt that
16 implementation of pathogen inactivation should not be
17 based solely on the results of an economic analysis
18 because the costs are currently not really known and
19 the benefits are difficult to quantify. And we can go
20 into that in detail if you would like. I'm sure Dr.
21 Custer will.

1 Costs and benefits should be assessed using
2 a societal perspective, examining both direct and
3 indirect costs in accordance with published
4 recommendations. Methods and models should be
5 transparent with assumptions highlighted and they
6 should be tested on their effect on the results. And
7 the uncertainty about these analyses should be
8 considered not only for the incremental
9 cost-effectiveness ratio but also for the total impact

10 on the budget.

11 And how should these be aligned with other

12 blood safety interventions or other healthcare

13 interventions? And the panel felt that a judgment

14 about whether the extra benefits outweigh the extra

15 cost is really context-specific. Perhaps in France

16 where after the HIV epidemic there were actual criminal

17 proceedings putting people in jail and threatening some

18 of the ministers such the Minister of Health, maybe

19 they would pay more for pathogen inactivation, I don't

20 know, but in any case one needs to look at the context.

21 It's probably inappropriate to assign a

1 single number like $50,000 for a light-year as the

2 cutoff threshold for cost-effectiveness. Again, it has

3 to be context-specific. Decision-makers should clearly

4 state their reasoning for the decisions with emphasis

5 on the budget impact, the extra cost for improved

6 patient outcome and something called opportunity costs.

7 Opportunity costs, let's say, what would you do with
8 that money if you didn't use it for pathogen
9 inactivation? And, frankly, the panel thought this was
10 a little slippery, for example, if we didn't spend a
11 billion dollars a year in something, perhaps for
12 Department of Defense, we could introduce pathogen
13 inactivation. It doesn't work that way, really, we all
14 know that, but you have to look at opportunity costs at
15 anyway.
16 Reasoning used for past decisions may not
17 be applicable for current or future decisions for new
18 expensive technology and, finally, decisions about
19 scarce resources must be consistent with the values of
20 the decision-makers and their patients. So, one
21 country might decide that this is incredibly important

1 and is willing to pay a great deal more than another
2 country might.
3 The final question is the question, the

4 panel felt, what other information, considerations and
5 research-related questions would need to be answered in
6 order to decide whether or when a particular pathogen
7 inactivation technology should be implemented? And the
8 panel recommended that consideration be given to robust
9 governmental support for a large-scale investment in
10 developing an integrated technology for all blood
11 components. The panel felt that mathematical modelling
12 could be used to develop credible scenarios for the
13 unknown pathogen risks and these models could be used
14 in an economic analysis of candidate technologies to
15 support the decisions about investment or to determine
16 the research agenda.
17 The panel felt that large
18 adequately-powered randomized clinical trials should be
19 performed to evaluate and confirm the effectiveness of
20 any new technology and, as we said, post-licensure
21 studies really need to be done.

1 Introduction of PI technologies may have
2 unanticipated consequences to the healthcare system.
3 For example, if we use pathogen inactivation and
4 weren't using new screening tests, perhaps screening
5 tests for diagnostic purposes wouldn't be developed
6 because there wouldn't be as much money, as big a
7 market if there were no screening market. Don't know.
8 Next to last would be prion diseases, which
9 we heard about yesterday. They're not really addressed
10 by the current PI technologies, so new technologies
11 need to be investigated to address these and other
12 resistant agents, as we mentioned earlier, and research
13 should address the relative risks and benefits of
14 pooled components versus single donor components.
15 And, finally, we're here to talk about the
16 United States but really research initiatives should be
17 directed toward a technology suitable for implementing
18 in developing countries, where the risks are so much
19 higher and the likelihood of using a screening
20 technology with multiple tests is really not practical
21 and even if you could do that, the risks of the blood

1 there would be so great that you would not have any
2 supply left if you eliminated all the positive units.
3 This was the steering committee that
4 planned the meeting and, finally, there are several
5 publications out. You have one of those. You have the
6 Transfusion publication which gives a full, detailed
7 report of this conference. And if you want even more
8 detail there are proceedings in the conference which
9 have recently been published in Transfusion Medicine
10 reviews. And, finally, I would like to encourage the
11 Committee, since I'm not a voting member, to consider
12 the importance of changing the paradigm from the
13 reactive paradigm of surveillance, identification and
14 testing to a new paradigm, a prospective paradigm of
15 pathogen inactivation. Thank you very much.
16 DR. BRACEY: Thank you, Dr. Klein, for that
17 very good review of the consensus conference.
18 Questions from the Committee? Dr. Epstein?
19 DR. EPSTEIN: Well, first just to thank
20 you, Harvey, both for chairing that magnificent
21 conference and for sharing a very helpful summary for

1 our Committee. A very minor point on your, I guess --
2 one two, three four -- the sixth slide when you
3 commented that there has been no transmission of HIV,
4 HBV, or HCV by a plasma derivative since '87, that's
5 true for clotting factors but there was transmission of
6 hepatitis C by a particular immunoglobulin product in
7 1994 after the introduction of so-called generation-2
8 screening for antibodies, hepatitis C.
9 So, it's a long story, I won't go into it
10 but it illustrates your key point which is that the
11 product was not fully safe, it had been thought safe,
12 but it wasn't until specific-validated viral
13 inactivation procedures were introduced that it
14 actually became fully --
15 DR. KLEIN: Yes, again, Jay that was
16 summarizing. I should have said when they used the
17 inactivation procedures they used appropriately
18 validated procedures, they used, there hasn't been an
19 introduction of it. But clearly there was some

20 hepatitis from albumin, I think at one point in time as
21 well but it looked like this was a failure of the

1 inactivation procedures.
2 DR. BRACEY: Dr. Sandler?
3 DR. SANDLER: Dr. Klein, this took place
4 almost a year ago. What difference did it make? We're
5 going to spend the afternoon trying to make a
6 difference. I would like to learn a lesson from this
7 to find out how to be effective.
8 DR. KLEIN: Well, let me tell you what
9 difference it made. I don't see any of our Canadian
10 colleagues in the audience but both Health Canada and
11 Hema-Quebec are planning to go forward with pathogen
12 inactivation technology. And I'm not the one to give
13 you the details of that but in fact both governments
14 are supplying new funds because they feel that again
15 context-specific to Canada, where in fact, as you know,
16 there were criminal charges and still are criminal

17 charges in place, they felt that this is the approach,
18 the proactive approach to take. And so this is going
19 to be implemented. I don't know whose technology or
20 what the timeline is but I think it was enormously
21 important for Canada.

1 DR. HOLMBERG: Yes, thanks Dr. Klein. I
2 apologize for the noise that was permeating from the
3 other room while you were trying to speak but what I
4 did glean from your presentation was that there
5 appeared not to be a statement on whether there should
6 be a gradual implementation as far as products or
7 whether they should wait for the entire package; did I
8 miss something there?
9 DR. KLEIN: Yes. I hope I made that clear,
10 because it was very clear at the conference that when
11 even one component has a safe and effective procedure
12 to inactivate infectious agents it ought to be
13 introduced and one should definitely not wait for the

14 availability of either an integrated system that takes
15 care of all components or three systems or four systems
16 that can do all components. Once again I think the
17 idea is not to let the perfect be the enemy of the
18 good.
19 So, they were very much against having dual
20 inventories, against holding introduction of one
21 component, which was safe, effective and cost effective

1 by the country's context until others were available
2 and felt that as soon as something was safe and
3 effective, it ought to be introduced.
4 Now, the only, again, the only hesitation I
5 have is that it was felt very strongly that this should
6 be introduced gradually in terms of finding out via
7 pilot projects but not gradually because we wanted to
8 see whether in fact this was safe and effective. That
9 needs to be demonstrated first and then the logistics
10 need to be worked out perhaps by pilot project

11 introduction.

12 DR. BRACEY: One last question and then

13 we'll have to move on. Dr. Epstein?

14 DR. EPSTEIN: Harvey, one issue that

15 troubles me is the issue of trading off of risks.

16 Let's say for argument's sake that there is some small

17 risk to patient groups from the inactivated product but

18 that that risk is statistically greater than the

19 current risk of a TTD. Did the Committee look at the

20 question of whether it is reasonable to trade a small

21 decrement of current safety for an advantage of

1 preparedness, in other words, precaution against

2 emerging agent? Because, I think one of the underlying

3 problems in the field is the naive assumption that

4 there will be no downside to safe and effective

5 pathogen reduction technology. There's no such thing

6 as absolute safety. What we're really talking about is

7 potentially shifting of risks.

8 DR. KLEIN: Jay, that was discussed in
9 great detail. We already know that you lose some
10 component when you pathogen inactivate so there's a
11 supply issue. We already know that you damage whatever
12 cell you treat to some extent so it's not quite as
13 good. Is there some small issue on safety? Obviously
14 you're really not entirely sure until you do
15 postmarketing.
16 So, that was discussed in great detail and,
17 as you know, the current risks in Canada are even
18 smaller than the risks in the United States, so this
19 was of great concern to the Canadian government. But I
20 think the issue of the certainty, that these are not
21 the last agents, that the preparedness argument was a

1 very powerful one, and while West Nile virus didn't
2 cause much in the way of morbidity and mortality and
3 you could maybe write that off, I don't know, the fact
4 that another agent like HIV could be introduced really

5 weighed very heavily on the panel members, particularly
6 those who weren't in the transfusion medicine field,
7 and I think that carried the day.
8 DR. BRACEY: We better move on in the
9 interest of time and fairness to the other speakers.
10 Thank you, Dr. Klein. Our next speaker is Dr.
11 Margarethe Heiden. Dr. Heiden joins us from the
12 Paul-Ehrlich Institute in Germany. She specializes in
13 hemostaseology, blood components and stem cells. She's
14 the head of the section of transfusion medicine. Her
15 main responsibilities include marketing, authorization
16 of blood components, including red cells, leukocytes,
17 platelets and she also is a member of the Task Force
18 for Blood Safety at the Institute and a member of the
19 National Advisory Committee. Welcome.
20 DR. HEIDEN: Thank you. Thank you very
21 much for the kind introduction. Thank you for the

1 invitation. And first of all I have to say that I

cannot say anything about the European experience, and that's why I am speaking about the German experience, and the second thing is I got the impression from this day and especially yesterday, that much information was already said but and hopefully I at least will add something new ideas, I hope.

Okay. European legislation regulating blood components, we three main directives, which involve the regulation of blood components, blood collection, the first one, and its technical directives giving standards of quality and safety for collection, testing, processing, storage, distribution of blood components, and the point is that details going over these standards have to be regulated by any country depending on its technical feasibility, also its epidemiological situation and also economic situation. The other two directives, giving standards for screening tests, IVD directive and the medical device directive, giving standards for apheresis and blood bag systems, and son on, these directives regulate the

1 marketing, the coming into the European market for
2 these medical devices in IVD but the use of these
3 depends again on each country in Europe.
4 Okay. Our national legislation for blood
5 components Germany, first of all, is to say that blood
6 components are considered strict according to our
7 definition in our drug law and the blood establishments
8 need a manufacturing license given by the regional
9 authorities together with the Paul Ehrlich Institute,
10 the competent authority for marketing authorization of
11 the blood components and the German Transfusion Act
12 regulates collecting, details in collection testing,
13 also donor protection details and use of blood
14 components.
15 We have different parties cooperating in
16 Germany for blood safety. I think it's similar like
17 here in the United States and in other countries. We
18 have the competent authority for marketing
19 authorization of blood components for hemovigilance and
20 IVD vigilance. We have the national authorities which
21 are doing GMP inspections and also surveillance. We

1 have German Medical Association, which puts national
2 guidelines together with our institute.
3 We have the Robert Koch Institute that's
4 responsible for donor epidemiology. And we have also
5 the National Advisory Committee Blood, perhaps similar
6 to this Advisory Committee, and in this Committee all
7 the parties, the cooperating parties are involved.
8 That means doctors of different types, hematologists,
9 pediatrics, and so on. Patient organizations, the
10 Robert Koch Institute, the Paul Ehrlich Institute,
11 scientific societies, representatives and also
12 representatives from patient organizations. It is to
13 note that the representatives from the Robert Koch
14 Institute or from our institute are not allowed to vote
15 when recommendations are prepared.
16 Okay. How are these cooperating parties
17 involved in decision-making for the blood safety? We
18 know they have three main strategies for
19 decision-making. It's something a little bit mixed up
20 but mainly for historic reasons it's development,

21 decision-making if Germany. Okay. We have one, the

1 first strategy, we have blood components are suspected
2 to cause concern. The source of concern may be
3 scientific literature, discussion in different
4 societies, and of course striking hemovigilance
5 reports. Our drug law gives us a definition, what is
6 concern? There is a provision. Which is very
7 important, I think. "Drugs cause concern, if according
8 to the state of scientific knowledge there is reason
9 for the suspicion that their use according to their
10 determination leads to harmful effects, which exceed a
11 degree which would be tolerable according to the
12 current state of knowledge of the medical sciences."
13 And, I think that this implies immediate and annual and
14 continuous reevaluation of the drugs, of the safety of
15 any given drug.
16 Okay. Then evaluation of all the data, the
17 Paul-Ehrlich Institute has to substantiate the concern

18 and to start a graduated pharmacovigilance plan. If
19 the concern is already substantiated, then we start
20 from step two of this pharmacovigilance plan. That
21 means we announce a measure. And, it starts with a

1 written hearing and depending on the impact on
2 availability of blood, on the economic pressure and so
3 on, a public hearing will follow to discuss all the
4 details of the impact of the measure. And, then the
5 step three, official order by the competent authority,
6 in case of blood components and blood derivatives and
7 so on; it's the Paul Ehrlich Institute. And example of
8 these orders is introduction of screening, NAT
9 screening for HCV, HIV-1, for anti-HBc antibodies,
10 donor deferrals or travel deferrals because of variant
11 CJD, travel deferrals for SARS, West Nile virus and
12 chikungunya. If there yet some doubts we start with a
13 step one of the pharmacovigilance plan.
14 That means we start with an exchange of

15 information with the blood banks and even during step
16 one and also during step two, the main questions which
17 have to be addressed to the blood banks, questions, for
18 example, is it technically possible, will the measure
19 have an influence on the availability of blood
20 components, what impact will it have on the cost of the
21 blood components, and if it's also in our interest to

1 know if we have one or more supplies of a certain
2 technique or a certain test. Okay. Then after all,
3 even after the official order, any blood bank has the
4 ability to make an appeal.
5 The second main strategy for
6 decision-making is used when we don't have
7 substantiated any concern or if you have a new kind of
8 testing or manufacturing which promises a higher safety
9 or higher overall blood component quality but the hard,
10 severe scientific evidence is missing. In this case
11 the matter will be discussed with all parties, by the

12 national advisory board, and depending on the outcome
13 of the discussion a recommendation may be given. This
14 recommendation has not set a certain concise deadline
15 like an order by the Paul Ehrlich Institute but it will
16 say that in the near future the blood establishment may
17 follow the recommendation. Example for this is, have
18 been leukocyte depletion, sterile docking procedure and
19 especially a good example is this introduction of
20 predonation sampling and we just at the end of last
21 year we collected the data from two years after

1 introduction of the predonation sampling of the
2 bacteria, quality control testing, and we saw that
3 indeed we got a significant decrease of contamination
4 in red blood cell concentrates. There was no
5 significant difference in the contamination rates for
6 platelet concentrates and there's also no significant
7 different between pooled platelet concentrates
8 and apheresis platelet concentrates. The results will

9 be published soon.

10 The third strategy for decision-making is a

11 new kind of testing or manufacturing is available;

12 however, according to the current assessment of safety

13 and quality of blood components in our country there's

14 no need to give order to a general use. That means you

15 can only give order to a general use of a new method

16 when you have a concern. It's according to our Act.

17 But, in this case we have a large advantage, then we

18 can, then nevertheless single blood establishments can

19 apply for this new or for a changed marketing

20 authorization in order to introduce the new innovative

21 technique into their product program.

1 And, I think it's a great advantage for us

2 in Germany, because we have the possibility to stepwise

3 introduce these new techniques and we have at the same

4 time we have different methods on the market, and we

5 can even compare the postmarketing surveillance data

6 from the different, not quality but the difference
7 techniques during our hemovigilance. An example for
8 this is screening for HBV by NAT, it's not so exciting,
9 but SD-inactivation of pooled plasma, MB light
10 treatment of single donor plasma, and Amotosalen light
11 treatment of platelet concentrates.
12 Okay. The next slide, why we use the
13 strategy number three for pathogen inactivation? In
14 Germany we have around, about 6 million blood
15 components instituted per year, more than 4 million red
16 blood cell concentrates and about 400,000 platelet
17 concentrates per year, 50 percent, 50 percent from
18 pooled and from apheresis platelets. And the residual
19 risk rate of undetected donor infections calculated,
20 adjusted incidence, window period model -- that means
21 it's based on the donor incidence of the given

1 infection or infectious disease or infected particle
2 and depends also on the window period. And this again

3 depends on the sensitivity of the assay. And you'll
4 see it's based on data from donor epidemiology from
5 2000 to 2002. And, unfortunately this method cannot
6 calculate the testing for hepatitis -- antibodies --
7 but therefore the value for HBV, 1 to 620,000, I think
8 is much better now in Germany.
9 Okay. Next situation from our
10 hemovigilance, for the three main viruses,
11 transfusion-transmitted, viral infections assessed as
12 probable. On this one, shown on the slide, we see that
13 until '98, had a lot of HCV transmissions despite
14 anti-HCV testing and especially the 11 in 1998, there
15 was a case of a combined test period with a
16 noncompliance of performance of Lobeck (phonetic)
17 procedure and though we had only in this year, nine
18 contaminated patients, from one donor, here, the three
19 cases until 1980 from HIV transmissions, had been two
20 of them window period transmissions and one of them
21 single test failure from antibody testing.

1 With introducing HCV, NAT, we had only one
2 case in 2004. After introduction of HIV NAT, we had
3 one case, unfortunately, last year. The
4 decision-making for the detection limit for the HCB and
5 HIV, one NAT was made based on scientific literature,
6 on experimental data, and on the evaluation of the
7 cases from the hemovigilance and as was seen yesterday
8 HIV as well as HCV have a high multiplication rate
9 after infection and you have a steep increase of virus
10 titer. And, so, a decision was made based firstly on
11 this knowledge of the steep increase of the virus titer
12 and then also of the feasibility for the introduction
13 of the method into blood bank routine and it's been
14 done by medical testing though we have a limit for HIV
15 of 5,000, no, 10,000 international units per MIL and
16 for HCV 5,000 international units per mil plasma of one
17 donor.
18 And, we introduced in 2006 anti-HBc testing
19 and there we see antibody testing after a long, long
20 story of discussion and this long story of discussion
21 depended on initially a very bad specificity of the

1 anti-HBc antibody tests and also on the hope that the
2 HBV NAT will overcome the problem but it didn't and so
3 we introduced anti-HBc antibody testing. And I think
4 it was very useful because cases slowed down rapidly
5 and in this period nine frequent donors had been
6 discovered which had been proven to be infectious by
7 single HBV NAT.
8 Okay. This is the valuation. Pathogen
9 inactivation of blood components is not required as a
10 nationwide measure with respect to risk of HIV, HCV,
11 and HBV transmission. It may be required in altered
12 epidemiological situations as shown yesterday but up to
13 now in Germany we don't have really problems with all
14 the other bacteria or viruses, and we have only one
15 transmission of malaria since 1994. And again,
16 however, establishments can apply for a marketing
17 authorization of pathogen inactivated blood components.
18 And, they did it already and they have already their
19 marketing authorization.
20 Another problem is bacterial contamination.
21 These are data from our hemovigilance report. We have,

1 in sum, 61 cases i this decade assessed as probable.
2 These are only severe cases, severe septic cases, and
3 in this decade we have nine deaths and in the last
4 years six by platelet concentrates so we can say,
5 according to one of the first slides, we have one
6 patient died on average per year or per
7 400,000 platelet concentrates administered.
8 And we think that action here is required
9 but what kind of action is required? We've seen that
10 pathogen inactivation at least as seen from the
11 experimental data may not be as safe as expected and
12 screening for bacteria may not detect critical
13 components. The question is, do we have further
14 solutions? That is a picture of experiments made
15 by Thomas Hunter (phonetic) from our institute and it
16 clearly showed that the Amotosalen light treatment of
17 platelet concentrates do not inactivate spores, and
18 it's known from experiments that also some Pseudomonas

19 strains not so efficiently inactivated. And I think
20 here the French hemovigilance data may give an answer,
21 if pathogen inactivation has really survived the right

1 way to avoid severe septic infusion reactions.
2 The screening for bacterial contamination
3 the right way, it is presented, the sum of six recent
4 studies on screening of bacterial contamination by a
5 culture method, BacT/ALERT, used since 1998 as a
6 standardized quality control testing, and, but we have
7 prepared with issuing as negative to date because it's
8 hardly impossible for drug release and blood components
9 are considered as such.
10 Okay. A summary of these studies is that
11 1.2 two million platelet concentrates have been tested
12 and shortly there is one interesting, two interesting
13 results. First of all, the platelet concentrates,
14 which at a later time revealed to be positive and had
15 been issued negative to date, nearly, the main part of

16 the patients did not show symptoms but only three of
17 them, there were 200 initially positive later on issued
18 negative -- later on positive -- 276 didn't show
19 symptoms and 3 of them did. And the most striking is
20 that in spite of testing we have 6 fatal outcomes, 28
21 false-negative results. That means fatal cases are not

1 avoided by screening.
2 Okay. Further solutions to avoid
3 transfusion-transmitted bacteremia, we've seen that
4 platelet concentrates causing severe sepsis with fatal
5 outcome had been stored for more than four days. And
6 by chance, if importance of the storage been shown in
7 the study by Eder, one donor give a platelet
8 concentrate by apheresis and two platelet concentrates
9 were prepared from it. The one given on day three of
10 storage with set direction to be handled and the second
11 one given on day five of storage and the patient died.
12 That means now we are thinking, is it wise to reduce

13 storage time to four days? Together with, combined
14 with the concise instructions to the transfusing
15 personnel, how to handle septic reactions, efficiency,
16 of course, had to be field tested and logistic problems
17 had to be expected but perhaps also there will be an
18 overall in quality because of shorter storage times.
19 Back to the strategy number three, how we
20 are performing licensing of pathogen reduced blood
21 components? We do it like we are doing licensing for

1 any other component or any other biological, like for
2 plasma derivatives and other drugs. In effect they
3 have to show state-of-the-art pharmaceutical quality by
4 experimental data of the applicant and sometimes which
5 new methods produce also our own data. The safety has
6 to be shown by experimental preclinical data and all
7 these experiments and variation of experiments have to
8 follow ICH guidelines, all guidelines for the
9 validation of virus infection from the European

10 Medicines Agency, and clinical data have to follow good
11 clinical practice. And, efficacy, the clinical data
12 should prove noninferiority but to tell you the truth,
13 one cannot expect that you don't have any data of
14 diminishing, or diminishing of the efficacy of a
15 treated component. It's been often true for the plasma
16 derivatives but it has to stay in a range which doesn't
17 do harm to the patients.
18 Okay. And then if you see some problems
19 with the -- not problems but some things with the
20 product with your license, then it's a normal procedure
21 to license under conditions, for instance, to introduce

1 specific impetus controls or quality controls for
2 release to introduce into package inserts with specific
3 safety information and, of course, postmarketing
4 surveillance really done with a yearly safety update
5 and, of course, immediate suspicious case reporting.
6 One of the examples of the older product is

7 the SD-treated pooled plasma. We clearly have a lot of
8 advantages of this product. It's relatively
9 homogeneous because of the pooling. It's particle-free
10 because of sterile filtration of the final product and
11 therefore hardly allergic, we do not see allergic side
12 effects and clinicians take it very voluntary and we
13 like to take it we didn't show any case of TRALI or any
14 antibody dilution by pooling and we have an official
15 batch release. That means we know all of the quantity
16 of this product.
17 In the disadvantages up here, we have no
18 pathogen inactivation capacity against non-enveloped
19 viruses, that means not, Parvovirus B19, HIV are not
20 inactivated but there are measures in case to overcome
21 this disadvantage, like they have a procedure, immanent

1 inactivation of important plasma proteins like
2 Alpha-2-Antiplasmin and Protein S, and we may have
3 variant CJD spreading by pooling.

Okay. Then we get the order to introduce special text in the package insert, with regard to Alpha-2-Antiplasmin deficiency in the product, and we gave hints to the side effect of the risk of B19 and HIV transmission, and as it in European line, European distributed product. It has to follow the European pharmacologic properties and therefore because of the disadvantages into the pharmaco-properties it has to be introduced in the necessity of Parvovirus by B19 testing with a limit of ten to the three, international units per mil for the plasma pool and it has to be introduced, a batch release test for anti-HAV antibodies with a limit more than one international unit and the batch release test for Protein S and all the proteins here is yet in this discussion; that means it will come but limit is yet in discussion.

Another example is Methylene Blue/light treated, fresh frozen plasma, single donor plasma.

1 Again in the package insert we have some things, again
2 precautions for use, a hint to perhaps impaired styptic
3 capacity of the component, hint to maybe allergic
4 reactions against Methylene Blue and its
5 photoderivatives and the possible transmission of HIV
6 and Parvovirus B19.
7 There are indications on the pharmacologic
8 properties of, especially of the diminished fibrin
9 polymerization capacity of Methylene Blue/light treated
10 plasma and however that it is say this diminishing of
11 the fibrin polymerization capacity to a large, large
12 extent depends on how the plasma is handled, how the
13 manufacturing is done.
14 And, these are more of the data from other
15 countries, from Spain, especially, which claim this
16 worse quality but we didn't see it at all in the
17 product we give the license for. And there are
18 indications for preclinical safety data that Methylene
19 Blue, photoderivatives have concentrations much lower
20 than doses which gave toxicological effects in
21 preclinical studies.

1 And, one of the safety measures is to
2 introduce an HBV test for, to have a really safe
3 product. And regulates time and measuring of
4 concentration was introduced for the quality control of
5 Methylene Blue for the manufacturer. And, it's the
6 same procedure was performed for Amotosalen light
7 treated platelet concentrates and again in the package
8 insert you have contraindications for known
9 hypersensitivity against Amotosalen-HCI or psoralens.
10 The main point is that newborns with hyperbilirubinemia
11 which had to be treated with light of a wavelength less
12 than 425 nanometers shouldn't be treated with,
13 transfused with this, Amotosalen light treated
14 platelets. As a side effect, again anaphylatoxic
15 reactions are listed here in the text. And up to now,
16 immunologic reactions by neoantigen formation are at
17 the moment not known.
18 As side effects also the possible
19 transmission of nonenveloped viruses and the possible
20 transmission of spore hormones is introduced in the
21 text and the further point with side effect is that

1 pyrogen load is not abolished by pathogen inactivation
2 because the treatment doesn't remove pyrogen from the
3 component.
4 And, again, the pharmacological and
5 toxicological properties of Amotosalen are listed in
6 the package leaflet and again it's listed that there
7 are no signs of phototoxicity, at least with the
8 concentration which is in the component.
9 Safety aspects, again, we have testing
10 despite pathogen inactivation to reduce bioburden, and
11 as a specific quality control it was introduced, the
12 measurement as a quality control procedure for
13 Amotosalen content.
14 That means, to summarize, why we introduce
15 pathogen reduced blood components despite an extremely
16 low risk of transfusion-transmitted viral diseases, and
17 it's clear that it adds to the already high safety
18 achieved by pathogen testing. For instance, in cases
19 of errors or test failures, we had sometimes already

20 noticed, and it's important for people to prepare in
21 case of new-emerging diseases without a test available

1 and especially now and we are prepared in case of a
2 pandemic without the chance of testing for new or for
3 the pandemic pathogen. Yeah. And, I like this, that's
4 why I have to show it again, different strategies we
5 have to supply the different wants. Thank you very
6 much for your attention.
7 DR. BRACEY: Thank you, Dr. Heiden, for
8 your presentation. Could you share with the Committee
9 your system's and/or government's approach to the
10 economic issues; how does that factor, how did that
11 factor or did it not factor into your decision?
12 DR. HEIDEN: Okay. I have to say that
13 first of all, when we make orders for nationwide
14 introduction of a test, for something like that, we are
15 totally independent from our government. We can order
16 it according to the result of the discussion with the

17 marketing organization holders. But, when we, when you
18 are not so sure that it's the right way to do it and
19 when we are not so sure of the impact which it will
20 have on the economic facts in the transfusion medicine,
21 it's wise to go to our government and to ask for

1 support. And, this was done, for example, for
2 introduction of leukocyte depletion because there had
3 been a lot of small points which really showed it will
4 be a better product but it was not the large strong
5 concern for the introduction. And, in this way we
6 asked our government do you support our decision even
7 if we don't have the strong concern, do you support our
8 decision to introduce leukocyte depletion and in this
9 it went to our government to get support.
10 And, the other point is the economic facts,
11 it's more discussed between our institute and the blood
12 establishments because when we want to have, introduce
13 a new measure, then they have to look, if they are able

14 to do it within their frame of doing it, they're able
15 to do it. That's more the approach.
16 DR. BRACEY: Questions from the Committee,
17 Dr. Triulzi?
18 DR. TRIULZI: Can you comment on which, if
19 any, donor test, donor questions or irradiation have
20 been eliminated with the adoption of pathogen reduction
21 for platelets?

1 DR. HEIDEN: At the moment, there is no
2 reduction because only, there's not a nationwide
3 introduction of this system of the pathogen
4 inactivation system but of course if you use an
5 Amotosalen light treated platelet concentrate you do
6 not need further irrigation of this flat component. We
7 will not require, for example, travel deferrals for
8 travel reasons like SARS, chikungunya and West Nile
9 virus, because it's shown by the manufacturer that it's
10 viral inactivated. But we didn't leave the testing for

11 the main viruses because we want to hold at the lower
12 level the bioburden of the component but we can stay
13 about we can stay at our approach to test the minipool
14 and we won't have to go single donor testing.
15 DR. BRACEY: Dr. Ramsey?
16 DR. RAMSEY: Thank you, Dr. Heiden. That's
17 very helpful. I have a question that I also might want
18 to follow-up on this with Dr. Scully later on this as
19 well. I'm wondering whether the introduction of
20 pathogen inactivated products leads to an increase in
21 use of those products because of the sort of a decrease

1 in a fear factor that the physicians may have and
2 patients may have for getting transfusions; do you have
3 any perspective on that as far as whether this might
4 lead to an increased use of blood components?
5 DR. HEIDEN: I think it's yet too early to
6 say something about the potential of use of the
7 pathogen inactivated components. I can say for C

8 plasma, which covers 10 percent of the old plasma used
9 in, well, in Germany and all of the years, they have 90
10 percent protein plasma and 10 percent SD-treated plasma
11 on the market. And, we had a large time starting from
12 '94 to, oh, early nineties to '97 or '8, we had
13 Methylene Blue treated plasma and it covered about 30
14 percent. And now it's coming again.
15 DR. BRACEY: We have two questions, one
16 from Dr. Holmberg and then Ms. Birkofer. Dr. Holmberg?
17 DR. HOLMBERG: Yes. Thank you for your
18 preparation. On slide number ten, maybe I just need to
19 understand this a little bit. This is assessed as
20 probable. And that's really based, are you projecting
21 what the potential transfusion cases are in slide

1 number ten with the number of especially the hepatitis
2 B virus slides, cases?
3 DR. HEIDEN: The hepatitis B cases, this is
4 the slide, yes?

5 DR. HOLMBERG: Yes.

6 DR. HEIDEN: And what do you want to know

7 exactly?

8 DR. HOLMBERG: It just seems like, for

9 instance, in 2003 the six cases of hepatitis B virus,

10 that seems awful high and I realize that you have up

11 here assessed as probable. Is this the difference

12 between without NAT and with NAT?

13 DR. HEIDEN: No. No.

14 DR. HOLMBERG: How did you determine this

15 probable?

16 DR. HEIDEN: HBV, we have not NAT testing

17 for HBV. We have only HBS antigen testing. We had it

18 until 2006. And because HBV testing doesn't give any

19 further, further safety, if it's done by medical

20 testing, you should have, because of HBS antigen tests

21 are very, very sensitive and you should have a much

1 more sensitive HBV NAT test and it is also important to

2 introduce a minipool in the routine and that's why we
3 didn't introduce HBV testing. And we thought a long
4 time for anti-HBc antibody testing. And in all, given
5 the relatively high number of HBV transmissions, any
6 year and assessed as probable means that, that only the
7 fingerprinting is missing, only the direct proof is
8 missing but it's all, it fulfills all the requirements,
9 to the transfusion and the donor positive and the
10 recipients prior to transfusion negative in a certain
11 period of time after the transfusion negative. That
12 means these are transfusion cases, that are relatively
13 high and so we finally we thought of introducing this
14 HBc antibody testing because nowadays, the specificity
15 of the test has increased dramatically and as we have
16 seen that really indeed the rate of transmission has
17 slowed down and moreover we had these nine cases in the
18 two years which we catch out from donors, we catch out
19 from donation and they had anti-HBc only positive and
20 they were tested, retested in a single donor HBV NAT
21 and they proved to be infectious. That means it was a

1 success.

2 DR. HOLMBERG: The other question is, you

3 put as a contra -- a disadvantage for the SD-treated

4 pool plasma the risk of spreading vCJD by pooling.

5 What are your pool sizes or do you have a limit on your

6 pool size for your SD-plasma?

7 DR. HEIDEN: The pool sizes are between 600

8 and 1,000, 200, 300, 500, pool plasma, single donor

9 plasmas per pool. That means round about 1,200 pooled

10 plasma contained in one pool.

11 DR. HOLMBERG: Okay. And then also

12 finally, on I believe it's slide 25 -- I can't see with

13 25 or 26 -- it's the contraindications for the

14 Amotosalen light treated platelets and it mentions

15 about the newborn babies with the hyperbilirubinemia

16 treated with the light therapy. Why is that, is that

17 because there are residual amount of products still

18 left in the platelets?

19 DR. HEIDEN: Yes. Yes. It's a

20 precautionary measure because of the procedure,

21 Amotosalen.

DR. BRACEY: Do you have a comment, Dr. Corash?

DR. CORASH: Just as a clarification, no infant should be illuminated with light below 425. There is a general agreement among neonatologists that you should always have cutoff filter, so, although this is in the contraindication because there is a small amount of residual Amotosalen, no child today should be photoilluminated with light below 425.

DR. HEIDEN: You're totally right. It's really, this is a totally precautionary measure.

DR. BRACEY: Thank you. Ms. Birkofer?

MS. BIRKOFER: Thank you, Mr. Chairman. Thank you, Doctor, for your presentation. I have a question on slide 18. When you license under conditions do you have any experience on how long the products remain licensed under postmarket surveillance before full licensure?

DR. HEIDEN: The product will be licensed, there's renewal five years after first licensing. And

21 then there's no further renewal. But, you have to

1 supply our agency any year with a periodic safety
2 update report and if there is a concern arising, you
3 can make a withdrawal, you can announce withdrawal of
4 the licensing.
5 DR. BRACEY: Dr. Busch, last comment.
6 DR. BUSCH: Yeah, I just wanted to speak to
7 Dr. Holmberg's question in that the beautiful data from
8 Germany in slide ten, on hemovigilance observed cases
9 and just to point out especially with HBV Jay's point
10 yesterday that we're not seeing cases as frequently as
11 the models predict. And I think the big difference is
12 in Germany, in many other countries they have
13 systematic donation repositories, retention samples, so
14 whenever donors seroconvert they can go back to those
15 samples and identify the low-level of viremic donations
16 and then find these cases. And unfortunately in the
17 U.S. we never had the resources to build and maintain

18 those. And there have been HBV transmissions last
19 four, five years, as Roger summarized, a half dozen.
20 Those are only documented by recipients developing over
21 a clinical hepatitis B. We don't have a process, and

1 then with HBV we don't have lookbacks so we don't find
2 these cases.
3 DR. BRACEY: Let's take a 15-minute break.
4 Is there a burning question, one burning question, Dr.
5 Kouides?
6 DR. KOUIDES: Yes. With your SD plasma
7 postmarketing surveillance, I'm sorry, I may have
8 missed it. Any adverse events, thrombotic events?
9 DR. HEIDEN: Please, again.
10 DR. KOUIDES: With SD plasma, your
11 SD-plasma experience have there been any --
12 DR. HEIDEN: Oh, SD plasma, now I've got
13 it. Okay. We had two notifications of
14 hyperfibrinolysis caused by SD plasma; however,

15 evaluating very carefully these two cases, I have to
16 say that the patients had been in status where all the
17 other plasma products would have been caused or not
18 caused -- this hyperfibrinolysis would have happened in
19 any case, and it didn't depend on the treatment of
20 SD-plasma.
21 DR. KOUIDES: I assume they had severe

1 liver disease probably, because that would be a risk
2 factor?
3 DR. HEIDEN: Is what?
4 DR. KOUIDES: They had severe liver
5 disease, I assume, those patients?
6 DR. HEIDEN: Yes. It's been liver
7 transplantation one, and hysterectomy, the second one
8 and it's known very well in hysterectomy that there are
9 a lot of plasma activity released and so in these two
10 cases we really after careful evaluation said it's
11 imminent on the disease and not on the product.

12 DR. KOUIDES: So to clarify, no thrombotic
13 events?
14 DR. HEIDEN: No, none at all.
15 DR. BRACEY: Okay. Dr. Holmberg wants to
16 make an announcement regarding lunch. We'll reconvene
17 in 15 minutes. By my watch that would be five of.
18 (There was a break in the proceedings.)
19 DR. BRACEY: Our next speaker is Dr.
20 Laurence Corash. Dr. Corash is Vice President for
21 Medical Affairs, Chief Medical Officer of Cerus, he is

1 Professor of the Department of Laboratory Medicine at
2 the University of California, in San Francisco. Dr.
3 Corash has extensive experience, publishing more than
4 150 basic research papers, and over the last ten years
5 has been essentially dedicated to the study of
6 inactivation of pathogens. The topic of Dr. Corash's
7 inactivation of pathogens. The topic of Dr. Corash's
8 presentation will be -- well, I have Cerus here but

9 INTERCEPT blood systems, pathogen inactivation of
10 labile blood components. Dr. Corash?
11 DR. CORASH: Thank you, Dr. Bracey and Dr.
12 Holmberg and members of the Committee for the
13 opportunity to present today. I am going to focus my
14 comments on our experience with the platelet and plasma
15 systems which have been commercialized. The red cell
16 system with S-303 is in the clinic today and we're
17 continuing development on that but I'm not going to
18 speak about that today. All of the information that
19 I'm going to present today has been published and there
20 are references on pages of the slides in the handouts.
21 These are the topics that I'm going to cover with you

1 today. And, during this presentation I am also going
2 to address the specific issues that were raised in the
3 premeeting communication on topics of interest to the
4 Committee.
5 Now, this is the slide which has been used

6 by many presenters thus far and I think some very
7 relevant points have been made from it but there are a
8 few additional points I think which are relevant that
9 grow out of this experience. And, of course, great
10 advances have been made to date in improving or
11 reducing the risk of transfusion of these three major
12 viruses, but, one of the things, of course, is that the
13 risk reduction is always presented in terms of residual
14 risk per donation.
15 And, I think one does need to remember that
16 from a patient perspective many of these patients
17 receive multiple transfusions. So, the average patient
18 with acute leukemia during the induction phase may see
19 between six and ten platelet transfusions and during
20 the entire period of therapy for acute leukemia or
21 other diseases there may be multiple exposures. So,

1 you have to think about risk in terms of the patient
2 and adjust those numbers accordingly.

3 Each of the inflection points in this curve
4 obviously represents the introduction of a new step to
5 further reduce the risk. And you can see that those
6 have been beneficial. However, there is a substantial
7 area under this curve over the three decades that
8 clearly indicates, as Dr. Alter emphasized, the
9 morbidity which is far greater than the mortality for
10 these types of diseases, that we need to consider. And
11 sometimes the consequences of some of these viruses,
12 for example, hepatitis C virus, formerly known as nonA,
13 nonB, are not always recognized. It took us a while to
14 establish the relationship between this virus and
15 hipatocellular carcinoma. So, I think that there are
16 morbidity considerations other than mortality that we
17 need to think about.
18 Despite these improvements, we still have
19 not reached high levels of safety for certain pathogens
20 such as bacteria. Although bacterial detection has
21 made some strides, the recent data from the Passport

1 study show us that with platelet products that are
2 stored from six to seven days, the residual risk of
3 contamination may be substantially greater than 1 in
4 3,000.
5 For common pathogens like cytomegalovirus,
6 despite leukodepletion in serologic testing there's
7 still a transfusion-transmitted incidence of infection
8 of 3 to 4 percent. So, we still have a need to further
9 improve the safety of labile blood components.
10 Now, the objective of the technology that
11 I'm discussing is to inactivate infectious pathogens, a
12 broad spectrum of them, and leukocytes, using a
13 targeted nucleic acid photochemical process. And,
14 evaluation of this technology has required
15 establishment of preclinical safety and efficacy, the
16 use of randomized controlled clinical trials to support
17 the therapeutic indications, and we have now embarked
18 upon a program of active hemovigilance to further
19 expand our experience and characterize not only the
20 safety profiles but also the efficacy of this product.
21 And lastly, it's very important that the technology be

1 operationally feasible and be cost-efficient. And I'm
2 going to directly address that later on in this
3 presentation.
4 These are the systems which are used for
5 platelets and plasma. They have been extensively
6 published. I'm not going to go into the technology in
7 great detail other than to say that they share a common
8 platform. It's a photochemical technology that
9 utilizes a psoralen compound known as Amotosalen. For
10 the platelet system, which you see on the upper panel,
11 it uses a platelet additive solution which is a
12 balanced salt solution called InterSol, that reduces
13 the burden of transfused plasma and adds some benefits
14 in terms of transfusion reactions and potentially
15 impacting noninfectious complications such as TRALI.
16 Both of these systems are configured to
17 operate in conventional plastic containers and utilize
18 technical skills that are known to blood banking
19 component room technologists today so the learning
20 curve to use this technology is relatively short and
21 we'll talk about that a little bit later as well.

1 One of the other aspects of this technology
2 is that both of them use a compound absorption device.
3 Although Amotosalen and the treated platelets and
4 plasma have demonstrated very high safety margins in
5 preclinical toxicology studies, in medicine less of
6 something is always more and we made a decision many
7 years ago to have a compound absorption device that is
8 a wafer or a flow-through device that you see in the
9 plasma set that allows us to have the residual
10 Amotosalen levels at extraordinarily low final
11 concentrations.
12 These systems then have been integrated
13 into the component rooms of blood centers. They are
14 compatible with products that are collected by
15 apheresis and by whole blood and by making pools of
16 whole blood-derived platelets or whole blood-derived
17 plasma components.
18 Now, the spectrum of inactivation with this

19 photochemical technology is very broad. Here you see a
20 list of pathogens that have been studied in a very wide
21 variety of assays. In green are the common blood-borne

1 pathogens that are currently tested for in routine
2 blood banking practice. In red there are the emerging
3 pathogens that have been demonstrated to be inactivated
4 by this technology.
5 The broad categories include the enveloped
6 viruses and viruses which are both cell-free,
7 cell-associated, and also the retroviruses when
8 sequences are integrated into host genomes. One
9 important aspect in considering these pathogens,
10 particularly for some of the cell-associated viruses,
11 for example, chikungunya infects megacariocytes and is
12 internalized in platelets. So, being able to
13 demonstrate inactivation of platelet-associated
14 chikungunya is very important.
15 For the nonenveloped viruses there is a

16 spectrum of activity. Parvovirus B19 is inactivated by
17 this technology using a human erythroid progenitor
18 infectivity assay to the levels that we can
19 demonstrate. That means a dynamic range of
20 approximately five logs but that is equivalent to a ten
21 genome equivalent titer in the material that was used.

1 Hepatitis A virus is resistant to this
2 inactivation because the external capsit is
3 extraordinarily tight. Fortunately, this virus has not
4 been a big problem in transfusion-transmitted
5 infections for the labile blood components. Bacteria
6 are extremely sensitive to this inactivation
7 technology. Bacterial spores, as pointed out by Dr.
8 Heiden, are not inactivated; however, studies have been
9 done with chlostridia and with Basilla cereus to
10 demonstrate that when these spores go into the
11 vegetative phase, these organisms are highly
12 susceptible to inactivation.

13 For bacteria, the encapsulated bacteria are
14 more resistant. Pseudomonas is the one bacteria for
15 which six logs cannot be killed but four logs of
16 Pseudomonas can be killed and we believe that that is a
17 very sufficient safety margin. The protozoens are
18 extremely sensitive to this, both cell-free and
19 intracellular, including parasitized red cells seeded
20 into platelet components and lastly, leukocytes are
21 extensively inactivated, preventing replication and

1 synthesis of cytokines, including T cells. And this
2 has permitted adoption of the technology for
3 replacement of gamma-irradiation for inactivation of T
4 cells and prevention of graft-versus-host disease.
5 Lastly, bacteria at very low levels are
6 effectively inactivated and we have done studies
7 particularly with some blood centers in Austria to
8 demonstrate that when one seeds 1, 10 or 100 CFU into
9 an entire platelet component, that they can't be

10 detected easily by bacterial detection systems but
11 they're completely inactivated by this technology when
12 you culture the units that have been stored for five or
13 seven days and culture the entire unit.
14 I would like to turn now to the preclinical
15 and the clinical experience. John Chapman, I think,
16 walked through the array of assays and studies that are
17 used to qualify these types of products. The platelet
18 and plasma systems in Amotosalen have been evaluated to
19 pharmaceutical standards, that has included all of
20 these studies, including three-month transfusion
21 studies in dogs with the treated components to look for

1 adverse events and none were observed in those studies.
2 These two products have demonstrated very, very high
3 safety levels and these data have been published in
4 detail.
5 This is the road map for the clinical
6 development program that was followed for platelets.

7 It was developed with guidance from FDA. I won't go
8 into it in great detail. All of the data have been
9 published. Phase one-two studies involved healthy
10 subjects with radiolabeled platelets to establish the
11 viability of these treated platelet components. Phase
12 three and later the phase four are postmarketing
13 studies, involved 843 patients; 3,700 units of these
14 platelets transfused.
15 The trial that I'm going to focus on today
16 and show you some data from is the SPRINT trial. Four
17 of the investigators from that trial are actually here
18 with us today and Dr. McCullough was the lead
19 investigator on that trial. And that was a trial that
20 was focused on evaluation of hemostasis. It's the
21 largest platelet transfusion trial evaluating

1 hemostasis that has yet been completed and the primary
2 endpoint of that was prevention of grade two bleeding.
3 Just turning briefly to the plasma program,

4 the rest of my comments are going to be focused on
5 platelets but the plasma program also involved clinical
6 trials starting in healthy subjects, including a trial
7 to demonstrate warfarin reversal with plasma prepared
8 with the INTERCEPT process and also a measurement of
9 the kinetics of Factor 7 replaced with that plasma in
10 warfarin-treated healthy subjects.
11 But, more importantly, phase three clinical
12 trials were conducted for each of the major therapeutic
13 indications for which plasma is used. This included
14 patients with congenital hemophilias who are not
15 treated with recombinant products or concentrates but
16 require fresh frozen plasma for their either
17 prophylaxis or support during hemorrhagic events. This
18 was done in combination with the Hemophilia Research
19 Group that maintains a registry in the United States of
20 these rare coagulopathies.
21 We did a study also that was a randomized

1 clinical trial of acquired coagulopathy, primarily
2 complex coagulopathy associated with liver disease,
3 including liver transplantation, because this is a
4 large-volume component used for support of these
5 patients and, lastly, a randomized clinical trial of
6 therapeutic plasma exchange for patients with
7 thrombotic thrombocytopenic purpura because this is a
8 very effective therapy for these patients and they use
9 very large volumes of plasma. Each of these studies
10 has been published.
11 Now, turning to the SPRINT clinical trial,
12 this was a randomized controlled clinical trial,
13 double-blinded, designed as an equivalence trial on a
14 noninferiority basis. The primary endpoint was
15 prevention for the incidence of grade two bleeding.
16 Grade two bleeding is the type of bleeding which is
17 most responsive to platelet transfusion. In addition,
18 we also looked at higher-grade bleeding, grade three
19 bleeding, which is bleeding requiring immediate red
20 blood transfusion support, grade four bleeding is
21 disabling bleeding, bleeding that results in fatality.

1 Patients were enrolled and supported for up
2 to 30 days with either the INTERCEPT or the control
3 product and evaluated each day by a trained research
4 nurse for grade two, grade three and grade four
5 bleeding. As you can see, there was equivalence in
6 terms of the number of patients that developed at least
7 one grade two bleeding event during this period of time
8 so by inferiority analysis that P value is highly
9 significant, rejecting inferiority and confirming
10 equivalence. The same was true with grade three and
11 grade four bleeding. The incidence of grade three and
12 grade four bleeding was actually lower in the INTERCEPT
13 treated group.
14 Another parameter that was looked at,
15 because the vast majority of platelet transfusions are
16 given for prophylaxis based on the morning platelet
17 count, and that's what happened in this trial; 90
18 percent of transfusions were administered for
19 prophylaxis of bleeding. However, primary care
20 physicians could order platelet transfusions whenever
21 there was breakthrough bleeding. And the proportion of

1 transfusions given for breakthrough bleeding was
2 actually statistically significantly lower in the
3 INTERCEPT group. And lastly, as a key endpoint, we
4 looked at mortality, and mortality was not
5 statistically different between the treatment groups.
6 One of the other things that we looked at
7 in the SPRINT trial, because platelets are given to
8 prevent bleeding, is the time to onset of the first
9 grade two bleeding event during the 30-day period of
10 transfusion support. And you can see here that there
11 was similar median time to onset of the first grade two
12 bleeding event in the 60 percent of patients who had a
13 grade two bleeding event and this was not statistically
14 significantly different.
15 Safety was another component of the SPRINT
16 clinical trial that was evaluated. This was an acutely
17 ill patient population. Eighty percent of the patients
18 in SPRINT underwent hematopoietic stem cell
19 transplantation during their time on the trial. That

20 involved complex ablative chemotherapy, radiation
21 therapy and, for a substantial number of the patients,

1 total body irradiation.
2 This is an analysis of grade three and
3 grade four adverse events by system organ class using
4 the MedDRA system. As you can see at the very top bar,
5 80 percent of the patients, as one would expect in this
6 population, experienced a grade three or grade four
7 adverse event. This presents a substantial challenge
8 then in looking at the safety of an intervention such
9 as a new platelet component because we're operating in
10 a background of a very large number of adverse events
11 but by system organ class we did not detect for grade
12 three and grade four adverse events any statistically
13 significant differences. For some of these classes
14 there was a higher incidence in the control group; for
15 some there was a slightly higher incidence in the
16 INTERCEPT group.

17 Now, this analysis was based on 898
18 individual preferred terms that could be selected by
19 physicians to describe an adverse event. And at this
20 level of granularity there were 11 terms that were
21 statistically significantly different. And the

1 question is, and a challenge and a potential barrier,
2 one might say, to how do you look at safety in a
3 product like this, is, how do you go on to evaluate
4 when you find low-frequency events, and these were all
5 low-frequency events and the question is, how does one
6 evaluate them?
7 We think that the best way to evaluate
8 low-frequency events that may have significance when a
9 product is ultimately used in a very large patient
10 population is to do a type of study that you can
11 conduct in a postmarketing setting where through
12 structured active hemovigilance one can gather a very
13 large amount of data.

14 This is a sample size estimation comparing
15 adverse event rates and looking at the sample sizes
16 required with 80 percent power to detect a 1 percent
17 difference in an event rate that occurs in the control
18 population ranging between 0.1 to 5 percent. If you
19 look at the topmost curve with a 5 percent incidence,
20 if you want to detect a 1 percent or rule out a 1
21 percent increase in incidence of an adverse event, you

1 need 17,000 patients. And we believe this can best be
2 accomplished in a postmarketing hemovigilance type of
3 program because it's not readily amenable to a
4 randomized clinical trial program.
5 So, what I would like to do now is walk you
6 through the hemovigilance experience that we have had
7 and show you the type of information that can be
8 gathered regarding safety and effectiveness for these
9 products. Now, the regulatory history goes back to the
10 European experience, some of which you have heard about

11 from Dr. Heiden. We received CE mark registrations or
12 approvals for the platelet and plasma systems. These
13 are class three drug device combinations. And, the
14 labeling for these were that the platelets and plasma
15 were not clinically different from untreated
16 components. There were no patient population
17 exclusions, although Dr. Heiden did, I think, emphasize
18 one thing very important, because there is residual
19 trace Amotosalen we did caution pediatric physicians
20 not to use a light source for photoillumination that
21 gave out light below 425 nanometers but, that is a

1 standard precaution absent even the use of a
2 photochemically treated product.
3 In many regions in Europe this product has
4 been approved for seven-day platelet storage where
5 seven-day platelets are allowed. Subsequently, the
6 biologic component, the treated platelets and plasma
7 have undergone national registration processes in

8 France for platelets and plasma and in Germany, last
9 year, of the first marketing for the platelet
10 component.
11 Thus far in Europe then the transfusion
12 experience has allowed us to gather information on
13 100,000 doses of platelets and plasma transfused in 60
14 centers and in 20 countries, and I'm going to now turn
15 to the ways in which we have gathered that information
16 but this has given us a very large experience. Our
17 intent then in what we did when this product was
18 introduced into commercial use in Europe was to set up
19 a system of hemovigilance that was consistent with the
20 national hemovigilance systems and to take advantage of
21 some very well-developed systems that were already in

1 place, such as the system in France, which is regulated
2 by the medicinal agency, AFSSAPS.
3 So, these are prospective observational
4 studies in routine use where we can compare the

5 experience with historical data that have been
6 collected in the same systems. In some countries there
7 is mandatory reporting already in place for all
8 transfusions. We adopted a standardized reporting
9 system. We were able then to look at safety in very
10 broad patient populations, specifically to look at
11 low-frequency adverse events, and also to gather data
12 in specialized populations such as pediatric
13 populations that could not be easily enrolled into our
14 clinical trials. SPRINT only enrolled 23 pediatric
15 patients down to the age of two years. This experience
16 in Europe gave us an opportunity to look at a larger
17 number of pediatric patients.
18 This is a summation of the studies which
19 have been completed to date and I'm going to give you a
20 high-level overview of the data from these studies.
21 We've done, the first study was 5106 transfusions in

1 multiple centers in four countries. We then followed

2 that with a second extension of this program, looking
3 at almost 7,500 transfusions, of which 2500 were in
4 French EFS centers at their request, and additional
5 studies, additional transfusions from Belgium and
6 Spain.
7 We have had an opportunity to use the
8 French hemovigilance system in the region of Alsace,
9 which converted to universal use of INTERCEPT platelets
10 and now plasma and provided data on 13,000
11 transfusions. We had a very unique experience in the
12 Island of La Reunion, because during an epidemic of
13 chikungunya virus the French National Transfusion
14 Service asked us to implement the INTERCEPT platelet
15 process and we acquired data on almost 2,000
16 transfusions, including almost 500 in pediatric
17 patients in that environment and, lastly, we did a
18 specific pediatric study at a hematology-oncology
19 service at the University of Ghent in Belgium that
20 involved 500 transfusions.
21 As I said, these were prospective cohort

1 studies for patients receiving INTERCEPT platelets in
2 routine practice. The primary endpoint were the safety
3 observations after each transfusion with mandatory
4 reporting for all transfusions for the first 24 hours
5 but no time limit on when an adverse event could be
6 reported and there was detailed reporting of serious
7 adverse events.
8 Specific forms were provided to require
9 vital signs before and after transfusions. Specific
10 criteria were given for transfusion-related acute lung
11 injury based upon the Bernard criteria that had been in
12 use for a number of years. When sepsis was suspected
13 we asked for cultures of patient and component.
14 Lastly, imputability or relationship of the events to
15 the transfusion to classify it as an acute transfusion
16 reaction or a reaction related to the component that
17 was either possibly, probably or definitively related
18 were conducted by trained hemovigilance officers and
19 primary care physicians.
20 This is then a high-level summary of the
21 experience that now involves about 28,000 transfusions

1 that had been reported to us, involving about 4,500
2 patients, and these are for the centers who have agreed
3 to participate in these active hemovigilance programs.
4 You can see that on a per transfusion basis the
5 reaction rates range from around or a little below 1
6 percent to about 1.6 percent in pediatric patients of
7 transfusions and on a per patient basis from around 2
8 percent to a high of 8 percent in pediatric patients.
9 Now, from the previously published
10 literature, the rates of transfusion reactions on a per
11 patient or per transfusion basis have ranged anywhere
12 between 5 and 20 percent when one looks in the
13 literature over a long period of time. But, we have
14 had the opportunity in several regions to obtain
15 comparative control data before INTERCEPT looking at
16 the same patient populations and after the introduction
17 of INTERCEPT.
18 So, in Alsace, which transfuses
19 approximately 2,000 patients per year with platelets,
20 out of a population in that region of 2 million

21 patients -- and they provide all of the products for

1 the people living in that region -- we could look at
2 data for a year before INTERCEPT and data for a full
3 year after INTERCEPT, so, around 2,000 patients in each
4 period. And on a per transfusion basis you see that
5 the incidence of acute transfusion reactions has
6 declined from about a half a percent down to 0.14
7 percent. On a per patient basis it's gone down from
8 about 3 percent to 1.7 percent in the Alsace region.
9 We also had an opportunity to look at
10 comparative data on the Island of La Reunion. They had
11 data through the French hemovigilance system before
12 INTERCEPT looking at around 1,000 transfusions; for all
13 patients on a per transfusion basis they had a reaction
14 rate of around 9 percent. After the introduction of
15 INTERCEPT, it fell down to a level of about 1 percent,
16 which was our experience in other parts of Europe.
17 Similarly, in the pediatric population in La Reunion we

18 had an opportunity to look at these patients and prior
19 to adoption of INTERCEPT the rate on a per transfusion
20 basis was 21 percent -- and this is primarily in
21 hematology-oncology patients who were repeatedly

1 transfused in that environment -- and after INTERCEPT
2 it went down by almost 90 percent to around a 3 percent
3 incidence.
4 Now, as I said before -- and you heard
5 yesterday from Dr. Leiby -- chikungunya virus has been
6 an epidemic in the South Indian Ocean. And we had a
7 unique opportunity starting in 2005 and going into
8 2006, about 35 percent of the population of La Reunion
9 was infected with chikungunya virus, so, about 266,000
10 cases. And this virus had undergone some genetic
11 mutations and the fatality rate from this virus was 1
12 per 1,000 of infected people.
13 In addition, 766 cases actually were
14 imported into metropolitan France by returning

15 travelers or citizens who live in both areas and there
16 was one needlestick transfusion from an infected
17 patient to a nurse in France. So, it was clearly
18 capable of transfusion transmission.
19 In terms of blood component availability,
20 the EFS had to stop collection of blood components on
21 the Island of La Reunion, so if you want an example of

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1 availability, there was none. It went to zero, for red
2 cells, plasma and platelets, they instituted transport
3 of red cells and fresh frozen plasma for metropolitan
4 France. And I would add that La Reunion is a
5 specialized care facility in the South Indian ocean.
6 They do liver transplants, they do pediatric
7 hematology-oncology, adult hematology-oncology and they
8 needed platelets but they could not import the
9 platelets because of shelf-life problems. And, so,
10 based on data that chikungunya virus was effectively
11 inactivated by this technology, we implemented the

12 INTERCEPT technology for production of platelet
13 components in La Reunion in March of 2006.
14 Recently there has also been a small
15 epidemic in the Amelia Romana region of Italy and
16 INTERCEPT has now been implemented in that region as
17 well by that Italian government.
18 The experience in La Reunion then was a
19 very positive experience because it enabled the
20 production of platelet components. It was implemented
21 in two weeks, and I would emphasize that because this

1 is a small center it could be done quickly and because
2 we had other centers in metropolitan France that were
3 highly trained, that they were able to train this
4 center in a short period of time. I would not assume
5 that this experience could be replicated on a national
6 basis in a country undergoing an epidemic in two weeks.
7 As you've seen, a reasonable number of
8 patients have received these platelet components and

9 there was a substantial reduction in acute transfusion
10 reactions and no cases of transfusion-transmitted
11 chikungunya virus and this was based on a surveillance
12 program using a serology and a PCR assay that had been
13 developed for research purposes by the EFS.
14 I would like to turn lastly then to the
15 technology impact in terms of resource impact on
16 platelet utilization, red cell utilization and also
17 cost, because I think that's a very important topic,
18 and I want to differentiate the type of cost I'm going
19 to be speaking about from cost-effectiveness or QUALY.
20 Dr. Custer is going to speak to that later on. QUALY
21 involves a lot of assumptions that go into the

1 modelling process and it's highly complex. In
2 addition, although there's a traditional threshold for
3 QUALY in some countries of 50,000 to be considered an
4 effective procedure, in other countries now $100,000
5 for an effective procedure. We know already that in

6 transfusion medicine that threshold has gone to almost
7 $2 million for certain interventions such as nucleic
8 acid testing. So, what I'm going to talk about are the
9 actual real costs of putting this technology in place
10 based upon European experience. As our friends in
11 Europe have said to us, "Well, when I'm going to reach
12 into my pocket, how many Euros do I have to pull out?"
13 In terms of platelet utilization, we have
14 had an experience in Belgium at the blood center of
15 Mont Godine, which underwent universal conversion to
16 INTERCEPT platelets in 2003, and this is a center which
17 supplies a tertiary care facility and has records for
18 all of its components transfused and had data for a
19 three-year period before the use of INTERCEPT and data
20 for three years after universal adoption of INTERCEPT.
21 So, you can see that for all patients before INTERCEPT

1 they had about 700 patients receiving platelet products
2 involving about 7,000 transfusions.

3 After introduction of INTERCEPT the
4 hospital had an accelerating cardiovascular surgery
5 program, and an oncology program, they got a little
6 busier, did almost 800 patients and about 8,000
7 transfusions. When we looked at the days of platelet
8 support per patient, it did not change in these two
9 periods. When we looked at the median number of
10 platelet transfusions and we've also looked at the mean
11 but the median, because it's a highly skewed use of
12 platelets in this diverse population, the median did
13 not change, and the total dose of platelets, the median
14 dose of platelets required to manage these patients did
15 not change.
16 The one thing that I will say is that this
17 center purposefully collected 10 percent more platelets
18 by apheresis during this period of conversion because
19 they wanted to ensure that they could cover processing
20 losses from INTERCEPT. And there are processing losses
21 from INTERCEPT of between 7 and 10 percent. This

1 required their apheresis donors to stay on the machine
2 an extra ten minutes.
3 We specifically looked at hematology
4 patients because they're intensively transfused. We
5 had about 270 patients in each period. The days of
6 platelet support per patient did not change
7 significantly during the two periods of observation.
8 The median number of platelet transfusions per patient
9 remained about the same, as did the total dose of
10 platelets. Obviously, the total dose of platelets
11 required to manage these patients is substantially
12 higher because they are large consumers of platelet
13 components.
14 We've acquired similar data in Alsace,
15 looking at the year 2003, and comparing it to the year
16 2006, after universal adoption of INTERCEPT platelets.
17 Again, this is a regional blood center that supplies
18 all of the blood components for the 2 million
19 inhabitants of the northeastern province in France.
20 The total dose of platelets per patient required -- and
21 these are now mean values -- did not change

1 statistically significantly. I will say that in this
2 region they use about 50 percent pooled buffy coat
3 platelets and 50 percent apheresis platelets.
4 When we looked at people who got both
5 platelets and red cells -- and you can see here that
6 about 80 percent of the patients get both components --
7 we looked at red cell consumption in terms of units per
8 patient and there was no statistically significant
9 change during the period of adoption of the INTERCEPT
10 technology.
11 In terms of resource impact, the way this
12 technology is used is it's used in the same timeframe
13 that serology and nucleic acid testing are accomplished
14 so that the products are available for release on day
15 one; in contrast, bacterial culture when it's used has
16 an inherent delay to increase the sensitivity of the
17 culture methodology and then, of course, requires
18 monitoring out during the period that these cultures
19 are incubating but product is released negative to date
20 sometime on day two in most systems. As I said before,
21 in some European regions product outdates at day five

1 and in other regions it's permitted with pathogen
2 inactivation or bacterial detection to outdate at day
3 seven.
4 So, this technology was very compatible
5 with conventional technology using serology and enabled
6 release of product at the same time. Compared to
7 bacterial detection, it improved the availability in
8 terms of effective shelf-life for these products. And
9 this is demonstrated by data from Mont Godine, Belgium,
10 that looks then at the age of products, the
11 distribution of the age of products with a five-day
12 expiration period before the adoption of INTERCEPT,
13 when they were expiring about 9 percent of their
14 products.
15 After they introduced INTERCEPT and could
16 have a uniform inventory in terms of CMV, because they
17 stopped doing CMV serology so that all of their
18 products were considered as CMV safe and they no longer

19 felt the need to hold onto CMV-negative product, they
20 experienced a small decline in their expiration rate
21 down to about 7.6 percent. When they went to seven-day

1 storage based on the INTERCEPT technology, they could
2 reduce their outdate rate down to 1.2 percent; they had
3 a uniform inventory of gamma-irradiated equivalent
4 product because they replaced gamma-irradiation,
5 replaced CMV serology and they were actually able to
6 begin transfusing more product at a younger age and
7 they didn't have to hang onto as many products to
8 ensure availability through five or seven days without
9 the INTERCEPT technology.
10 So, lastly, I want to conclude then with
11 cost. This is the price in dollars of an INTERCEPT
12 platelet kit including labor and covering use of the
13 device either by rental or purchase. And you see that
14 the full list price is $96. This price obviously
15 varies depending upon the volume that a blood center

16 would utilize.

17 Many of the blood centers are collecting

18 double doses so that they can treat a double dose of

19 part of their production with a single INTERCEPT

20 treatment and so that results in a savings of around

21 $24 when they can do a split. In Europe the centers

1 have replaced CMV serology, bacterial detection and

2 gamma-irradiation, and this is composite data for a

3 number of blood centers but this results in a reduction

4 of a cost for them of about $45.

5 So, instead of spending that money on

6 bacterial detection or gamma irradiation or CMV and in

7 some areas West Nile virus testing, they are using this

8 instead to fund INTERCEPT technology. Because they use

9 InterSol, they are getting recovered donor plasma which

10 they are then using for fresh frozen plasma and that

11 gives them per therapeutic dose of platelets a savings

12 of around $20 or $20 in value. Some centers are now

13 looking at replacement or avoidance of T. cruzi and a
14 test for Dengue. We've based on their information
15 assigned a dollar value for these two tests that would
16 come to around $7.
17 Now, because we are conservative in terms
18 of the way in which these blood centers are using these
19 various strategies to affect their cost impact, we
20 would say that the net cost impact of INTERCEPT
21 implementation is $45 or less. If you add up all of

1 those numbers you could actually get to $96 but we're
2 not saying that everybody is doing this in such a way
3 that they could become completely cost neutral. These
4 numbers do not take into fact the improved availability
5 and in Mont Godine the decrement of wasted-dray
6 (phonetic) from 9 percent to 1 percent paid for half of
7 the INTERCEPT adoption. We also have not included into
8 this any of the economic benefits that might accrue
9 from reduced transfusion reactions.

10 So, in summary, we have data that shows
11 that INTERCEPT inactivates a broad spectrum of
12 pathogens and leukocytes, that it has been implemented
13 in routine use. And I would include in that an
14 epidemic area with an emergent pathogen and I'll tell
15 you that in Alsace now, which is 100 percent INTERCEPT
16 platelets and plasma, production of 30,000 components
17 per year has required the addition of one FTE to their
18 prior staff to accomplish this. We have experience
19 with more than 100,000 transfusions and confirming what
20 we believe is an acceptable safety profile with the
21 reduction in acute transfusion reactions and no adverse

1 impact on other component utilization. So, we believe
2 that this technology in fact has enabled effective
3 management of net cost impact. Thank you for your
4 attention.
5 DR. BRACEY: Thank you, Dr. Corash. That
6 was a great amount of very good information. Questions

7 from the Committee, Dr. Kouides?

8 DR. KOUIDES: Thank you. Dr. Corash, as a

9 hematologist who cares for leukemic patients, I want to

10 echo the fact that this is a four-plus sick population

11 and with adverse events that you had reported in the

12 SPRINT study, I was curious to know, for any of those

13 where there seem to be a higher rate in the study

14 patients, is there any mechanistic explanation? It

15 looks like when I was eyeballing that slide that

16 biliary was slightly increased. Is there anything that

17 suggests perhaps that there is some indeed, you know,

18 toxic effect in any pre-lab, preclinical studies?

19 DR. CORASH: We have not seen any toxicity

20 in preclinical studies. If you give 45 milligrams of

21 Amotosalen per kilo to an animal, you will get acid

1 base in balance and toxicity but we have never seen any

2 of that type of effect. The residual amount of

3 Amotosalen in a transfused component is about 50

4 micrograms. For platelets that gives you a peak
5 immediate posttransfusion level of about one nanogram
6 per mil. It has a half-life of about 40 minutes, so,
7 it's cleared quite rapidly. It's not impacted by
8 either hepatic failure or renal failure because there
9 are multiple ways to clear it and we have not seen
10 anything in preclinical studies that would associate
11 with any of the adverse events that we've, you know,
12 described in the clinical trials.
13 DR. KOUIDES: And I was curious if you
14 applied the same grading system that you mention in the
15 European studies of the investigators stating whether
16 they thought it was related; what was that data in the
17 SPRINT study? Remember, when you showed the European
18 data?
19 DR. CORASH: In the SPRINT study, when
20 investigators had assigned causality there was no
21 difference between the two treatment groups in terms of

1 any of these adverse events.

2 DR. KOUIDES: And in a smaller population

3 of patients who received it, who have factor

4 efficiencies, let's say the Factor XI patient, where

5 there's clearly a need for such a product, the adverse

6 event rates?

7 DR. CORASH: We've seen very low adverse

8 events. Those patients of course at the time of their

9 transfusions unless they had a spontaneous traumatic

10 event had a background incidence of adverse events

11 going on that was extraordinarily low. So, it's been

12 very well-tolerated in that patient population and that

13 included treatment of people with Factor 2 deficiency,

14 5 deficiency, 7 deficiency, 11 deficiency, Protein C,

15 Protein S and two patients with disfibrinogenemia.

16 DR. KOUIDES: And finally in the European

17 data where you concluded that there is a reduction in

18 acute hemolytic reaction, could you clarify, in those

19 studies was the product also leukodepleted like in the

20 SPRINT study?

21 DR. CORASH: Yes. The products in that

1 study have all been leukodepleted because that's the
2 standard in Europe of universal leukodepletion.
3 DR. KOUIDES: So there seems to be then
4 some direct beneficial effect beyond leukodepletion
5 then with the psoralen inactivation?
6 DR. CORASH: There is. And I think it
7 comes from two factors. One is that we are replacing
8 65 percent of allogeneic plasma with a balanced salt
9 solution so there's a lower plasma burden. But, in
10 addition, of course, although you do leukodepletion,
11 there are still residual leukocytes in these platelet
12 components and INTERCEPT completely inhibits cytokine
13 synthesis and antigen presentation by residual
14 leukocytes. In the SPRINT trial we actually showed a
15 significant reduction in HLA alloimmunization due to
16 the inactivation of these residual leukocytes.
17 DR. BRACEY: In the interests of time we're
18 going to have to limit this to one more question. Did
19 you have a question, Dr. Holmberg?
20 DR. HOLMBERG: Dr. Corash, thank you for
21 your presentation. And, one of the concerns that I

1 have is that you were commenting that your
2 postmarketing surveillance really relied heavily on
3 hemovigilance. How would you envision that taking
4 place in this country as we're just now in the infancy
5 of getting a hemovigilance program started?
6 DR. CORASH: So, except for the system in
7 France, which was highly structured, to which we could
8 piggyback onto, we put into place in Europe our own
9 active hemovigilance system. We established a
10 database, which is a centralized facility, and an
11 Internet-based reporting system. Each of the centers
12 that participated in this have been trained by Cerus.
13 We've created protocols, put them into place, gather,
14 collect, analyze the data.
15 This database is available to each of these
16 participating centers to either look at their data as
17 part of a pooled meta-analysis or on an individual
18 basis. This is something which has been very
19 attractive to some of these centers. This month we are

20 converting the Kuwait National Blood Center. They did
21 not have a hemovigilance program. This now gives them

1 a structured hemovigilance program. So Cerus has paid
2 to put this into place and borne these costs. I would
3 expect that in the United States we will do the same if
4 the product is approved.
5 DR. BRACEY: One short question.
6 DR. KUEHNERT: Yeah, I had just one quick
7 clarification. When you looked at the reaction,
8 adverse event rates in the trial that you showed, I
9 just wondered, are you specifically excluding the
10 difference in, say, febrile nonhemolytic reactions?
11 Because you would think you would see that in the
12 control group compared with the treated group. So, did
13 you exclude those?
14 DR. CORASH: No, they're not excluded.
15 They're included. Which, are you referring to SPRINT
16 or are you referring to postmarketing --

17 DR. KUEHNERT: Well, I was referring to
18 SPRINT.
19 DR. CORASH: Yes.
20 DR. KUEHNERT: So, are those not examined?
21 DR. CORASH: No, they are examined.

1 DR. KUEHNERT: Okay.
2 DR. CORASH: In fact, in the SPRINT trial
3 there was a separate case report form that required
4 evaluation for acute transfusion reactions including
5 pretransfusion and posttransfusion temperature and
6 vital signs after each transfusion. And, there were
7 specific criteria that said if you had a temperature
8 elevation of 1 degree centigrade with a shaking chill
9 or 2 degrees centigrade that the patient had to be
10 cultured and the blood component had to be cultured.
11 And those are included in that analysis.
12 DR. KUEHNERT: So when you showed this
13 chart by organ class, those were --

14 DR. CORASH: Yes, yes, yes, those include
15 acute transfusion reactions. In SPRINT the acute
16 transfusion reaction rate, which was statistically
17 significantly less in the INTERCEPT group, was 4
18 percent in the control group and 3 percent in the
19 INTERCEPT group.
20 DR. KUEHNERT: Okay. And do you know what
21 the breakdown was between infectious and noninfectious

1 events that were prevented in the group that was
2 treated?
3 DR. CORASH: We saw in SPRINT --
4 DR. KUEHNERT: Did you look at etiology?
5 DR. CORASH: Yes. In SPRINT we saw no
6 septic transfusion events in either group; however, and
7 most of the transfusion reactions are due to urticaria,
8 (phonetic) some hypotension, some dyspnea, the expected
9 spectrum of acute transfusion reaction events. SPRINT
10 was really too small to look at septic transfusion

11 events. I will say that in the experience that we have
12 in Europe thus far, out of the 28,000 monitored
13 transfusions, we have seen no incidences of
14 transfusion-transmitted sepsis. We have seen one case
15 of TRALI. It was reported just recently in France and
16 it was from an apheresis donor who had a very high
17 titer of HLA antibodies and the recipient developed
18 TRALI from this and was treated and recovered.
19 DR. KUEHNERT: That's very helpful. Thank
20 you.
21 DR. BRACEY: We have to move on. Thank you

1 very much, Dr. Corash. Our next speaker is Dr. Raymond
2 Goodrich. Dr. Goodrich is currently the Chief Science
3 Officer for Navigant Biotechnologies. His
4 responsibilities include oversight of research and
5 development of blood product processing and blood
6 safety. He will speak to us on their system for
7 pathogen reduction. Thank you.

8 DR. GOODRICH: Well, thank you very much.
9 I want to echo the other speakers in saying I'm very
10 pleased with the invitation to come here and give a
11 presentation today on the work that we're doing with
12 technology for pathogen reduction of blood components.
13 I'm going to focus primarily on the work that we've
14 done with the platelet system but I'm also going to try
15 to address some of the questions Dr. Holmberg actually
16 posed. That's something that was of interest to this
17 group in addressing specifically quick questions about
18 the barriers to achieve acceptable levels of
19 transfusion and transplantation safety, how safe is
20 safe, what are the needs, what is or are the pathways
21 to consider in transfusion-transplantation safety.

1 Some of that I think will fall out from the material
2 that I present and a couple of these I'll try to
3 address head on.
4 I think that as we sit here you hear and

5 over the last many years you will have heard about the
6 many benefits that may come as a result of doing
7 pathogen inactivation technologies. That includes
8 inactivation of pathogens, the infectious risk that
9 they pose, reducing or eliminating the infectious
10 complications that are due to transfusion, whether
11 those be from virus, bacteria, or parasites,
12 inactivation of white blood cells -- put those in
13 category of noninfectious risk -- things such as
14 prevention of GVHD, microchimer as an alloimmunization
15 -- could there potentially be effects due to TRIP or
16 other effects that are associated with residual or
17 white cells that are present in donated blood products.
18 I think ultimately everyone is aimed --
19 everyone I think is aimed -- at the goal of having
20 better patient outcomes and that means both benefits to
21 patient health and well-being and ultimately, if it's

1 done correctly, benefits to health economics because if

we prevent complications, we can also prevent the costs that are associated with dealing with those.

And, so, with these fundamentals in place of all these potential benefits that may result from doing pathogen inactivation, I think it absolutely begs the question as to why have we not adopted more rapidly. What are the reasons for slow adoption? And I think that this just reproduces what Harvey Klein showed earlier, the reasons for slow acceptance. And being a very optimistic pessimist, I would like to start with these and try to address in the presentation I give what we have done or the approaches that we have taken to try to address some of the concerns that have been raised both in the past and are currently being raised today about these technologies in general.

Now, in preparing for this, I saw an episode of the Today Show earlier in the week where they had an individual on there -- I don't recall his name -- who was taking a silver compound for treating a skin irritation or affliction that he had and he

1 literally turned blue. I mean blue as a smurf. And
2 they had him on the Today Show and they had a doctor
3 there with him and they were saying that they were very
4 concerned about the fact that his skin had turned blue
5 and what might be happening internally, his organs, his
6 liver, and they were very concerned about this. And
7 they asked him, "Did it at least cure your affliction?"
8 And he said "No, it didn't. It didn't improve my skin
9 condition." And they said, "Well, are you still taking
10 this?" And he said, "Absolutely, every day." And they
11 said, "Why?" And he said, "Well, it's because of the
12 benefits I get from it."
13 So, I think that one of the things that I
14 have seen over the years -- and I have to say my
15 disclosure statement here is that I have been doing
16 this for about 20 years now, and one of the things that
17 I have seen with message in terms of pathogen
18 inactivation or pathogen reduction technologies in
19 general, and I've heard it here today, is that part of
20 the message is, well, we kill everything and that's our
21 goal and we don't hurt -- blank -- and you can fill in

1 the blank, whether it's platelets, plasma, red cells or
2 patients. We don't hurt them too much. And because we
3 want to kill everything, that benefit is worth the risk
4 that we entail by hurting not too much some of these
5 components.
6 And, several years ago now, probably about
7 eight or nine years ago in total, we decided, my
8 colleagues and I decided to look at this in a very
9 different way, and that is, can we look at this from
10 the standpoint of taking a position and taking an
11 approach in which our goal and of the vision for this
12 product, which we call Mirasol, is to improve product
13 quality, safety and performance.
14 And, that really is the approach that we've
15 attempted to take, and I guess based on the results
16 that we have obtained the community needs to be the
17 judge as to whether or not we've succeeded in that or
18 not and I'll talk a little bit more about what we've
19 done. How we went about taking this approach was to
20 look at types of agents that might be used in the

21 photochemical application to treat blood products, to

1 inactivate pathogens and white cells that may be
2 present in these blood products. And I was very
3 intrigued at the time of a lot of the literature and
4 with a lot of experience with the negative effects of
5 other compounds and things that I'd evaluated in my
6 career, that the properties that were described for
7 this particular molecule, Riboflavin, or vitamin B2,
8 the fact that it's a naturally occurring agent, the
9 fact that there is a lot known that is known about its
10 toxicology, the fact that it was known to be able to be
11 carry out nucleic acid chemistry in a specific way, the
12 fact that it was very well-characterized in many ways
13 made it very appealing.
14 And, to me it was the type of molecule that
15 as a chemist I'd spent many years trying to design into
16 new synthetic agents that would have properties that
17 would make them appealing and potentially worthwhile to

18 consider as a pathogen inactivation or pathogen
19 reduction agent. And, so, we decided many years ago to
20 pursue this and to evaluate its capabilities of
21 carrying out these processes.

1 This is an overview of the program, the
2 platelet program, as we have conducted it. So, with
3 this very simple concept we started off -- this was
4 back in 1998, '99 -- we spent a lot of time on
5 prototype design and in vitro studies. In a lot of
6 ways you will see the program as I describe it here as
7 a program that we've generally followed of going from
8 the in vitro to the in vivo with initially radiolabel
9 recovery and survival studies to eventually using the
10 product in clinical settings with randomized
11 prospective clinical trials to evaluate the performance
12 of the product for specific endpoints, which I'll
13 describe in more detail later.
14 We did an initial study in an exploratory

15 trial that was done in South Africa -- that study is
16 published -- in which we looked at correlations between
17 the in vitro and in vivo results and I think we found
18 some good correlations for this particular system.
19 That helped us to predict and to set conditions that we
20 wanted to use for a subsequent trial, which we did in
21 the United States under an IDE, and that was done at

1 two sites. The data from that study is also published,
2 has been presented.
3 We then used that information to submit for
4 a clinical study which we did in Europe. It had a
5 minimum enrollment target of 100 patients. It was done
6 on five sites. Actually, all of the sites were in
7 France. That study was completed after 22 months. It
8 was completed late last year and we did submit the data
9 and the product has been CE-marked and is now available
10 in the market in Europe. During this period of time we
11 have had a program going on with plasma, FFP. We are

12 expecting to have CE-mark for that product this year.
13 And we also initiated a program with red cells and
14 whole blood. I'm going to talk to you a little bit
15 about that later. To me that's the ultimate goal here,
16 to be able to treat all three blood components in a
17 practical and efficient way. And, so, I will tell you
18 a little bit about that program. It's in its infancy,
19 in its early stages, but it's beginning to grow.
20 So, I'm going to start here with some of
21 the concerns which I have summarized into four

1 categories, from the same general line along which the
2 Canadian Consensus Conference summarized with the six
3 points that were mentioned in that document. Reduction
4 in efficacy, difficult processes to implement in blood
5 centers, with concerns over product handling both
6 before and after treatment; toxicity and
7 neoantigenicity in the short and the long-term, people
8 being exposed over prolonged periods of time.

9 Reduction in efficacy -- I heard that question asked
10 earlier -- is there need to transfuse more platelets,
11 is there need to transfuse more red cells, are there
12 increased frequencies in transfusion, is there
13 increased product loss as a result of doing these
14 processes?
15 Then the risk-benefit and
16 cost-effectiveness and then, quite frankly, why do we
17 need this given that the safety of the blood supply is
18 where it is today and, really, where is the benefit? I
19 understand the hypothetical benefit in case there's
20 another HIV that comes along but where is the benefit
21 as it exists today in treating patients where that

1 doesn't exist, there isn't a new emerging HIV today.
2 This is the process that we've come up
3 with. And the study was done in France using both
4 buffy coat and single donor platelets. Our in vitro
5 work has been done with both single donor and buffy

6 coat platelets. Much of that work has been published
7 over the last several years. It involves using a
8 collection -- we don't specify the collection platform
9 that's used. As long as the product, whether it's
10 buffy coat, manual, whether it comes from a Baxter, a
11 Gambro, or Hemanetics device, as long as it fits the
12 parameters and the specifications for product input of
13 volume cell concentrations, et cetera, it can be used
14 in this process.
15 Transfer to an illumination storage bag,
16 the Riboflavin solution is sterile. Docked onto that
17 is a 35 mil solution of Riboflavin, is added to that.
18 That covers a product volume range from 170 up to 360
19 mils, incoming product. And then the product is
20 exposed to light with an illuminator for six to ten
21 minutes. Light dose is determined by the size of the

1 product. We dose on an energy joule per mil basis and
2 that is monitored, recorded throughout the process.

3 We've also put in place process controlling
4 documentation systems that allow people to do this in a
5 blood center using documentation controls that are
6 required from a quality control standpoint and a
7 traceability standpoint for these products. And, this
8 system manager approach allows you to network several
9 of these units together that would be required in order
10 to fully convert to this process if that were desired
11 by the center.
12 To give you an idea of performance with
13 pathogens, we actually looked at this list that was put
14 together. I'm not sure what the disposition of this
15 list was but I thought it was really an excellent
16 document. It was put together I think by a group of
17 AABB and ISBT where they looked at and tried to
18 quantify the risks that were associated with certain
19 types of agents and then categorized them according to
20 where benefit was high and action was favored or the
21 concern was high and action was favored. So, the

1 things that appear in this upper quadrant here of
2 course are those that you might say have the greatest
3 amount of interest relative to the risks that they may
4 propose. And this was from these committees from both
5 ISBT and AABB.
6 So, what we've tried to do is to focus our
7 work in those areas. We've looked at these agents.
8 The agents in green are agents where we have done
9 studies with these agents and have evaluated the
10 performance of the technology in that regard. I'll
11 show you some of the specific data. The item in blue,
12 the light blue up there for variant CJD or new variant
13 CJD is just to highlight the fact that what was
14 mentioned earlier, these technologies and certainly our
15 technology does not address that. We have done some
16 studies with a separate technology that involves a cell
17 washing system which looked very encouraging but that's
18 not a topic for discussion today.
19 We've looked at a variety of enveloped and
20 nonenveloped viruses. The performance of this
21 technology with these agents varies considerably from

1 agent to agent. But in general, there's a three to
2 greater than six log inactivation looking at both
3 enveloped and nonenveloped viruses. We used a variety
4 of model viruses or actual human pathogens where those
5 model systems were available.
6 The methodology for how we've done these
7 studies is described in the Transfusion article, as
8 well as some of this data by Patrick Ruan, et. al. It
9 was published in Transfusion in 2004. In general we've
10 tried to apply the methodologies in the systems that
11 are described in CPMP guidelines, which are used for
12 validation of virus inactivation procedures for other
13 components.
14 We have looked at a wide variety of
15 bacteria, gram-positive and gram-negative bacteria.
16 We've done studies both in a high-titer format to look
17 at the total capability of inactivation with these
18 systems as well as low-titer formats where we've done
19 direct head-to-head comparisons with agents that are
20 reported in hemovigilance studies. We've now expanded
21 this list, actually, in a publication which I'm about

1 ready to submit, to cover 22 different strains of
2 bacteria that have been identified in hemovigilance
3 studies such as the SHOT report, as bacteria species
4 that have been associated with septic transfusion
5 events.
6 And I believe the performance is very
7 robust. As was mentioned earlier, I do not believe
8 that this technology will be effective against spores
9 but that's different than saying that it's not
10 effective against spore-forming bacteria. These agents
11 do go into a vegetative state and I believe when
12 they're in that form they are susceptible to these
13 treatments.
14 We've also done a large body of work with
15 parasites. Again, much of this work is published. A
16 lot of this work was done in collaboration with people
17 like David Leiby's group at the American Red Cross.
18 Some of that data with babesia will be published this

19 year, presented in abstract form only last year. Dr.
20 Lisa Cardo's group at Walter Reed Army Institute of
21 Research did work with leishmoniasis as well as with T.

1 cruzi. We've done this work in platelets and plasma.
2 In some cases we've done work with red cells as well.
3 There are additional studies which are funded by a
4 Department of Defense grant which we will be conducting
5 this year. We've done work with malaria, which was
6 done both at Walter Reed and most recently Dr. Jim
7 Sullivan's group at the Centers for Disease Control.
8 And again all of these studies were sponsored under DOD
9 contract. Publications are available or will be
10 shortly available in that work.
11 And again when these levels say "greater
12 than," we have been able to inactivate these agents to
13 the limits of detection. In the case of the babesia
14 and the Orencia, those are limits of detection as
15 measured by actual parasite transmission studies in

16 animal models, where one parasite, one viable parasite
17 would have been able to induce disease.
18 I mentioned that the process is meant to
19 apply for reduction in pathogen load and inactivation
20 in white blood cells. We've done a series of studies
21 looking at the ability of this technology to inactivate

1 white blood cells, that include looking at in vitro
2 assays, mixed lymphocyte reactions, response to
3 anti-CD3/CD28, stimulation of allogeneic responder
4 cells, activation of cells used in response to PMA, and
5 the general conclusion has been, which is published
6 data in Transfusion, that the treatment has inhibited
7 responses in all of these assays.
8 No evidence of changes in cell phenotype,
9 prevention of cytokine expression, proliferation
10 response to mitogen or allogeneic stimulator cells in a
11 mixed lymphocyte reaction is gone. No engraftment in a
12 recipient xenotransplant model, no induction of GVHD in

13 a xenotransplant model -- that data is published -- and
14 increased DNA damage as measured by molecular analysis
15 and PCR analysis. These studies have also now recently
16 been completed with the whole blood including the
17 xenotransplant model with absolutely identical results.
18 We'll be reporting those this year.
19 We have also looked specifically at the
20 ability of this process to prevent alloimmunization.
21 We've used animal models as well as in vitro models.

1 The most recent publication is an article that appeared
2 in Transplantation at the end of last year where we
3 looked at the ability of this process to inactivate
4 white cells in platelet products, in a rat model, and
5 then looked subsequently at the effect both on
6 production of allo-antibodies as well as rejection of
7 heart transplant material that went from a donor to
8 recipient animal.
9 There are ongoing studies this year which

10 follow-up on this. There's a work with Dr. Sherrill
11 Slichter's group at Puget Sound Blood Center looking at
12 prevention of platelet alloimmunization. That's in a
13 dog model. We are doing a study in collaboration with
14 MPI Research in Michigan looking at prevention of
15 transfusion-related immune modulation and
16 susceptibility in an animal model to infection after
17 challenge with multiple transfusions. Neutrophil
18 priming, there's work going on with Dr. Dan Ambruso's
19 group -- these are both in vitro and in vivo
20 evaluations -- and Dr. Lisa Cardo's group at Walter
21 Reed Army Institute of Research, and then some work

1 looking at microchimerism and antigen presentation with
2 Dr. Philip Norris at Blood Systems Research, Inc., and
3 we hope to be able to report that data as we have in
4 the past as it becomes available and published.
5 This is not meant to be an eye test. It
6 really is just a listing of the various clinical

7 studies that we did up unto the point of the design
8 validation trial, which was just completed in France,
9 and to show you that our general approach has been to
10 do, as these are phased in with larger exposure to
11 subjects and with broader parameters of exposure to
12 subjects, we phase in different toxicology programs
13 which support that.
14 And we've looked at things such as
15 mutagenicity, genotoxicity. We've looked at subchronic
16 exposure, we've looked at, in standardized toxicology
17 testing. This data will be published in the April
18 issue, I believe, of Transfusion Medicine Reviews.
19 It's a 22-page article. I don't have the preprints on
20 it yet but they will be available shortly, which
21 details all of the results from these toxicology

1 evaluations that were done in this program and
2 essentially the answer that we obtained repeatedly was
3 no observations of adverse effects or toxicities

4 associated with the product despite multiples of
5 infusions of the product at dose levels much higher,
6 much higher than what you would anticipate seeing in
7 routine clinical practice.
8 I'm going to give you a brief summary of
9 the data from an Interim Analysis Report, from a study
10 that was done in France, just completed. We did
11 perform an interim analysis that was done by an
12 Independent Data Monitoring Committee, a group of
13 individuals who were sent from the company. Dr. Jeff
14 McCullogh, who I know is here, was the chairman of that
15 committee. They worked with their own statistician in
16 analyzing all data from the study. We also had an
17 independent data safety monitoring board. Professor
18 Sean Daniel Tiso, Red Cross, was the chairman of that
19 group. They were responsible for adjudicating all
20 adverse and serious adverse events. Those were all
21 done in a totally blinded fashion. And, their report

1 was a part of the report that went into this interim
2 analysis as well.
3 We looked at platelet corrected count
4 increment at one hour measured 30 to 90 minutes after
5 transfusion, during a 28-day treatment period. We had
6 an null (phonetic) hypothesis, a noninferiority
7 analysis, had a 97.5 percent confidence limit,
8 one-sided, and statistical analysis on the data looking
9 at this particular endpoint. We also looked at the
10 count increment at 24 hours and because of the
11 questions that had been raised previously we also
12 looked at things like number of days between each
13 platelet transfusion, number of transfusions per
14 subject, number of platelets used, the frequency of
15 refractory platelet transfusions, which was defined as
16 at least two consecutive transfusions having a CCI at
17 one hour less than 5,000.
18 In the case of refractory transfusions we
19 looked specifically for the potential of neoantigens
20 being present and we assayed that in a specific assay
21 for neoantigenicity. We also looked at the number of

1 red blood cell transfusions, the impact of serious
2 adverse events related to these transfusions, any
3 adverse events related to the platelet transfusions,
4 the occurrence of bleeding episodes and the degree
5 evaluated by the WHO scale for classification of
6 bleeding incidents and we also looked at the
7 longitudinal regression for patients receiving more
8 than eight transfusions during 28 days of treatment.
9 So, I want to go back and present this data
10 in the context of the information that we have so far,
11 which, as I say, it's interim data and it's a small
12 number of subjects. So, I want to, however, talk about
13 it in a context of what we know so far, and how does
14 that point relative to being able to address some of
15 the concerns with pathogen reduction technologies.
16 I'll refresh your memory from the Canadian Consensus
17 Conference, and in specific talking about these
18 particular issues as they relate mostly to the product.
19 So, what we've seen so far overall in
20 adverse events for Mirasol, a reduction of about 10
21 percent overall compared to those in patients with

1 reference platelets. I should mention that our process
2 does not require additive solution so these products
3 are collected in plasma and they are treated and
4 transfused in plasma. We are working on a process that
5 will allow people to use an additive solution of their
6 choice if they prefer to do that and we expect to have
7 that available again under a CE-mark in 2008. But, for
8 this study we also compared products directly against
9 untreated products that were in plasma. That was the
10 standard control product that was used, whether it was
11 buffy coat or apheresis at each of the centers so we're
12 comparing apples to apples.
13 We saw a reduction in posttransfusion
14 infections. Now, that's not due to the product being
15 contaminated, just infection infestations, one of the
16 categories in that system organ classification, in
17 patients after, that was the largest difference that we
18 observed, I think was about 45 percent of the patients
19 in the untreated group had these events compared to 28

20 percent in the treated group.

21 There was a two to one ratio in HLA

1 alloimmunization which favored Mirasol. All patients
2 were required to be HLA negative prior to entry into
3 the study. There was no drop in CCI number as
4 transfusion numbers increased. I'll show you that in
5 more detail. There were increased days between
6 transfusion as transfusion numbers increase relative to
7 the control untreated product. There was no evidence
8 of neoantigen formation and no evidence of photoproduct
9 accumulation. The behavior that was observed, we
10 assayed every product and every patient after every
11 transfusion for the levels of photoproduct and for
12 Riboflavin that were present after transfusion at 1
13 hour, 24 hours, and 28 days. And there is clearly a
14 long-term history which this data appears to agree with
15 very well on the human exposure to these agents without
16 ill effect.

17 Blood product utilization -- and this is
18 addressing some of those specific points -- one, three
19 and five in the Canadian Consensus Conference -- we
20 actually saw with the Mirasol-treated platelets a delta
21 of zero between the patients who received

1 Mirasol-treated platelets and platelet units per
2 patient compared to the control. In red blood cell
3 utilization we actually saw fewer red cell units used
4 in the Mirasol group, 2.6 units per patient compared to
5 3.3 units per patient. I should mention none of these
6 values reached statistically significant levels. We
7 did not expect that for the interim analysis because
8 there was an insufficient number of subjects.
9 If you look at the total platelet dose
10 which was given to the patients, comparing the Mirasol
11 group with the treated group, there was actually less
12 than a 3 percent difference in total dose that was
13 given to each of the patients. That actually has

14 agreed with some of the routine use trials which we
15 have implemented since C-Mark in five different centers
16 in Europe. We're actually seeing on average about a
17 1.7 percent difference between what's collected and
18 what's actually given to the patient at the end of the
19 storage period for the platelets. So, there are very
20 little losses of the product as a result of doing this
21 treatment.

1 If you look at the data in terms of going
2 from the lowest to the highest CCI value, in
3 patients -- this is for all patients in the Mirasol
4 group and in the reference group -- basically these two
5 lines overlap with one another. There were no
6 significant difference in the behavior of the platelet
7 products that were observed either treated with Mirasol
8 or untreated with regard to the CCIs that were observed
9 in the patients between the treated and the control
10 group. This is normalizing, of course, for differences

11 in patient variables that might occur.

12 If you look at it, however, not doing that,

13 just looking at total number of platelets, in the

14 Mirasol group these subjects received 132 platelet

15 products. In the reference group they received 133.

16 The mean number of platelets was 5.5 in the Mirasol

17 group and 5.3 per patient in the reference group. The

18 median number at a 95 percent confidence interval was

19 identical at 4. The mean number of transfusion per

20 days of platelet support was 0.5 and that number was

21 identical in the reference group. For transfusions one

1 through eight we observed that the frequency of

2 transfusion, number of days between transfusion for

3 both the Mirasol and the reference group were

4 approximately 2.4 and 2.8 days respectively. Very

5 interestingly, we observed that that number remained

6 constant for patients who received platelets in the

7 Mirasol group and it decreased, so frequency of

8 transfusion actually increased for patients who were
9 receiving the untreated product down to 1.2 days in the
10 control group. It did not reach statistical
11 significance at the interim analysis. We're looking
12 very carefully at the final analysis, don't expect it
13 to be disappointing in that regard.
14 Cumulative number of days between
15 transfusions one to eight was 15.8 versus 14.3 in the
16 reference group. To give you an idea about this drop
17 that occurs in CI or CCI as well as the increase in the
18 frequency of transfusion as the transfusion number
19 increases, this actual data came from a publication by
20 Sherrill Schlicter looking at the TRAP study. This is
21 for untreated products, leukoreduced products. And

1 this effect has been known for some time. As you
2 increase transfusion number, you see a drop in CCI and
3 you also see an increase in the frequency of
4 transfusion. Why that occurs, I'm not exactly certain

5 that people know. I have asked.

6 We analyzed this data and as I mentioned if

7 you look at the values for the control group we see

8 that drop. This is one thing out of all the data that

9 we analyzed in this particular piece that did reach

10 statistical significance at a P value of less than

11 0.0001, and for the Mirasol group that number basically

12 stayed the same. The 1-hour CCI showed the greatest

13 delta and we did see an 8 percent lower CCI at 1 hour

14 in the Mirasol group compared to the untreated group;

15 that was not statistically significant. That actually

16 crossed over at about four transfusions where actually

17 we start seeing the Mirasol-treated products are

18 demonstrating better CCIs in patients compared to those

19 receiving similar numbers who were in the reference

20 group.

21 We looked specifically for refractoriness

1 and alloimmunization, again very small numbers but in

2 general no statistically significant differences.
3 There was a difference of about twofold, which I
4 believe will hold for the final analysis as well with
5 the last group of patients and the number of patients
6 who are reporting to become HLA positive during the
7 course of therapy. These patients also received
8 off-protocol transfusions. If you add up the
9 off-protocol transfusions for both Mirasol and for the
10 treated group, there was about a 20 percent difference
11 in favor of Mirasol, fewer transfusions if you count
12 both on and off protocol compared to those who received
13 the control products.
14 On the neoantigenicity data we collected,
15 as I mentioned, data on every single transfusion.
16 Those were analyzed by an independent laboratory. At
17 the time of the interim analysis we had 20 to I think
18 maybe 22 patients analyzed. There was no evidence of
19 neoantigen formation in that separate assay. We also
20 looked at photo-product, as I mentioned.
21 We have done PK studies with C-14 labeled

1 Riboflavin and its photoproducts in animals. Those
2 studies had been done previously for Riboflavin in
3 humans. Our data supported those findings, both our
4 own and the prior data that's been reported previously.
5 There was less than 50 nanomolar concentrations of
6 Riboflavin or lumichrome, the major photoproduct of
7 Riboflavin present at one hour posttransfusion. There
8 was no evidence of accumulation of Riboflavin or
9 photoproducts, that was consistent with the PK data and
10 clearance data obtained in the animal models. The
11 levels of photoconversion that we observed in every
12 single product observed from the test sites was
13 consistent with our prior historical experience and
14 indicated they were performing the process correctly.
15 The overall conclusions from the interim
16 assessment was that the treated platelets were safe and
17 efficacious as assessed to date. There were no
18 statistically or clinically significant differences
19 between the treated platelets and untreated platelet
20 concentrates found in the primary or secondary
21 endpoints and the study also demonstrated the

1 feasibility of providing these treated platelets in a
2 real-world setting to patients requiring multiple
3 platelet transfusions in a short period of time.
4 So, what do we know again going back to
5 these risk-benefit and cost-effectiveness questions?
6 The technology has a broad -- but I will say not
7 perfect. I don't believe any of these technologies are
8 perfect. I think the point was made earlier that if
9 you're considering trading off risk and benefit you
10 have to make sure that if you're saying it's 100
11 percent risk elimination that it really is. I don't
12 know any technology known to mankind that's 100 percent
13 effective. So, I think that these reduce the risks
14 that are associated with pathogens whether they're
15 parasites, bacteria or viruses but they may not
16 eliminate them.
17 It has the ability to inactivate white
18 blood cells. This may offer the potential to address
19 concerns of transfusion of allogeneic blood other than
20 just dealing with rare disease transmission events and

21 I really hope that this may be an area where we can

1 show a clinically proven benefit by designing
2 appropriate studies to do this and we're pursuing that
3 route.
4 Risks, in terms of risk versus benefit,
5 cost versus benefit, I think it can make sense but in
6 order for it to make sense you have to demonstrate the
7 benefit and the risk has to be low. I'm not a
8 mathematician but I think that if concern is directly
9 equal to the risk divided by the benefit, if the
10 benefit is zero, that number is infinite. And so I
11 think that the obligation has to be there to be able to
12 demonstrate some type of benefit associated with that.
13 And, clearly when benefit is demonstrated, the cost has
14 to been reasonable.
15 I saw this cartoon in the New Yorker and I
16 thought the key to understanding, it says, "We need a
17 leader who is not afraid to dream incremental dreams."

18 And obviously I think that in order to really
19 understand this you have to know what the size of the
20 increment is. Sometimes certain steps are easier to
21 take than others.

1 I wanted to tell you about our program of
2 product vigilance that we've initiated. It's very
3 similar to what you heard earlier by Dr. Corash. A lot
4 of these cases, we've gone in, we've set up our own
5 electronic data capture system, we've developed
6 protocols, so in the centers where we're now rolling
7 this out in routine we have a system where they can
8 report data into this electronic database system as
9 they enroll patients into the study. Our goal is to
10 collect data as we go, as we roll this out to more and
11 more centers throughout Europe. And Europe, Middle
12 East and Africa, the product actually is being used in
13 routine use in all of those geographies right now as we
14 speak. And, we are collecting that data, entering that

15 data. It will be used in routine reporting and
16 frequent reporting of results as we obtain them,
17 includes reporting of adverse events, serious adverse
18 events. It also includes reporting capabilities in
19 terms of platelet utilization, red cell utilization,
20 frequency of transfusions, frequency of
21 alloimmunization, et cetera. It's tailored according

1 to the ability of the center to be able to collect that
2 particular type of data.
3 And, finally, I really want to mention
4 something that's last but definitely not by least.
5 There was one of the comments that I took from the
6 Canadian Consensus Conference statement, one of the
7 concerns being the absence -- and I heard it here today
8 -- of any single method to treat whole blood or all
9 components. And the statement of course coming from
10 the group was that this should not be a reason for not
11 proceeding but I think deep in our hearts and our minds

12 it has been and it will probably continue to be.

13 We are very fortunate to be funded by the

14 Department of Defense because of some specific needs

15 that our troops in the fields have for whole blood and

16 for transfusion, to develop a process that would be

17 applicable in that particular setting, in the field

18 setting for treating whole blood products. And, so,

19 we've spent the last several years doing that. And I'm

20 very pleased to tell you that we've submitted an IDE

21 for whole blood treatment -- and this actually involves

1 treating whole blood and then separating it into

2 components. The initial study will involve following

3 the path I mentioned before -- we've done in vitro

4 studies, we will do radiolabel recovery and survival

5 studies -- treating, storing that product for 42 days,

6 the red cell component, looking at in vitro and

7 radiolable recovery and survival.

8 There will be many phases to this clinical

9 work as we move ahead but this is a start. I think
10 it's also an indication of at least the willingness of
11 the FDA and other groups to look at this technology and
12 evaluate it and allow the evaluation of it here in the
13 United States. We're very excited about this and
14 looking forward to initiating this work and being able
15 to report the results.
16 Finally, I want to come back to one
17 specific question and that is, how safe is safe? I
18 think that's a very good question but I think it
19 depends upon the time in which you ask that question.
20 If you asked me or a lot of other people, who are
21 probably even more knowledgeable, whether or not the

1 levies in New Orleans were adequate and provided
2 adequate protection against hurricanes coming into that
3 region, they would have probably told you it was, yes,
4 before Katrina but not after. If you asked people
5 about whether or not our screening processes at

6 airports were adequate in providing safety to the
7 airline passengers, they would have probably told you
8 yes, before 9/11 and not afterwards.
9 I think that the answer to the question how
10 safe is safe, is, it's safe until it's not, proven not
11 to be. And so the question perhaps should be, can we
12 and should we do better? And that's going to be
13 dependent upon what we in industry, from at least from
14 my perspective, are able to deliver and what the
15 evaluations are again of what the benefits may be from
16 these technologies. And we're certainly willing, eager
17 and able, I think, to have a dialogue about that. So,
18 thank you very much.
19 DR. BRACEY: Thank you. In the interests
20 of time, I'll have to limit the questions to one or
21 two, because we do have two other presenters. Dr.

1 Triulzi?
2 DR. TRIULZI: A quick question. The

3 "Miracle study" -- I like the name.

4 DR. GOODRICH: Sure.

5 DR. TRIULZI: It has a laboratory primary

6 endpoint, a CCI endpoint; is it anticipated that you

7 will need to do a follow-up study with a hemostatic

8 endpoint?

9 DR. GOODRICH: I think clearly for the

10 United States we have heard that many times from the

11 FDA, that a hemostatic endpoint would be required. I

12 think we want to have a dialogue and will have dialogue

13 as we move forward with that. For Europe that was not

14 a requirement. We measured a hemostatic endpoint but

15 it was not the primary endpoint for that study. And I

16 think that was very similar to the SPRITE trial that

17 was done in Europe where those parameters were clearly

18 measured but those were not primary endpoint. And it

19 may vary. When I say Europe, we tend to think of

20 Europe as one country. It clearly is not. There will

21 be different requirements in different geographies so

1 that requires discussions with places like the
2 Paul-Ehrlich Institute, with the health authorities in
3 France, AFSSAPS, as well as with health authorities in
4 the UK.
5 DR. TRIULZI: Yeah, I asked that just to
6 get a sense for how far away it might be before a
7 product could be available in the U.S.
8 DR. GOODRICH: Right. Sure.
9 DR. BRACEY: Thank you. We better move on
10 to our next speaker. Our next speaker is Marc Maltas.
11 Marc Maltas is the International Business Manager for
12 Intensive Care and Emergency Medicine at Octapharma.
13 He will present a brief overview of Octaplas.
14 DR. MALTAS: Mr. Chairman, ladies and
15 gentlemen, thank you for inviting Octapharma. I will
16 go or try to go very fast in summarizing 15 years of
17 experience of Octaplas in Europe. First of all, and
18 because FDA is here we're speaking about medicine
19 product, I would like to disclose that Octaplas is not
20 yet licensed in the U.S., and that I am or I was this
21 morning still a full-time employee at Octapharma. I

1 have to be after the talk.

2 As I said, Octaplas is a biopharmaceutical

3 plasma so it's not a CE device, it's as such a

4 medicinal product and it's not only under hemovigilance

5 rules, it's also under pharmacovigilance rules. So, it

6 has to go through the whole regulatory process and that

7 means that we are obliged to all the most stringent

8 controls and batch releases for each batch of product

9 that's put on the market.

10 Those are the countries where the product

11 is actually distributed. Some of them like Norway and

12 Finland are using Octaplas as the sole source of plasma

13 for the whole country and for all the indications where

14 Octaplas is like plasma.

15 And then we have all the countries like,

16 for example, Austria, who has approximately 75 percent

17 of plasma in the countries, Octaplas, in Portugal where

18 it's about 100 percent. In the United Kingdom, in 2006

19 the National Health Service issued a recommendation of

20 using Octaplas to treat specific ETTP patients.

21 Now, if we go back 16, 17, 19 years when

1 Octapharma had the idea of developing this product, we
2 have to go through the rationale of Octaplas, and as
3 you will see in this slide, the rationale was not only
4 to get a product that was somehow virally inactivated
5 against HIV, HBV and HEV, but of course we're looking
6 to all those noninfectious adverse events that you had
7 with the infusion of plasma.
8 So, we thought that, for example, pooling,
9 which has been mentioned several times as something
10 negative, would be actually something very positive
11 when you think about what happens with the high-titer
12 HLA unit that comes into the pool. Of course, as you
13 will see during the presentation we also took into
14 account sepsis although we recognize that sepsis is not
15 one of the main concerns when you infuse plasma and is
16 more related to infusion of platelets.
17 How we achieved all of these things is,
18 well, basically we used the solvent-detergent method,

19 which has been established as a very robust method.
20 There's a complete removal of cells and cell debris.
21 This is not a local reduction filter as we will see.

1 And then we have optimized integration of donations
2 just to account for a good level of coagulation factors
3 practice and for a good level of immunoglobulins to
4 neutralize those HEV and Parvovirus, B19 possible virus
5 particles, the manufacturing process to get the most
6 out of the plasma, and, a standardized filling of 200
7 mil per bag and of course a sterile filtration at 4.2
8 microns.
9 Now, the indications for Octaplas are
10 exactly the same as those indications for FFP and, as
11 Dr. Heiden already said, we have some warnings for SPC
12 regarding protein S and plasma inhibitor content in the
13 product.
14 Now, when looking at safety of
15 plasma-derived products we can look at safety between

16 infectious adverse events, transmission of pathogen
17 viruses, bacteria prions. I'm going to speak a little
18 bit about enveloped viruses safety. This is a
19 solvent-detergent product. As we know,
20 solvent-detergent destroys the lipid membrane that
21 involves the virus, so that the capability of the virus

1 to infect the cells are gone. Those are the
2 leukoreductions that we have for enveloped viruses, and
3 as you will see it's some more or less in the same
4 range as all the other plasma-derivative products.
5 This is an animal study we did with PRV and
6 CP Vero cells where you see before heat treatment there
7 was destruction of the cells and after heat treatment
8 there's no infectivity involved. And I think most
9 important is to look at the robustness of this step
10 where you will see that the total inactivation to below
11 the detection limits occurs within two minutes of the
12 process. So, 99 percent of the time that the

13 solvent-detergent is in the pool accounts for safety
14 margin.
15 Now, this means that potential
16 life-threatening viruses like West Nile virus, SARS,
17 chikungunya, are all enveloped viruses and would thus
18 be inactivated with the SD method. And if we speak
19 about emerging pathogens and referring to some slides
20 we have seen before, all the emerging pathogens that we
21 have seen were enveloped viruses, not nonenveloped

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1 viruses and this maybe have has to do -- and a
2 virologist would be a better specialist to speak about
3 it but this has to do with mechanisms that envelope
4 and nonenveloped viruses use to penetrate cells and to
5 impact cells. It's much easier for enveloped viruses
6 to penetrate a cell than for nonenveloped viruses where
7 they need protein carriers through membrane to impact
8 cells.
9 Regarding immunoneutralization of

10 nonenveloped viruses, we have experience on two main
11 concerned viruses, it's HAV and Parvovirus P19;
12 however, we have a trial, different kind of viruses in
13 laboratory scale and in the plasma pool. By the way,
14 there was a question about the plasma pool size for
15 Octaplas and this is 650 to 1150 units per batch
16 depending on the content of the plasma that we receive.
17 So, basically we are pooling together each batch,
18 around 380 liters of plasma. Number of donations will
19 depend on how much plasma we get in each unit. As you
20 see, the immunoneutralization for all these
21 nonenveloped viruses show very good reduction logs;

1 however, we have to be aware that the reduction or
2 inactivation by naturalization of a virus has to do
3 with the virus load that we have in the unit, has to do
4 with the antibody content in the plasma and the viral
5 container.
6 So, we have some release specifications for

7 those two viruses. For hepatitis A we have a minimum
8 amount of IgG, that was said by Dr. Heiden to be one
9 international unit ML. I put down the figure we have
10 abroad for Europe in the "MRP" countries, this is two
11 international units ML, and of course the pool has to
12 be tested negative by NAT testing. For Parvovirus B19
13 we have a put-off limit on the NAT testing of four logs
14 and this is because Parvovirus B19 is really present in
15 huge amounts in many plasma units. So the off-limit
16 has to be a little bit higher; if not, we wouldn't have
17 plasma.
18 On the other hand and to ensure safety we
19 have to have a much higher titer of IgG against
20 Parvovirus in the plasma pool. In this case, it's more
21 than 20 units per ML. Regarding sterile filtration,

1 Octaplas is sterile filtered in two filtration steps,
2 4.45 microns, 4.20 microns, which is considered in all
3 labs as sterile filtration. It's filled in a filling

4 line under GMP procedures on the whole manufacturing
5 procedure. Bags are sealed in an outer wrap avoiding
6 port contamination during the thawing of plasma.
7 You're using water bags or other systems and then of
8 course each batch undergoes pyrogens testing.
9 Regarding the possible pathogen load in
10 plasma, these are the figures that we are using
11 regarding HCV, Parvovirus B19 and variant
12 Creutzfeldt-Jakob's disease. For those of you that are
13 interested in knowing how we come with those figures,
14 can discuss later. I mean, it's taking into account
15 all the figures that we have seen on the possibility to
16 find prions or viruses in one plasma unit.
17 Now, I would like you to see that the
18 quantity of prion particles in plasma regarding variant
19 Creutzfeldt-Jakob's disease is much less than regarding
20 any virus that we know. So, that means that we
21 shouldn't expect the same logarithms of inactivation of

prions when we think about prions than we are used to see with viruses.

Now, in order to know what happens with prions in Octaplas we conducted several experiments. The first thing that we have to bear in mind is that Octaplas is filtered with reduction filters. It's not the same leukoreduction filters that blockers are using. There are some specifications on how many leukocytes can remain in plasma after leukoreduction. In the case of Octaplas this limit is zero. There are no cells and there's no cell debris because of using those filters. We did some tests on the availability of the filters that we were using, with a pool of one micron to filter into A-cells, and we saw that after passing through those filters there was no remaining cell in the product. So what we did is we used the cells which were infected with cells of the hamster, , scrapie, we did three arms. One arm was containing around 600,000 cells, the other arm was containing much less cells and the third study arm was containing at least 3 million, over 3 million cells. And the FFP

1 specification, as I said, is around 100,000 to 500,000
2 cells.
3 What we did was a Western blot and we
4 compared before filtration and after filtration the
5 amount of cells or cellbound adapted hamster scrapie
6 that were present and we found by filtration a
7 reduction log of one. This is for the cellbound
8 hamster-adapted Scrapie. Then we also looked at
9 cell-free hamster-adapted scrapie, what happens during
10 the sterile filtration and here we saw there was a
11 difference in about 1.5 logs before filtration than
12 after filtration.
13 So, altogether we have a 2.5 log reduction,
14 which is more than a three-fold production of prions in
15 plasma. Is this enough? Well, we consider that it's
16 not enough and so did the PIE-2 (phonetic) and that's
17 why we investigated further. And I'm not able yet
18 to disclose the way that we're using and how we are
19 doing it but we filed in last December, to the PIE, the
20 report on prion filtration, and we can say that we have
21 achieved more than five logs reduction in prion in this

1 product, with this new system.
2 We have to bear in mind that the PTP
3 patient can act as a live plasma pool container. Some
4 of them receive more than 200 units and nobody tends to
5 think about it when we're speaking about how difficult
6 or how dangerous it is to pool plasma and then to
7 inactivate it or filter it against prions. What about
8 those patients who received single-unit products.
9 Finally -- and I think this is the most
10 important thing and I think is this is where Octaplas
11 can really make a difference is about noninfectious
12 adverse events, the allergic reactions, TRALI, how can
13 Octaplas influence this. Well, as has been already
14 been mentioned, there was this pathogen inactivation
15 consensus conference in Toronto and there it was said
16 that we don't have to go through pathogen inactivation
17 methods, we have to look at the actual risk of
18 transmission of viruses. We should look at what
19 happens with those known viruses and then if there is a

20 pathogen inactivation system to put in place, it would
21 be very nice if it would take care of those

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1 noninfectious adverse events.
2 This is some data presented by Dr. Heiden,
3 at this pathogen inactivation consensus conference and
4 what we see here is that, well, the red bar which
5 accounts for TRALI is increasing and I think it's
6 increasing because there's an increased awareness and
7 people are really looking for TRALI but then we see
8 that the most common adverse reaction are those fibrill
9 reaction those allergic reactions.
10 According to the FDA, TRALI is the leading
11 cause of transfusion-related fatalities, 30 percent,
12 followed by hemolytic transfusion reactions with 16
13 percent. And in the International Forum of
14 Hemovigilance it was said that surprisingly large
15 number of cases of TRALI are reported. It seems that
16 the frequency of TRALI has to date has been

17 underestimated and we will see that there is some
18 specific data on specific countries like UK in the SHOT
19 data that show that when somebody stresses TRALI people
20 start to identify TRALI and the number of TRALI cases
21 start to raise.

1 In this paper published in Intensive Care
2 Medicine by Professor Solheim, transfusion-related lung
3 injury, danger in intensive care, he says most probably
4 they haven't seen TRALI in Norway because of the use of
5 Octaplas. There has been no case reports of TRALI in
6 the 13 years that they are using Octaplas in the
7 country with plasma transfusion. One would think this
8 has to do with the hemovigilance system, who is not
9 looking at the TRALI. We will see that's not the case
10 because there have been TRALI case reports with red
11 blood cells in the platelets. And then we have this
12 paper published in 2007 by Dr. Scully which compared
13 the adverse event rate of cryosupernate and Octaplas in

14 treating TTP patients. The overall conclusion was that
15 when using Octaplas they have seen 50 percent less
16 adverse reaction than when using cryosupernate. We
17 have other papers who have published even an 80 percent
18 decrease.
19 Now, and this is data published by
20 Professor Fleslin (phonetic) from Hemovigilance Systems
21 in Scandinavia and in UK and you will see that all the

1 countries report TRALI with some kind of ratio per
2 inhabitant except Norway. There is no case of TRALI
3 reported in Norway with the use of Octaplas in
4 comparison with the other countries.
5 Now, why should this be? What is the
6 explanation? Why does Octaplas have a low incidence in
7 15 years, more than 5.3 million units used of TRALI and
8 we believe it's because of two things. The first one
9 is the total absence of cells or cell debris (phonetic)
10 in Octaplas. We are not leukoreducing with

11 leukoreduction filters, as I said, we are eliminating
12 all cells so there's no way that the cell can react
13 with antibodies of the patient. And this is the number
14 of cells that you have in normal fresh frozen plasma.
15 Of course there will be, all of them will not be viable
16 after freezing and thawing but they're still there and
17 they don't need to be alive in order to be able to
18 react.
19 Soluble substance in plasma, we looked at
20 soluble substance in plasma and we found out that after
21 Octaplas is being put in a bag levels of histamine

1 content, for example, are what you expect as normal
2 levels, while in fresh frozen plasma it will depend on
3 which unit you have the luck to be infused.
4 Regarding TRALI, we specifically looked for
5 HLA antibodies in Octaplas and this was in two clinical
6 trials, one done by Dr. Sachs, where he compared 20
7 batches of Octaplas and was looking for HLA antibodies

8 and he couldn't find HLA antibodies in Octaplas. And
9 then we had this other trial done by Dr. Sinit who
10 compared in this case eight batches of Octaplas with 58
11 units of some single donor FFP for HLA reactive
12 antibodies and again he couldn't find these antibodies
13 in Octaplas while he had found units which were
14 reactive in the case of fresh frozen plasma.
15 Going further, we tested for HLA antibodies
16 content in Octaplas in 53 consecutive batches and what
17 we have seen is that we are much below what, or we are
18 equal to a negative control for HLA. And while the
19 explanation for this is exactly the same as for what we
20 see with coagulation factors, this is what you can
21 expect in terms of coagulation factors content in

1 single unit FFP. Each unit will have different
2 coagulation factor levels depending on the levels of
3 the donor.
4 When you pool all of this together, what

5 you expect is a standardization and this is exactly
6 what you see when using Octaplas, where all the factors
7 have been standardized to certain value. The same will
8 happen with HLA antibodies. For one HLA unit that you
9 will have with a very high titer, when you pull it
10 together with all the other units, you dilute the HLA
11 antibody and it becomes nonreactive.
12 So, regarding probability profile, there
13 has been no pathogen transmission and no reports of
14 TRALI in all these years of use of Octaplas. Clinical
15 trials account for 229 patients, 1,290 bags, 58
16 batches, and then we have postmarketing experience,
17 pharmicovigilance, hemovigilance, 1.8 million patients
18 treated, more than 5.3 million bags, 3,000 batches, and
19 no viral transmission, no reports of TRALI and a very
20 low adverse event rate. Thank you very much.
21 DR. BRACEY: Thank you. In the interest of

1 time can we move on to the next speaker and then we'll

2 take one or two questions after. The next speaker is
3 Dr. Marie Scully. Dr. Scully is a consultant and
4 hematologist at the University College, London
5 Hospital, subspecializing in hemostasis and thrombosis
6 and she will speak to us on the clinical experience
7 with Octaplas.
8 DR. SCULLY: Many thanks to the Committee.
9 I promise to revert to my hypoglycemia and I will not
10 continue for half an hour, you'll be please to know. I
11 didn't realize till this morning I have that long so I
12 am quite restricted but hopefully I'll be quite
13 succinct. I think I am have a relatively independent
14 opinion. I don't work for the National Blood Service
15 in the UK. I have no conflicts of interest. I don't
16 work or have ever had any monies from any of the
17 pharmaceutical industries although our department has
18 unrestricted educational grants from both Baxter and
19 Octapharma but I don't personally receive them,
20 unfortunately.
21 Now, to clear up the first two slides, one

1 very important point. There have been two types of
2 solvent-detergent plasma developed in the world. The
3 first is Octaplas and the second is Plas-SD. And
4 Plas-SD has been withdrawn but I think it's very
5 pertinent that you know the differences between the two
6 products because they are not the same. They both have
7 an initial similar step so the addition of the solvent,
8 which is 1 percent triisobutyl phosphate and the
9 detergent, 1 percent Triton-X-100, four hours at 30
10 degrees to plasma pools. Thereafter, the production is
11 quite different. The pool sizes are different. For
12 Plas-SD there is used 2,500 single units and you have
13 heard from Marc that Octaplas, in fact the upper limit
14 is only about 1100, 1200 single-units.
15 The plasma protein stabilization and the
16 oil used to extract the solvent and the detergent is
17 thought may affect the final product composition and
18 again now different. For Plas-SD coagulation factors
19 were stabilized with calcium chloride and the solvent
20 and detergent removed with soybean oil; however, for
21 Octaplas they used sodium hydroxide phosphate kept at a

pH between 6 and 7.4 and used caster oil to remove the solvent and detergent.

Another problem with the Plas-SD is the final concentration and ultrafiltration steps are not used with Octaplas, and this is very important with regard to coagulation levels in the final product. Both products do use a second freeze and thawing step which is common and this may have an effect on certain clotting factors, specifically Factor V, VIII, and IX, which I will go into that slightly more in a couple of slides down. And finally the citrate concentration in the bags appears to be very important. If it's less than 10 millimolar, and this has been determined by parties other than the drug companies -- it suggests to activate coagulation factors in fibrin formation.

Now, this slide, I hope you can see the values between Octaplas and Plas-SD but the important thing even though they're given loads of P values on the right-hand side, which I think actually are relatively meaningless because the levels of the

21 majority of factors, concentrates in routine screening

1 are in the normal range given, there is a significant
2 reduction in the Protein S activity in Plas-SD and a
3 significant reduction in the pathogen inactivator with
4 Plas-SD. And finally, again, as I mentioned a moment
5 ago, the citrate concentration in bags is significantly
6 reduced in the Plas-SD. So, as I said, right at the
7 very beginning, Plas-SD is not used. It was used in
8 the U.S., had known problems mainly with thrombosis but
9 Octaplas is used certainly in Europe but again not in
10 the U.S., hopefully yet.
11 So here is a list really of the advantages
12 and disadvantages of Octaplas as it stands currently.
13 As we know Octaplas eliminates all the lipid-coated
14 viruses including West Nile, and the nonlipid-coated
15 viruses are screened and a starting material for DNA,
16 for Parvo, RNA for hepatitis A and we've got
17 neutralizing antibodies because of plasma pools and

18 reduction of any virus threshold because of dilution.
19 There's also the hydrophobic-step. The plasma pooling
20 reduces antibody teases (phonetic) against blood cells
21 and plasma proteins and there's an excellent

1 standardization of these plasma protein potencies and
2 removal of residual blood cells and cell fragments
3 eliminates the risk of blood cell mediated reactions.
4 And so therefore in the disadvantages of Octaplas,
5 where it says pooled product, that really makes much
6 more sense because I've already described two
7 advantages with it being pooled.
8 The second disadvantage is reduced Factor
9 V, VIII and pathogen inactivator. Now, if you are
10 decidedly deficient in pathogen inactivator you will
11 not bleed, and what's the relevance of having or is
12 there a relevance of having a reduced Factor V and
13 Factor VIII in the laboratory; does that extend into
14 clinical practice? One important factor I haven't put

15 a slide in for is the time that the plasma is frozen.
16 For the UK Octaplas that we use it's frozen within 15
17 hours but in Norway and some of the other Scandinavian
18 countries freezing within four hours, there is no
19 reduction in these Factor V, VIII and Protein S.
20 This table is basically again looking at
21 the baseline's clotting screen prothrombin, activated

1 prothrombin times and fibrinogen and coagulation
2 factors and what I would like to draw your attention
3 to, even though the often-suggested significant
4 difference in the Factor V and Factor VIII, the Factor
5 V's and Factor VIII's in Octaplas are still within the
6 normal range and I think that's very relevant. Protein
7 S level is not within the normal range and it would
8 suggest a 50 percent decrease. So therefore by pooling
9 you're reducing or expecting to reduce the coagulation
10 factor by about 10 percent but this data would suggest
11 that it's somewhere between 20 percent Factor V and

12 VIII, and probably 50 percent for Protein S.

13 So, moving onto my area of interest and

14 expertise, which is TTP, for those of you who do not

15 know what TTP is, it's an acute life-threatening

16 illness mainly affecting young people in the third and

17 fourth decade of their life. If they do not receive

18 plasma therapy, they will die, or 90 percent of them

19 will, and even with plasma therapy around 20 percent of

20 patients die.

21 And the longer you take to diagnose and

1 treat them, the increased mortality so it's very

2 significant that we get right type of plasma as soon as

3 possible for our patients. Dr. Yarrington, who was at

4 UCL and did some research before my time, looked

5 retrospectively at 68 consecutive patients and found

6 that eight of them had venous-thrombo-embolic events in

7 seven patients. And the type of VTEs were DVTs, which

8 are mainly Lyme-associated. There were three episodes

9 of pulmonary emboli and one preliminary-artery
10 thrombosis, which is actually not a VTE, it's an
11 arterial thrombotic event.
12 Now, the time for thrombosis, it was a long
13 time out after the first plasma exchange; 53 days is a
14 very long time. And I think actually, since 2003, when
15 this was published, the whole management and treatment
16 of acute TTP patients has changed. And I would be very
17 worried if any of patients was still having plasma
18 exchange at day 53. The types of plasma included three
19 patients exclusively had Octaplas, one patient did not
20 receive any Octaplas and the remaining had some prior
21 or FFP and Octaplas. Usually what happens, patients

1 were unresponsive or refractory or had severe allergic
2 reactions; they used to be changed from prior -- to
3 Octaplas. And, as you can see, we did review the
4 Protein S levels in the three components and there is
5 about a 50 percent decrease in Protein S in the

6 Octaplas; however, it is within the normal range.
7 And this is a table summarizing the
8 patients and you can see other than two of the
9 patients, they all have normal platelet counts. And as
10 I said previously, some of them were really a long time
11 out from their first plasma exchange before they
12 developed venous thrombosis. But what this highlights
13 is a number of issues.
14 Firstly, when you treat patients, new
15 platelets are extremely reactive; secondly, this is a
16 very prothrombotic disorder and thirdly, there's often
17 other acquired and often inherited problems which as a
18 multi-hit hypothesis you're going to potentially get a
19 number of patients who develop VTEs. And as a
20 consequence of this paper we did change our practice so
21 now patients once their platelet count is over 50

1 receive prophylactic low molecular weight heparin, the
2 results of which I will show you in a couple of slides

3 down.

4 Another important issue with plasma is the

5 allergic reactions, and obviously it's been thought

6 that per patient they receive about 40 liters of plasma

7 per TTP episode so it's significantly substantial. And

8 this is just one of many papers where 27 of the 41 TPT

9 patients had 51 urticarial reactions of which 10

10 percent was associated with recompromise, so

11 significant and luckily none of them had anaphylaxis.

12 So, as a consequence of Yarrington's paper, and really

13 -- our work actually has any impact by using

14 prophylactic low molecular weight heparin in reducing

15 VTEs and also to look at the effect of plasma and any

16 associated complications, we looked at 50 patient

17 episodes incorporating 32 patients up until the end of

18 2005, December 2005. Now, that date was chosen because

19 as of the first of January 2006 as per department of

20 health recommendation all patients now receive Octaplas

21 front-line. We have no episodes, in those 50 patient

1 episodes that we looked at, of venous-thrombo-embolism
2 other than a superficial thrombotic event that did not
3 require anticoagulation.
4 As you can see when we did look at the
5 citrate and allergic reaction there was a significant
6 decrease in the Octaplas group, which was not something
7 we originally intended to look at but was very useful
8 data. In fact, since we have used exclusively Octaplas
9 it's been very difficult to imagine life without
10 allergic reactions. We don't really see them at all
11 now.
12 So, in TTP the reason we give plasma is to
13 replenish this missing enzyme, ADAMTS-13, which used to
14 be called metalloproteinase, and so it was very
15 pertinent to look at the compounds available to see the
16 level of ADAMTS-13 present in them. And as we can see
17 from this chart in the first left-hand column that they
18 all contain adequate amounts of ADAMTS-13. So if
19 that's the case, and since the introduction in the UK
20 in 2002 of Methylene Blue treated FFP for all children
21 born after the 1st of January 1996, why did we not use

1 Methylene Blue in our patient cohort?
2 The reason was there was two albeit
3 retrospective and relatively small papers from Spain.
4 The first looked at seven Methylene Blue patients
5 comparing to 13 FFP-treated patients and the Methylene
6 Blue required a greater number of plasma exchanged
7 remission and had a longer hospital stay. In a
8 subsequently retrospective review of 56 patients if you
9 look at the treatment results the number of plasma
10 exchanges to remission, the recurrence during treatment
11 and the death rate was increased in patients who
12 received Methylene Blue, FFP. So, it was quite
13 fortuitous that we actually suggested that we did not
14 want to change our patients from Octaplas to Methylene
15 Blue. And subsequently and presented to ASH in
16 December 2007, ASH the Spanish have compared Motherly
17 Blue with FFP in a multicenter prospective trial and
18 again the patients in the Methylene Blue group require
19 more plasma, they require more plasma exchanges and
20 they're more likely to have recurrence.
21 Now, just moving onto TRALI, which is a

1 very important condition, a bit like TTP, it's rare and
2 associated with significant mortality. And Marc has
3 already presented this slide, which is like a point in
4 time of TRALI cases related to FFP and you can see the
5 implicated blood products account for about 50 percent
6 with FFP but the others caused problems, too. The
7 Norwegians have used Octaplas for over 12 years now and
8 not only have they not seen any TRALI but also
9 importantly they have had no viral transmissions, no
10 thrombotic complications and no thrombolytic
11 complications.
12 The Irish in 2002 on the back of new
13 variant CJD and problems that they had in the past
14 where patients had developed hepatitis C were very
15 eager to move to nonUK-sourced FFP viral inactivation
16 steps and they opted for Octaplas. And they presented
17 the first 18 months worth of data, which I think is
18 very important, using about 25,000 units of SD a year.

19 The importance is the group of patients, neonates from
20 24 weeks old, OB/GYN patients and liver disease in
21 several patients when there was liver transplantation.

1 Within the neonatal group, three patients had
2 coagulation factor deficiencies. In the obstetric
3 group there was a patient with Factor V, inherited
4 Factor V deficiency. And I've put the volumes of
5 plasma use in each group which are really as you would
6 expect with standard FFP and they have observed no
7 adverse reactions.
8 In the UK we had a voluntary reporting
9 system which is now no longer voluntary, called SHOT,
10 and the latest report suggest the use of over 300,000
11 this does not include Octaplas, and last year ten cases
12 of TRALI and when they looked at the HLA antibody
13 status in seven of these, three were positive and they
14 were all females. They were not related to fresh
15 frozen plasma.

16 And this graph looks back from the start of
17 SHOT showing the number of TRALI cases an the number of
18 deaths. And we will see in '96, '97 it was very low
19 because it was a voluntary reporting system, and
20 certainly the whole country was not involved and you
21 can see there is almost an exponential rise up until

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1 from 2001, 2002 and then it's dropped off. And this is
2 because between 2002, 2003 the preferential male donors
3 and also leukodepletion as a result of new variant CJD.
4 If we look at the components implicated, FFP has not
5 been implicated in 2005 or 2006. But this is quite
6 important. The cumulative mortality and morbidity
7 data, TRALI accounts for the greatest amount of
8 mortality in patients with transfusion reaction
9 problems and indeed the major morbidity again was
10 related to TRALI.
11 Now, just very briefly solvent-detergent
12 plasma in liver transplantation is very important

13 because obviously patients have mass coagulation
14 abnormalities and as a result of the six deaths from
15 pulmonary emboli by using the Plas-SD product that's no
16 longer used in the States, retrospectively they looked
17 to Octaplas and did find there was hyperfibrinolysis
18 compared to standard FFP but there was no overall
19 difference in blood loss and this hyperfibrinolysis
20 when they looked further was thought to be due to
21 actually the blood loss per se. And certainly now in

1 Norway and in other European countries in patients with
2 very, very severe liver disease, they use low dose of
3 protein. They see no complications with VTE or
4 abnormal bleeding.
5 And, Laura Williamson in 1999 and other
6 English and hematologists did a randomized control
7 trial of Octaplas and FFP in patients with stable liver
8 disease, that required correction of the coagulation
9 and also those who were undergoing liver

10 transplantation, i.e., extreme coagulopathy. And the
11 chart is there but I'm certainly not going to go
12 through it but the important features are all the
13 patients received standard FFP, 12 to 15 mils per kilo.
14 There was no difference. They both had equally good
15 correction in the FFP or the SD group. There was no
16 increased blood product requirements in either group.
17 Both of them were exactly the same. And finally, while
18 previously as I've said perhaps a 20 percent decrease
19 in Factor VIII, for example, in SD, it seems to have no
20 effect on the overall volume of plasma that's infused.
21 This is just very brief. Octaplas has also

1 been used in congenital coagulation factor
2 deficiencies, and not associated with new antigen
3 formation or inhibitor formation. And, very finally, I
4 think it's imperative from an ethical and a
5 medical-legal point of view to use the best possible
6 plasma we have available not only for known pathogens

7 but we have to get rid of unknown pathogens. Also the
8 effects of allergic reactions or immunological
9 reactions and TRALI. This is pertinent not only for
10 our high-volume uses but also those that just require
11 maybe plasma once or twice in their life because to
12 have a major morbidity or mortality is detrimental.
13 Many thanks for your attention.
14 DR. BRACEY: Thank you for a very efficient
15 review of the subject. I would like to open up the
16 floor for questions. Dr. Klein?
17 DR. KLEIN: Thank you for a very nice
18 review. And I think especially the issue comparing
19 Plas-SD and Octaplas, which I guess a lot of people
20 don't appreciate that the process is different.
21 However, you suggested that the clinical effects are

1 effects are different as well and I was wondering if
2 you would care to comment on the quality of the data
3 suggesting that in fact the clinical thromboses seen in

Plas-SD really are an issue compared with Octaplas.

DR. SCULLY: I think it's very difficult because when the paper suggested that, well, or when the thrombosis was presented in the literature obviously it was removed from use. And really what I was trying to get across is there may be no difference but the manufacturer of Octaplas is not the same and we do not see the level of thrombosis that we was initially suggested with plasma SD. Whether, you know, after ten years experience we would be able to say, well, because of X, Y and Z we will never know but I just wanted to get across my that they are completely different manufacturer processes and we can't really make much assumption about any similarities between the two products.

DR. KLEIN: If I could just follow up for a second. I just thought the other way around. I'm familiar with the cases that were reported and your

slide said that the thromboses were caused by Plas-SD and as I remember those were very weak associations. Clearly the precautionary principal suggested that we needed a black box at the time but as to being causative I think that was a long way from proved.

DR. SCULLY: My apologies.

DR. BRACEY: Dr. Benjamin?

DR. BENJAMIN: Dr. Scully, excellent presentation. We're discussing at this meeting the implementation of pathogen inactivation in the U.S. I couldn't fail to note that the UK when they imported U.S. plasma chose to treat it with SD before use. Could you comment at all about the process of that decision, why the decision was made?

DR. SCULLY: The UK actually imports Methylene Blue so we get, the SD is almost just for a small population of patients. Are you talking about the whole total UK or just the SD?

DR. BENJAMIN: The SD-plasma I believe was imported from the U.S. and then treated with SD plasma so the decision was made that the U.S. plasma needed to

1 be pathogen inactivated before use in the U.K.
2 DR. SCULLY: Yes.
3 DR. BENJAMIN: Could you comment on the
4 decision that was made?
5 DR. SCULLY: I might move that one over to
6 Marc. That's a manufacturer issue.
7 DR. MALTAS: Actually, what happened is,
8 when the UK decided to use Octaplas, Octapharma had to
9 find out some new sources of plasma. We were using
10 plasma coming from Sweden, from Austria and from
11 Germany and the increasing number of units of Octaplas
12 use obliged us to go for new source of plasma and we
13 used U.S. plasma. It's not that plasma is imported
14 into the UK, it's Octapharma who buys the plasma in the
15 U.S. and then afterwards runs the process and sells
16 that Octaplas in the UK.
17 DR. BENJAMIN: It just fascinates me that
18 somebody made a decision that the U.S was not, needed
19 treatment.
20 DR. SCULLY: Well, I think the reason we
21 used U.S. is because of new variant CJD and obviously

1 we weren't particularly happy to use European for that
2 reason but the viral inactivation steps I think are not
3 a reflection of U.S. plasma. I think they're a
4 reflection of the volume of plasma we have to give our
5 patients and we have to make it as safe as possible.
6 DR. BRACEY: Dr. Kouides?
7 DR. KOUIDES: Could you clarify the
8 experience you had published in the British Journal of
9 Hematology, of eight thrombotic events? I think you
10 implied that you thought it was probably a
11 manifestation of the disease itself. I was curious to
12 know, do you have any prior registry data? I haven't
13 been aware of the data at least in the 30 years in the
14 U.S. though I have one thrombotic event last year with
15 regular FFP for a TTP but is there prior data that
16 there is a baseline VTE risk in these people or at
17 least at University College?
18 DR. SCULLY: No, there isn't, actually, and
19 there's very scanty data throughout the world for

20 baseline VTE risk.

21 DR. KOUIDES: There is or isn't?

1 DR. SCULLY: There's very scanty, there's

2 not much data at all.

3 DR. KOUIDES: So why wouldn't you implicate

4 the Octaplas, is it because the levels were not that

5 different?

6 DR. SCULLY: Firstly it was preceding my

7 time and reading the paper I will would necessarily

8 implicate the plasma that was used, although, obviously

9 seven out the eight had received Octaplas. I would

10 actually put it down to a number of other environmental

11 and sort of inherited factors and that TTP itself, you

12 know, when the platelets come up, as I said, they are

13 hyper-reactive and the patients were obviously admitted

14 for very long times, and which is much greater than we

15 use now. So you probably would see -- and in fact

16 since 2006 we have introduced SD exclusively we have

17 had two thrombotic events and we see between 20 and 25
18 patients a year. One was in a patient who had a
19 pulmonary embolus and had a number of factors that
20 could have precipitated that, massive protein leak from
21 his kidneys and long, hard journeys, because of having

1 to travel to our center from quite away and immobility,
2 et cetera, et cetera. And the other lady was scanned
3 not looking for VTEs and she had thrombosis extending
4 up both her legs into her IVC, which was not an
5 expected finding. And I think it was very, they're
6 both elderly patients, over 65 and they are the only
7 two episodes we have had, with over 50 patients now.
8 And I think it's very difficult to implicate just
9 plasma.
10 DR. KOUIDES: It's probably related to
11 other additional issues? I beg to differ, though. I'm
12 not sure the platelets are truly hyper-aggregable
13 because, for example, in other thrombocytopenic states

14 we have normal marrow functions; such as IDP undergoing
15 splenectomy, you have a rebound thrombocytosis. Those
16 platelets usually are not going to, you know, lead to
17 clotting even though people worry when they see the
18 platelets go above 600,000, let's say.
19 DR. SCULLY: But it's multiple-hit, isn't
20 it? They're reactive. It doesn't mean they're going
21 to clot but it's usually multiple-hit.

1 DR. BRACEY: Based on your knowledge of
2 thrombosis, if you had to specify a given activity in
3 anticoagulant protein S, protein C, what would you
4 suggest what the minimum level be considering an
5 exchange?
6 DR. SCULLY: We don't, firstly we don't
7 ever check it and secondly, I would rather that they
8 had levels within the normal range but obviously if you
9 are pooling loads of plasma into patients it will drop
10 even when the FFP group drops. And, so, for that

11 reason we don't check it but I would prefer that it was
12 within the normal range at least when we start it.
13 DR. BRACEY: Dr. Triulzi?
14 DR. TRIULZI: Thank you for the talk. You
15 showed some limited data that Methylene Blue may be
16 inferior to Octaplas for TTP. Is that explainable by
17 ADAMTS-13 levels in Methylene Blue and if not what is
18 the proposed mechanism of why that would be?
19 DR. SCULLY: The levels In Methylene Blue
20 are normal of ADAMTS-13, and given that standard F is,
21 compared between standard FFP and the only difference

1 is obviously the Methylene Blue manufacture, it must be
2 something in the processing. And indeed we know that
3 outside of TTP, you know, there's no fibrinogen
4 Methylene Blue so again it must be a manufacture
5 process.
6 DR. BRACEY: One last question and then
7 we'll take a break. Just point of information. We'll

8 reconvene in an hour after -- sorry, that would be
9 2:15. Dr. Epstein?
10 DR. EPSTEIN: Yes. In comparing the
11 manufacturing processes for Plas-SD and Octaplas you
12 were suggesting that they're the cause of the different
13 levels in the end but I'm just wondering if anyone has
14 looked at the effect on the conditions of collection of
15 those plasmas in the first place because as you also
16 pointed out in case of Norway there are some levels
17 that are affected by, you know, the process of
18 freezing.
19 DR. SCULLY: I'm not sure we'll ever know
20 the results for that question, just because Plas-SD is
21 no longer available.

1 DR. MALTAS: Your question was if there is
2 any difference in the re-collection of the plasma to
3 produce both products?
4 DR. EPSTEIN: Do we know whether the

5 starting plasmas have significant factor levels based
6 on conditions of collection and storage and freezing?
7 DR. MALTAS: Well, there was a paper
8 published in 2007 by Hager, et al., who compared
9 coagulation factor levels in FFP treated with Methylene
10 Blue and Octaplas and I think there is data there from
11 the initial levels of the factors before treating the
12 plasma. And there we saw that there is no difference
13 in both products before you treat. So, it depends, the
14 difference in coagulation factors that you have in the
15 plasma will depend in a directed motion on how long it
16 takes to freeze the plasma. What we know is that
17 Plas-SD used up to 15 hours to freeze the plasma. For
18 Octaplas it's standard to be around six hours so there
19 must be or there could be a difference in the initial
20 levels.
21 DR. KOUIDES: Could you also clarify, I

1 missed it on that side. I couldn't carefully see it.

Is the ADAMTS-13 levels statistically higher in SD and Octaplas compared to normal FFP?

DR. MALTAS: Which levels?

DR. KOUIDES: The ADAMTS-13.

DR. MALTAS: There are several papers published with ADAMTS-13 levels and I think there was a difference in between cryosupernate and Octaplas in favor of Octaplas. What we have seen in the characterization of ADAMTS-13 levels in Octaplas is that -- and I think this is important when considering TTP -- is that Octaplas lacks the high-weight multiples so probably this has some influence on the efficacy of the product.

DR. BRACEY: Okay. We should break for lunch. Sorry, we should break for lunch now and we'll reconvene then at 2:15 and any of the members of the audience who would wish to sit in on the working committee are welcome to do so.

(There was a break in the proceedings.)

DR. BRACEY: Welcome back to the closing

1 session of the meeting. During the lunch hour, many of
2 the Committee members worked on fusing a draft document
3 for a recommendation to the Assistant Secretary. We
4 had three draft documents and so we will go through
5 edits after we hear our final two speakers. Our next
6 speaker is Dr. Jaroslav Vostal. He is the Chief of
7 Laboratory and Cellular Hematology in the division of
8 hematology, the Office of Blood Research and Review.
9 He has been very carefully reviewing the subject of
10 pathogen reduction and the impact on cells that are
11 being potentially affected and the topic, title of his
12 talk will be regulatory issues of pathogen reduction
13 technology.
14 DR. VOSTAL: Thank you very much. Thank
15 you for the invitation to come present to you some of
16 our current thinking the evaluation of pathogen
17 reduction technology. Unfortunately, after a day and a
18 half that we have been discussing this, pretty much
19 everything I can think of has been covered already so
20 I'm going to apologize ahead of time are for some
21 redundancies.

1 So, for pathogen reduction as a process as
2 a concept, the FDA actually encourages pathogen
3 reduction in transfusion products and we encourage
4 application of existing technologies and the
5 development of novel technologies. We encourage the
6 use of prevention with donor screening for risks of
7 infectious diseases. We encourage for skin
8 disinfection, use of diversion pouches, aseptic
9 collection and the use of closed systems. Then in
10 terms of detection, we encourage donor testing and
11 support bacterial detection in transfusion products.
12 And, we also encourage the development of new and not
13 yet approved products, for example, alternate storing
14 conditions such as cold-stored platelets which will
15 prevent bacterial proliferation, and certainly pathogen
16 reduction with chemical additives and also the
17 development of substitute or manufactured products
18 which would be done under sterile conditions.
19 However, since we're talking about chemical
20 and photochemical pathogen reduction, we have to start

21 considering the risks and benefits as we have been

1 discussing over the last couple of days. And, here you
2 can see that the benefits are, the target for pathogen
3 reduction is, the reduction of viruses, bacteria, and
4 parasites, and especially the potential reduction of
5 emerging and unknown pathogens.
6 So, this has to balance out against the
7 risks that could come as a result of application of
8 these processes to transfusion products, and these
9 risks could include damage to the transfusion products,
10 adverse events to the recipients of such products, also
11 toxicity to processing personnel, because those people
12 actually could come into contact with very high
13 concentrations of the chemicals, and also the toxicity
14 to the environment because if those chemicals are
15 mutagenic or potentially carcinogenic there may be an
16 issue about their disposal.
17 So, to think about what the benefits are, I

18 have to review the data that was presented earlier by
19 Dr. Dodd, and this is for the current risk from
20 bacteria in transfusion products and this is very
21 nicely documented in this paper published by the

1 American Red Cross and Dr. Eder, and this is a very
2 exciting study because it has such a large number of
3 products tested, and it pretty much single handedly
4 defines the contamination rate of untested products to
5 be about 1 in 5,000 and also defines the septic
6 transfusion rate at 1 in 75,000. So, this is for
7 products that were actually tested and determined to be
8 negative. And for fatalities the risk is 1 in 500,000.
9 Now, after a collection of this data, the
10 American Red Cross reviewed their collection and
11 testing procedures and found places to optimize it even
12 more, and they think that by applying their diversion
13 strategies and increasing the sampling volume for
14 bacterial testing, they can reduce their septic rate by

15 70 percent, 75 percent, which could bring it down to
16 one in the 1 to 300,000 range.
17 Now, for the risks from viral products,
18 this was also reviewed by Dr. Dodd, and you can see
19 that the usual suspects are listed over here. HBV is
20 the one that has the highest risk at 1 to 150,000 and
21 the other viral pathogens come in at about 1 to 1.5

1 million.
2 So, the current level of transfusion
3 product safety is achieved by testing and prevention.
4 And testing has a very good risk-to-benefit ratio.
5 It's performed on a sample of the product, testing does
6 not damage the transfusion products, it does not
7 present a toxicity risk to the patient because nothing
8 is added to the transfusion product, and overall
9 testing has made the blood supply very safe. So, the
10 risk-benefit analysis is very favorable, and if you
11 look at our little teeter-totter, the benefits

12 significantly outweighs any type of risk that may be
13 associated with testing.
14 Now, if you try to apply this type of an
15 analysis to chemical or photochemical pathogen
16 reduction, we put on this side benefits, and we have
17 the target, and the target would be a reduction of the
18 current viral risk, which is 1 to 150,000 and a
19 reduction of bacterial septic risk, which is at 1 to
20 75,000. So, in order not to shift the risk from
21 transfusion transmitted disease to some other adverse

1 event, this side of the teeter-totter should be
2 somewhere around also 1 to 75,000.
3 And, this is a relatively tall order
4 because this next slide shows you the size of a study
5 that will be required to assure that you're eliminating
6 a risk of 1 to 75,000. And the size of that study to
7 achieve 95 percent upper confidence limit would be over
8 200,000 patients. So, it's not likely that any sponsor

9 or company will be able to achieve a study of this size
10 up front. So, more likely you're going to be able to
11 see studies in the hundreds patient range. And, so,
12 the strategy has been to conduct studies that will look
13 at efficacy in some adverse events and hope that if the
14 study does not demonstrate any adverse events, then it
15 could be approved and sizes of this type of a
16 population could be achieved by doing a postmarket
17 study.
18 So, what are our concerns about novel
19 pathogen reduction methods? The pathogen reduction
20 process creates a novel mixture of chemicals and
21 biologic products that is infused intravenously to a

1 wide range of patients of different ages and condition
2 states of health. So, the concerns are that the
3 pathogen reduction chemicals interact with nucleic
4 acids, they are frequently mutagenic and frequently
5 carcinogenic, and may require a long-term postmarket

6 study to determine if there is a risk associated with
7 carcinogenesis. An additional concern is the
8 application of light energy which can damage cells and
9 can certainly damage the products themselves, and then
10 the chemicals are nonspecific in that they can also
11 bind, once activated, to proteins, lipid and cell
12 organelles. So, the damage or the potential damage
13 caused by these chemicals can be widespread and may be
14 difficult to detect with the current testing strategies
15 that we have.
16 So, the strategies that we have for
17 approval of products such as these is to go through the
18 classical FDA pathway, and as we go through phase one
19 study, starting with phase one in vitro study, and
20 these study identify gross lesions to cell
21 biochemistry, to cell morphology. In addition to that

1 phase one you would have animal studies to evaluate
2 toxicity, and earlier today and yesterday we heard

3 about the pathogen reduction chemicals that have been
4 tested, that have gone through this in vitro study
5 process, and actually they are found to be relatively
6 safe based on the outcomes of these studies. Because
7 they had a relatively safe profile, they progressed
8 through to phase two clinical trials, which included
9 radiolabeling studies in human volunteers to define the
10 transfusion product kinetics. And, some of these
11 studies actually indicated that there is a loss of the
12 ability to circulate and decreased recovery in healthy
13 human volunteers. That by itself does not actually
14 indicate whether there's any additional loss of
15 functional efficacy.
16 So, the next step after phase two study is
17 to progress through phase three clinical studies, which
18 specifically assess efficacy, will define a transfusion
19 frequency of these transfusion products and identify
20 any adverse events on toxicity associated with
21 application of these products to a specific patient

1 population. Then if the phase three clinical trial
2 works out and the product gets approved and gets on the
3 market, then to identify and follow any type of very
4 low frequency adverse events in toxicity, phase four
5 studies would need to be put in place so we could
6 monitor the performance of these products.
7 Now, I wanted to talk about the Cerus S-59
8 treated apheresis platelets because this is the product
9 gone the furthest along this development pathway and I
10 think we can learn something from what we've seen out
11 of the outcome of their phase three clinical study. So
12 that as we heard earlier this study done by Cerus was
13 called the SPRINT trial, and we heard a description of
14 it earlier today, and it was a phase three randomized,
15 controlled, double blind, noninferiority study. The
16 objective of the study was to compare safety in
17 hemostatic efficacy of photochemically treated
18 platelets to conventional platelets. And the primarily
19 endpoint of this study was the proportion of patients
20 with grade two bleeding assessed by a standardized WHOV
21 scale.

1 What I'm going to present to you are tables
2 taken directly from this report. And, you can see this
3 table five here talks about proportion of platelets
4 with grade two or higher bleeding, which was the
5 specific primary endpoint. This was quite a large
6 study, had 318 patients in the treated arm and 327
7 patients in the control arm. If you look at any grade
8 two bleeding, both of these studies are equivalent to
9 the proportion of patients that had a grade two
10 bleeding. So, from that viewpoint the study was
11 successful.
12 Now, the sponsors also broke out the
13 bleeding by different bleeding sites. The only thing I
14 would like to point out here is that in the
15 mucocutaneous bleeding -- that's bleeding that's known
16 to be dependent on the level of platelets or function
17 of platelets -- it's not a statistical difference but
18 there's a trend toward being increased mucocutaneous
19 bleeding in the treatment arm.
20 Now, if you look at, the other thing I
21 would like to point out to you, there's also a

1 difference between bleeding in the respiratory organs,
2 slightly higher, not statistically significant, but I
3 think it's something that we should keep in mind
4 because it may come up a little bit later.
5 So, here's table six from the same paper,
6 and this table looks at the platelet and red cell
7 transfusion used during the study. If you look at the
8 platelet transfusion, the total number of transfusions,
9 platelet transfusion in the treatment arm was 2,678 as
10 compared to 2,041, so, about a 30 percent increased use
11 of platelets to support these patients; this is four
12 patients with hematologic malignancies.
13 Now, if you look at, you know, where did
14 that number come from? You look at the mean number of
15 transfusions per patients, that's higher, 8.4 versus
16 6.2. If you look at the mean interval between
17 transfusions, as the shorter interval, it's 1.9 versus
18 2.4 days. You can also look at the dose that these

19 patients received, and this may be part of the problem
20 that the processing of the platelets during the
21 pathogen reduction treatment uses up some of the

1 platelets and so the dose that's actually going into
2 the patients is lower than in the control arm. You can
3 see also here that the percentage of doses that were
4 less than three times ten to the eleventh, which is the
5 standard platelet dose, the percentage in the treatment
6 arm is 20 percent of the patients received less than a
7 standard dose versus 12 percent of the patients in the
8 control arm.
9 The additional thing that should be pointed
10 out is the use of red cells in this trial, and although
11 it's not statistically different, there's a trend
12 toward a higher use of red cells in the arm that's
13 fully supported by the pathogen-reduced platelets,
14 about a half the a unit difference between a treatment
15 arm and control arm.

16 So, on table seven in this paper, the
17 authors summarized the platelet responses following
18 platelet transfusions. And here we're looking at the
19 platelet count and you can see the starting platelet
20 count in those patients was equivalent between a
21 control and a test arm. And if you look at the

1 one-hour posttransfusion, the platelet count in the
2 treatment arm is about 37,000 versus about 50,000\in
3 the control arm, so already a significant decrease. If
4 you look at specifically the platelet increment, you're
5 going from 34 in the control arm to about 21,000 in the
6 treatment arm, and if you look at the count increment,
7 you also see a decrease.
8 And the same results or same trend is
9 observed in the 24-hour CCI or that 24-hour evaluation,
10 and you can see there's significant differences in the
11 platelet count, in the count increment and also in the
12 CCI. So, based on these results it appeared that the

13 patients are receiving the treatment, a treated product
14 could have been underdosed with a platelet product.
15 Table eight from this paper talks about
16 refractoriness to platelet transfusions, and
17 refractoriness in this study was defined as two
18 episodes, two consecutive platelet transfusions with a
19 one-hour CCI count of less than 5,000. And, the
20 treatment arm, you can compare the treatment arm to any
21 refractory episode that was examined. It was 21

1 percent in the treatment arm versus 7 percent in the
2 control arm.
3 The following line would be that any
4 transfusion with CCI less than 5,000, we have a 27
5 percent versus 12 percent in the control arm. So, it
6 appears that there's significantly more refractory
7 patients that are transfused by the treated platelet.
8 Now, the interesting thing in this observation are
9 these, if you look at immunologic refractoriness, there

10 is actually no difference between the treatment arm and
11 the control arm so the refractoriness that we see, the
12 overall refractoriness is probably due to cell damage
13 and not necessarily due to an immunological alteration.
14 So, this slide summarizes the results of
15 the hemostatic effectiveness from the SPRINT clinical
16 trial. The trial itself met the primarily endpoint of
17 proportion of patients with grade two bleeding.
18 However, it failed a number of other indicators of
19 platelet efficacy, for example, it increased platelet
20 utilization by 30 percent, it decreased the time
21 between transfusions, decreased posttransfusion

1 platelet count response, increased the number of
2 platelet refractory patients and also increased a trend
3 towards a higher red blood cell usage.
4 So, if you take all these together, they
5 could reflect some potential adverse effects. For
6 example, if you have increased usage of transfusion

7 products, you could be mediating an increased frequency
8 of transfusion-transmitted diseases, particularly if
9 you are looking at red blood cells that have not been
10 treated by this product. And also the 30 percent
11 increase in platelet use and the increase in red blood
12 cell use may eventually have a negative impact on the
13 blood supply.
14 Now, this study was published in several
15 papers. The one I just went over looked at the
16 efficacy of the platelets. The second paper that came
17 out looked at the safety of these products in the same
18 trial, so this is looking at the adverse events in the
19 SPRINT trial published by Dr. Snyder and colleagues and
20 was published in Transfusion in 2005.
21 Now, once again I'm just going to highlight

1 some of the tables that are published in this paper.
2 And, I think the most telling one is table five, which
3 summarizes the adverse events that are different

4 between the treatment groups and these are
5 statistically significant differences between the
6 treatment group and the control arm of the study.
7 And you can see there's actually 11 cases
8 or 11 types of adverse events that were statistically
9 different between the treatment and the control arm.
10 In each case the difference went against the treatment
11 arm. And, so, we have increased number of petechiae,
12 increased fecal occult blood positive, increased
13 dermatitis, increased rash, pleuritic pain, muscle
14 cramps, pneumonitis, mucosal hemorrhage and acute
15 respiratory distress syndrome.
16 So, out of these adverse events there were
17 also events that were graded as grade three or four so
18 that means clinically significant, clinically serious,
19 and these four adverse events were hyporcalcemia,
20 syncope, pneumonitis and again acute respiratory
21 distress syndrome. It's interesting to point out that

1 in the control arm these significant adverse events
2 actually don't show up. For example, for ARDS there's
3 5 cases out of 318 patients of ARDS and none in the
4 control arm. Also, if you look at syncope, you have 6
5 cases in the treatment arm and no cases in the control
6 arm. In hypocalcemia, over 20 cases in the treatment
7 arm and only 6 in the control arm.
8 So, in this paper the sponsor actually
9 claimed that there may have been an issue in
10 identifying ARDS in some of the patients that were
11 coded as having ARDS and so they went back and
12 reanalyzed the data with a blinded group of experts to
13 see if they could come up with different results. And
14 those experts looked at a number of different
15 respiratory events but in the end, after the
16 reanalysis, the ARDS was still present with 12 cases in
17 the treatment arm and 5 cases in the control arm, a
18 loss of statistical significance that we saw initially
19 but the issue of ARDS or some kind of acute lung
20 problem did not go away.
21 So, here's a summary of the SPRINT adverse

1 events data. This is actually a typo. It should be
2 nine types of adverse events significantly different
3 between the treatment and the control platelets, and
4 they all went against the treatment platelets. Four
5 types of these adverse events are clinical grade three
6 and four and the organ systems involved here are the
7 respiratory, cardiovascular system, dermatologic system
8 and the parathyroid-renal system possibly based on the
9 hypocalcemia.
10 So, if you look at the risks that could be
11 associated with the use of these platelets, it appears
12 that 1 in about 60 patients supported by treated
13 platelets could have grade three or grade four adverse
14 events. So, if you put this on the teeter-totter, you
15 have on this side the risks, documented risks from a
16 prospective blinded clinical trial of 1 per 60 adverse
17 events and you're stacked up against trying to reduce a
18 risk of 1 in 150,000 or 1 in 75,000. So, based on this
19 type of analysis, it's difficult to see how this type
20 of risk would be able to justify general use of these
21 products to offset a bacterial and viral risk.

1 Now, one of the important concepts in
2 pathogen reduction is the ability or the potential to
3 prevent unknown and emerging pathogen
4 transfusion-transmitted diseases. And pathogen
5 reduction may have a favorable risk-to-benefit ratio if
6 the pathogen is widespread and has a high mortality
7 rate. There may be populations that more susceptible
8 to the new or actually current pathogen, and pathogen
9 reduction chemical risk may be offset in this type of a
10 group. However, the use of pathogen reduction products
11 in the general population in anticipation of having an
12 unknown pathogen occur years from now is not justified
13 by the current risk-benefit profile.
14 Now, as many studies do, the SPRINT study
15 actually generated more questions than it answered.
16 Some of these questions I'm going to sort of try to go
17 through right here. For example, one question can be,
18 why did the ARDS adverse events not show up in the
19 phase one or phase two testing? Well, the answer to

20 this is not really clear. But, there are differences
21 between the earlier studies and the phase three SPRINT

1 clinical trial.
2 For example, the phase two clinical studies
3 were small. They only used 20 to 24 volunteers and
4 only used a small volume of treated cells that were
5 infused into these volunteers. The volunteers were
6 healthy and ARDS may develop only in a specific
7 clinical situation. Finally, the animal toxicity
8 studies were also done only in healthy animals so the
9 specific clinical situation may not have been
10 reproduced in those types of animals.
11 Another question that could come up from
12 these observations is, is there a plausible mechanism
13 that can explain why ARDS developed with the treated
14 platelets transfused into highly complex hematology
15 patients? And the answer here is possibly yes. There
16 is a plausible mechanism that involves activated

17 platelets and a recruitment of neutrophils to lungs.
18 And this plausible mechanism, that was published by Dr.
19 Kuebler, in a summary that looked at selectins and the
20 emerging role of platelets in inflammatory lung
21 disease. And this body of literature talked about how

1 platelets can actually recruit and tether neutrophils
2 to endothelial cells and in particular in activated
3 platelets they're expressing P-selectin and with
4 trapping of these neutrophils in the lungs may set up
5 an inflammatory-type response and lead to clinical
6 situations such as acute lung injury and ARDS. So, it
7 would be interesting to see if pathogen treated
8 platelets could actually play a role or replace these
9 activated platelets and also lead to the similar type
10 of neutraphil accumulation.
11 So, the next question could be, are there
12 animal models to evaluate whether treated platelets can
13 participate in lung inflammatory disease? And the

14 answer is yes, there are animal models that can be
15 used. One of these animal models talks about
16 acid-induced acute lung injury, and this injury can be
17 blocked by removing the platelets, so it would be
18 possible to set up an experiment like this. This is
19 done where you could replace protein platelets with
20 treated platelets to see if those treated plates could
21 support neutraphil aggregation and accumulation in the

1 lungs.
2 So, with these observations how can we move
3 forward with pathogen reduction? Well, there are
4 several options available for discussion. First of
5 all, we would repeat the clinical trial and see if we
6 can have a better focus on adverse events, particularly
7 the ones that we saw in the original study. The study
8 should be prospective, randomized, blinded, with an
9 active control.
10 It should have a -- well, this is up to

11 discussion but one aspect would be to adjust the dose
12 of treated platelets to be equivalent to the
13 conventional platelets. The trial should actively
14 monitor adverse events, particularly the ones that were
15 grade three and grade four, such as pneumonitis, ARDS
16 and syncope and hypocalcemia. And the size of the
17 study should be comparable to the original study so we
18 don't lose out any sensitivity to detect those adverse
19 events.
20 Another option that could be discussed is
21 to utilize existing clinical data. There is data that

1 we heard about that's available from Europe through the
2 biovigilance networks. Now, to be able to use this
3 data we'll need to have adequate sensitivity to detect
4 respiratory adverse events and passive surveillance may
5 not be sufficient to be able to do this. And, in order
6 to be able to discern the adverse events that are
7 specific for these types of products, those studies

8 should have a control arm of conventional platelets.
9 And finally there's an additional option, that is to
10 design an active surveillance using existing
11 transfusion data from Europe to capture appropriate
12 safety data. That will be relevant to the observed
13 adverse events that we saw in the clinical trial.
14 So, to summarize our current thinking on
15 evaluation of pathogen reduction for transfusion
16 products, the initial step would be to identify the
17 transfusion-transmitted disease risk, and this can be
18 done, as we talked about, by following septic rates or
19 transmission rates. Then the next step would be to
20 evaluate transfusion product safety and efficacy with
21 preclinical and clinical trials and to get a

1 quantitation on the adverse event rate and then do a
2 comparison between the adverse event rate and the
3 transfusion-transmitted risk. If the comparison is
4 favorable, we would be able to approve the PR-treated

5 platelets for use; however, if there are problems with
6 the treatment and some injury to the platelets, there
7 may be a limitation to the use of those products, for
8 example, they may be used only for therapeutic
9 interventions instead of prophylactic interventions.
10 And, finally, if the risk-benefit is not
11 favorable you can consider approval of these products
12 only for situations where the transfusion-transmitted
13 disease risk goes up, and this could be in situations
14 with an emerging pathogen epidemic. So those are our
15 thoughts about pathogen reduction and I thank you for
16 your attention.
17 DR. BRACEY: Thank you, Dr. Vostal. I'll
18 open up the floor for questions and comments. Dr.
19 Benjamin?
20 DR. BENJAMIN: Dr. Vostal, thank you for a
21 fascinating view on the data. I should say I do have

1 some conflicts here. I sit on the scientific advisory

2 board for Cerus. So, I'm not talking for Cerus yet. I
3 want to direct one part of your trial and that is
4 around bacterial risk because clearly I want to compare
5 apples to apples. The American Red Cross data which
6 -- showed a risk of 1 in 75,000 for reported septic
7 transfusion reactions. The data is quite clear that
8 probably only 10 percent of reactions are actually
9 reported. And I think you do need to compare the data
10 to the accumulating data that suggests that about 1 in
11 1200 apheresis platelet products are contaminated with
12 bacteria, even after bacterial testing is implemented.
13 So, you do need to compare the right numbers on the
14 other side of the slide.
15 DR. VOSTAL: I think that's a very good
16 point. I think we have to get a good handle on what
17 the true septic rate is. I think your study was
18 wonderful because it had such large products that were
19 tested. The number that you quote for 1 for 1200, that
20 was from a relatively small study that's still ongoing
21 so I don't think we can actually rely on the data until

1 the study is finished.

2 DR. BENJAMIN: I believe that the data is

3 coming from three studies that show very similar data.

4 I think you were at the presentation by Dr. Larry

5 Dumont on this. It is consistent with other papers

6 published that suggest that -- errors are a major

7 problem with bacterial testing and therefore that we

8 probably are missing, that's the appropriate number,

9 whether it's 1 in 1,000, 1 in 2,000, we'll find out

10 with more data, I agree, but clearly a whole lot higher

11 risk than 1 in 75,000 that you referred to.

12 DR. VOSTAL: The other thing is actually

13 the number that you quote, 1 in 1200, is a contaminated

14 product so it's difficult to translate that to a septic

15 transfusion rate because not all contaminated products

16 will lead to a septic reaction.

17 DR. BENJAMIN: Right, but I suggest that

18 the general public is interested in a sterile blood

19 product and that just because the patient doesn't get a

20 fever doesn't mean that the transfusion of live and

21 viable bacteria is not bad for the patient.

1 DR. VOSTAL: Well, I agree. I mean, I
2 think it's best to transfuse sterile platelets but, you
3 know, I think we have to look at the data as it falls
4 out and if you're going to compare adverse events such
5 as ARDS you want to compare it to an equally
6 significant adverse event and that would be a septic
7 transfusion and I think you have to take the data where
8 you have it. Right now the data indicates that it's 1
9 to 75,000.
10 DR. BENJAMIN: I do want it on record that
11 I think that's misquoting the American Red Cross data.
12 DR. BRACEY: The question that I've got,
13 you refer to the hemovigilance effort in the EU that
14 suggests that the use of these products is not
15 associated with an inordinate number of adverse
16 pulmonary events. Obviously it's not a clinical trial.
17 The question is, is that hemovigilance system so weak
18 that it's, you know, the clinical data doesn't suggest
19 that -- and that's where I'm a little confused.
20 DR. VOSTAL: Right. I think it's difficult

21 to know how sensitive the hemovigilance data is or data

1 collection is for detecting those types of adverse
2 events. Those are very complicated, patient is very
3 sick. I think it may be difficult to correlate the
4 transfusion to a reaction that happens six, 12 hours
5 later so I think it would be very difficult to do.
6 You know, one thing that struck my mind
7 when we were talking about hemovigilance, Dr. Corash
8 put up a slide that showed that the patients in the
9 hemovigilance studies had a reaction rate of about 10
10 percent and I believe earlier on he said that the
11 adverse event or reaction rate in the SPRINT clinical
12 trial was like 80 percent. So, it's difficult to
13 imagine that a study that's picking up 80 percent
14 adverse events wouldn't be more sensitive than a study
15 that's only picking up 10 percent.
16 DR. BRACEY: Yes, Gerald?
17 DR. SANDLER: In the spirit of everyone who

18 wants to get pathogen-reduced products out there as
19 fast as possible, I would like to just make some
20 comments from the bedside regarding the impact on
21 efficacy. With regard to red cells, as I think

1 everyone knows, if you get a unit of blood from someone
2 with a low hematocrit, you get 175 mils of red cells;
3 if you get one with someone with a high hematocrit, you
4 get 250 and we give them out a low unit, high unit. No
5 one knows the difference. At the bedside the
6 difference of 10, 20, 30 mils of red cells in the bag
7 is not noticeable in adult transfusion.
8 With regard to platelets, as you know, we
9 count how many unit equivalents there are in a bag.
10 Six unit equivalents is the requirement, we get that,
11 and then if they get all the way up to 12 we get a
12 double. So, that means that I get six-unit equivalent,
13 7, 8, 9, 10, 11, and there's a big difference in terms
14 of real numbers but I can't tell the difference,

15 whether some are in a bag of six or whether some are in
16 a bag of 11 although there's an enormous difference.
17 So, as you look at the data it's absolutely essential
18 scientifically the way you do it, keep in mind that at
19 the bedside it's not very easy to see the difference.
20 Dr. Corash pointed out so we run up 7 more minutes and
21 we get some more and that does it; I'm in that camp.

1 DR. BRACEY: Dr. Duffell?
2 DR. DUFFELL: You mentioned in your
3 presentation, Jay mentioned earlier today at lunch the
4 difference between active and passive adverse event
5 reporting. And I think I know conceptually what you're
6 talking about but just for clarity purposes, I mean, on
7 the active adverse event reporting are you expecting
8 that there will be some sort of an employed test
9 methodology that is specifically geared to list
10 potential side effects? For example, like TRALI, there
11 are certain diagnostic criteria, right, that confirm

12 that diagnosis; is that what you mean, that you're
13 looking for that level of follow-up in these types of
14 trials?
15 DR. VOSTAL: Right. I think you have to
16 have someone who is actually looking for adverse events
17 to be able to, you know, recognize one when it's
18 happening.
19 DR. DUFFELL: So it's more than just a
20 query of the event, but a testing for it, is what I'm
21 getting at. I mean, you know, in a drug trial

1 sometimes I have had it where you list a whole bunch of
2 different -- anything that can happen in these areas
3 but then you could go a step further -- this is where
4 I'm trying to get to, Jay -- I mean, are you expecting
5 that in a respiratory area, I actually go further yet
6 and say no, I'm interested in TRALI so I'm going to ask
7 these 12 questions?
8 DR. VOSTAL: Yes --

9 DR. DUFFELL: Is that the expectation from
10 a development standpoint, from a data collection?
11 DR. BRACEY: I think we can get a comment
12 from Dr. Corash on that.
13 DR. CORASH: Yeah, several points of
14 clarification. So, first of all, in the SPRINT trial
15 these patients were monitored for 35 days for all
16 adverse events, whether or not there was a suspected
17 relationship to the transfusion, collected all adverse
18 events. When we did the extended analysis with the
19 expert panel who went back to primary medical records,
20 they reviewed all adverse events in patients with any
21 clinically suspected grade three, four and some grade

1 two pulmonary system adverse events. They were blinded
2 and they looked at all adverse events for a total of 49
3 days because we wanted to make sure we were capturing
4 any late events.
5 And, they put acute lung injury into a

6 single category so the people who are experts in acute
7 lung injury actually do not make a distinction between
8 ARDS, which has one level of inspired O2 to the PA02
9 ratio versus they looked at what they call acute lung
10 injury the entire spectrum and we saw no difference.
11 In the hemovigilance studies these patients were not
12 monitored for all adverse events, although these
13 hemovigilance officers could report any adverse event
14 they wanted to. They were specifically looking at the
15 first 24 hours after each transfusion. They had
16 specific criteria, though, for transfusion-associated
17 lung injury with a very specific form and specific
18 checklist. And, you know, Dr. Vostal is raising an
19 interesting hypothesis, that if these platelets are
20 damaged one might expect the most acute period of time
21 for this lung injury to occur immediately after the

1 transfusion when the circulating platelets are at the
2 very highest level. I would point out that in the

3 hemovigilance study 50 percent of the patients in these
4 studies received multiple exposures so these patients
5 were having longitudinal, in some cases for up to three
6 years, repeated assessments for adverse events
7 associated with these transfusions, including TRALI.
8 DR. BRACEY: We have time for maybe two
9 more questions or comments. There was one from Dr.
10 Kuehnert and then we'll take one more.
11 DR. KUEHNERT: You probably won't have to
12 time to explain this all through but this just may be
13 more of a comment about the FDA teeter-totter. I don't
14 know exactly what goes into it. I'm a little confused
15 as far as, you know, what the approach is to the
16 risk-benefit analysis. Is it just -- and I missed the
17 first part of your talk, maybe you explained it but
18 you're just looking at, it looked like viral risk,
19 bacterial risk. What about, you know, risk from
20 noninfectious complications which might be affected by
21 this technology? I mean, and also are you comparing

1 the severity of events on each end also? I mean, is
2 there some sort of prospective approach to the
3 risk-benefit analysis, I guess is what I'm asking.
4 DR. VOSTAL: So, what I showed on these
5 slides is a very simplified view and it's really a
6 process where you weigh the benefits on one side, weigh
7 the risks on the other side. It's, you know, I think
8 you can't really put one risk on it or one benefit.
9 You have to take it as an aggregate.
10 You know, it's difficult to quantitate, you
11 know, but what I was trying to point out is, you know,
12 on one side you have the good things and on the other
13 side you have the bad things and I think we have to
14 come together as a transfusion community and decide
15 what are the benefits and what are the risks. But here
16 I'm trying to point out a documented risk, risk that
17 was documented by a prospective blinded clinical trial
18 that actually did not come up for discussion so far
19 after a day and a half of discussion. So, I think, you
20 know, a phase three blinded clinical trial is the gold
21 standard for evaluating drug and biologic and I know if

1 you get results coming out of that study that are not
2 favorable to the product, I think we have to at least
3 discuss it and, you know, most likely investigate what
4 the cause was.
5 DR. KUEHNERT: Yeah, I mean, I think you
6 definitely convinced me there's something worth looking
7 into. I'm not sure you've convinced me that, you know,
8 it's not, that it's not justified by the current
9 risk-benefit profile. That's where I just wasn't so
10 sure because I'm just not sure what these mean. I
11 mean, I think they need further investigation. ARDS
12 is, I mean, it's a huge sort of category of things
13 which can mean a lot of different things, even
14 over-transfusion. So, that's where I just had some
15 questions.
16 DR. BRACEY: Last question or comment from
17 Dr. Kouides?
18 DR. KOUIDES: In the bigger picture, you
19 were focusing, obviously some of us have mentioned that
20 your focus has been, in terms of reducing the
21 infectious transmission rates, but there's

1 non-infectious issues, TRALI being the number one cause
2 of fatalities. Could you clarify, so, based on your
3 analysis of that data, there is this concern about
4 perhaps acute lung injury, ARDS type picture. Perhaps
5 could Dr. Corash clarify, I thought I caught right at
6 the very last part of your presentation, you mentioned
7 based on the European data -- again I'm not sure how
8 active the surveillance is but there's only one case of
9 TRALI out of 20,000, is that --
10 DR. CORASH: One case of TRALI, and when we
11 say active surveillance what we mean is the data that
12 comes from France, from the EFS system, has a legal
13 requirement for reporting the response to each
14 transfusion. The system that we put into place in
15 other countries that did not have an active
16 hemovigilance system in place required that the
17 physicians fill out a report for each transfusion.
18 From that database of 28,000 transfusions we have one

19 case report of TRALI. It comes from France. It's an
20 apheresis platelet product. The donor was a
21 multiporous female with high titer of anti-HLA

1 antibodies. So those are the data that we have to
2 date.
3 DR. BRACEY: I think we need to move on to
4 the final speaker. Thank you, Dr. Vostal. Our next
5 speaker is Dr. Brian Custer. Dr. Custer is Assistant
6 Investigator of Epidemiology and Health Policy at Blood
7 Systems Research Institute of San Francisco, and he
8 will speak to us on economic issues of pathogen
9 reduction.
10 DR. CUSTER: Thank you. Actually, if I
11 could entitle this I would actually call it health
12 economic issues so I'm not an economist in the sense of
13 a traditional economist but I tend to think of things
14 in terms of health outcomes and the cost that we
15 actually might spend to get a health outcome.

16 I do have a disclosure that I am currently
17 have an unrestricted grant form Navigant to look at
18 health economic issues related to Mirasol technology,
19 no other potential conflict to disclose.
20 I'm going to talk a little bit about the
21 pathogen activation Consensus Conference in Canada.

1 The question, which is question five, which was how
2 should the costs and benefits of pathogen inactivation
3 be assessed. In the preliminary report the response
4 was PI should not be based solely nor even primarily on
5 the results of an economic analysis; the costs are
6 currently unknown and the benefits of difficult to
7 quantify.
8 At the final report, sort of released about
9 six months later, I think that's sort of the
10 development of that thinking went on so that now, the
11 response to that question is economic evaluations of
12 all PI procedures should be conducted but

13 implementation of PI, however, should be based on other
14 considerations in addition to the results of the
15 economic analysis. This practice is consistent with
16 economic evaluation results, how economic results are
17 used to assist with decisions in other areas of
18 healthcare.
19 Okay. So, now getting to economic
20 evaluation, there really are sort of two very broad
21 kind of economic evaluation studies. The first is a

1 budget impact analysis. This is actually an estimate
2 of the financial consequences of the adoption and the
3 diffusion of new technology or new healthcare
4 intervention within a specific healthcare system or
5 context given inevitable constrained resources. It's
6 essentially a question can we, they or you afford it.
7 What are the cost tradeoffs? Often these results are
8 not publicly disclosed.
9 The next version is cost-effectiveness

10 analysis, or CEA, and this whole group of things that
11 try to estimate costs and outcomes of alternative
12 healthcare interventions over a specified time period
13 in order to determine the efficiency of an
14 intervention. In other words, does it increase health,
15 if so, at what cost, does it represent the value for
16 money? These studies are often reported in scientific
17 literature.
18 Now, I should say out of fairness, this is
19 the pharmacology or the pharmaceutical model but that
20 this model applies to blood safety has certainly been
21 debated and will probably continue to be debated but I

1 think it's a useful structure for thinking through
2 these issues.
3 All right. The basic economic concepts
4 are, of course, if there's scarcity, which is that we
5 have limited resources. Because we have limited
6 resources we have to make choices. In making choices

7 we actually do what is called opportunity cost. This
8 point was made earlier but I think that there's more to
9 opportunity cost than just sort of choosing one thing.
10 It's actually when you make that choice you are
11 willingly foregoing the benefits of other alternatives
12 so it's not just as simple as we made the best choice
13 but we also are saying that the choice we made is more
14 valuable and more important than what we have foregone,
15 what we didn't get. I hope to make that a little more
16 clear as I work through this talk.
17 And then finally, healthcare economics, of
18 course, attempts to kind of put things on a common
19 denominator. That common denominator is usually
20 quality adjusted life years. So, what we're trying to
21 do is compare the relative severity of the disease in

1 some sort of way that we actually can say is TRALI as
2 bad as HIV or something like this.
3 All right. The methods -- actually I'm

4 just not even really going to touch on these, because I
5 think many people are familiar with them. The only one
6 I'm going to point out is the fact that the comparator
7 is critical. These cost effective analysis results are
8 relative comparisons of usually current practice -- new
9 intervention -- so, in other words, they're
10 relativistic, comparing the difference in cost between
11 intervention B and A divided by the differences in
12 ineffectiveness of intervention B and A. This
13 generates what's called the incremental cost
14 effectiveness ratio. And so when I say ICER, that's
15 what I mean.
16 Okay. So, now sort of moving on, this is
17 more background kind of conceptualization of this
18 issue, this is what's called the health production
19 function. It's looking at sort of the total cost of
20 the input, how much money are you spending and how many
21 health benefits in terms of QUALYs are you achieving.

1 I use this example for hepatitis B screening quite a
2 bit before we did screening at all. For sure are were
3 probably substantial health costs and lack of benefits
4 being incurred. When you start doing surface antigen
5 screening, cost-saving technology, meaning all of those
6 infections that were being missed are now being
7 interdicted and so you actually save downstream
8 healthcare costs. You can move up this curve all the
9 way to what is perhaps -- some people might disagree
10 but what's called -- take all the current screens we're
11 doing and we compare that to pathogen reduction
12 technology we're seeing where the cost-effectiveness
13 ratio comes out.
14 I do want to make a point that this is just
15 a pictogram, as it were, that I am not in any way
16 suggesting that all current screens and moving to
17 pathogen reduction technology represents -- there may
18 be much more value there than we appreciate. But the
19 other thing that I wanted to point out with this figure
20 is that, you know, if we had the luxury -- which we do
21 not -- of comparing pathogen reduction technology to no

1 screening at all, we would all know right now that it's
2 very cost-effective and you might not be having this
3 discussion in this way.
4 All right. This is just a quick slide to
5 sort of make you familiar with the terms that I will be
6 using, so, I'm going to say psoralen light treatment,
7 when I say PLT -- of course I'm not saying platelet in
8 this case, I'm saying, psoralen light treatment and
9 then specifically Riboflavin light treatment. It's
10 just something with the terms, because the other terms
11 are available in the handout the Committee has.
12 In the cost-effectiveness studies that have
13 been conducted so far -- and I guess at this point I
14 will point out that I'm going to talk a little bit
15 solvent-detergent treatment and then I'm going to talk
16 about actually INTERCEPT, the technology from Cerus.
17 Cerus has actually done a very good job of doing health
18 economic studies along these lines and publishing them
19 so that is the literature that is available that I'll
20 basically do most of this talk off of. In those
21 analyses what has been included so far, HIV, hepatitis

1 C, hepatitis B, bacteria and sometimes HTLV.
2 These are all sort of methodologies that
3 are standardly accepted but also you see that they're
4 being used in the studies being conducted for this
5 product. Definitely you like to see at least a couple
6 of reference populations, two or more, considerations
7 with respect to age and gender being transfused.
8 Sometimes results are not aggregate-reported, break
9 them out by patient populations. There's multiple
10 procedures included within these analyses. Common
11 assumptions are that pathogen reduction technology is
12 100 percent effective, that there are no secondary
13 transmission events, and that there no adverse events
14 resulting from the use of the technology.
15 Okay. So, kind of going back into history,
16 I think history does have a little lesson for us, which
17 is at the time of the decision or that there was
18 discussion about using solvent-detergent treatment --
19 the product is no longer available, and I want to make

20 clear this is not Octaplas -- but just before actually
21 that technology sort of came out and was going to be

1 used, estimated cost-effectiveness was about $300,000
2 for quality adjusted life year.
3 Soon after and sort of the reality of what
4 it was going to cost to do it and some other factors
5 that came into plate, that jumped quite dramatically in
6 order of magnitude so there was almost $10 million for
7 quality of adjusted life year. So, the point of the
8 story -- it's just a precautionary tale -- usually the
9 premarket estimates are almost always lower than the
10 postmarket estimates.
11 Similar analysis that actually did look at
12 some of technologies available in Europe, actually
13 found about $2.2 million for quality adjusted life year
14 for the setting in Spain -- and then more recently
15 there was a look at this issue that tried to actually
16 incorporate some of the effects due for TRALI

17 reduction. And if you are able to actually reduce
18 TRALI in any sort of efficient way you see a pretty
19 dramatic change in the ratio, because now you're
20 looking at something depending upon the patient
21 population here between 50 to 100 or $200,000 for in

1 this case quality of life year gain. So, the point of
2 the story is that this evidence usually is all over the
3 map and it has to do with the assumptions that are
4 built into the analyses. And that's actually all I'm
5 going to say about that.
6 So, I want to spend most of the time
7 talking about sort of I think where the future is, what
8 we're thinking about. I'm going to use this one
9 example for the INTERCEPT technology. The other
10 studies that have been conducted in other settings, I'm
11 going to briefly cover that literature but many of the
12 assumptions that were built into those analyses are
13 exactly the same as the ones that I'm going to cover

14 right here.

15 So, this one, which is a study by Bell and

16 colleagues actually looked at apheresis random donor

17 platelets prepared using psoralen light treatment, the

18 pathogen for HIV, hepatitis C, hepatitis B, HTLV and

19 bacteria in the U.S., four-setting, four patient

20 groups, used estimated life expectancy in the

21 transfused patient population, that's a critical issue,

1 and studies that really need to include this and not

2 the general population, did not look at productivity

3 losses. Estimate the cost of the treatment at about

4 $100. That's not that different from where we are here

5 today. And that's in 2001 U.S. dollars. The results

6 of this, which I'll be showing you in just a second,

7 were most sensitive to sepsis and death attributable to

8 bacterial contamination, keeping in mind this study was

9 actually conducted prior to the use of bacterial

10 culture in platelets here in the U.S. increased

11 transfusion of platelet units resulting from reduced
12 platelet recovery was something that -- was sensitive
13 to so it should be thought about and looked at. They
14 did actually say that in HCV like virus actually the
15 results were sensitive to that and then actually the
16 results were sensitive essentially to age.
17 So, here actually are the results from that
18 study and also a couple of other studies that I'll just
19 sort of briefly walk through. I don't have a pointer
20 but we'll start just looking at the pediatric
21 population. That is sort of the first column

1 after intervention, then goes into hip replacement,
2 CABG and then nonHodgkin's lymphoma. If you look at
3 single donor apheresis prepared with pathogen reduction
4 technology compared to all current screens at the time,
5 with bacterial culture it was about 4.8 million for
6 quality adjusted life year. Without it, it was 1.3
7 million per quality adjusted life year. As you move to

8 the right of this slide you see that actually
9 increasingly it was more expensive in terms of less
10 efficiency in these different patient populations
11 looked at.
12 For random donor prepared platelets,
13 actually you have a cost-effectiveness ratio that's
14 actually around $500,000 without bacterial culture and
15 about $1 million for quality adjusted life year with
16 bacterial culture. In the pediatric patient
17 population, once again moving up, it's still relatively
18 cost-effective considering some of the technologies
19 that have been discussed.
20 A similar study was actually conducted in
21 Japan. Actually, I'm just reporting the results. The

1 natural units are the yen. Don't fall off your chair,
2 it's 99 million yen, not dollars. In parenthesis is
3 actually the U.S. dollars, which was around 818,000 per
4 quality adjusted life year in the pediatric population

5 going up to as high as $3.6 million for non-Hodgkin's
6 lymphoma in adults.
7 This slide is a little bit difficult to
8 read but basically building off of the same sort of
9 approach to doing the studies. This one looked at two
10 different populations in Europe. Here the ratios are a
11 little bit more favorable. You see around $340,000 for
12 life year gain, for pediatric oncology, going up once
13 again to substantially more.
14 Then this study, actually, I believe the
15 "S. Morlin" (phonetic) study which actually is from
16 Belgium, looked at nine different patient populations,
17 really quite extensive. It's a nice paper to look at
18 to try to think through what are the different benefits
19 that might accrue for different patient populations.
20 However, moving on, there is another study
21 by another group of authors that used a totally

1 different set of assumptions and methods and they were

2 actually looking at the question in the Netherlands
3 should you use bacterial culture to deal with bacterial
4 contamination or should you look at pathogen reduction
5 technologies. And so those results are actually
6 substantially different. If you're looking at
7 bacterial culture compared to just doing nothing it's
8 about $91,000 for quality adjusted life year. Pathogen
9 reduction compared to doing nothing is about $500,000
10 for quality adjusted life year but if you look at
11 pathogen reduction after you've already adopted
12 bacterial culture, now you're in the range of $3.6
13 million for qualify adjust life year.
14 This is a summary of that same information.
15 The point here is actually just to sort of show that
16 this study I think did a very nice job of trying to say
17 there are many aspects of this question that are
18 uncertain, that are unknown, and so you get quite a
19 substantial range of results for bacterial culture.
20 The actual dotted lines actually represent the
21 confidence intervals for the two different

1 technologies.

2 And I would make one point about bacterial

3 culture. It's the smaller dotted line. You can

4 actually see the 95 percent confidence interval, this

5 is shockingly wide so there are definitely assumptions

6 there that we're going to get into. Pathogen reduction

7 has narrow confidence limits with this $500,000 for

8 quality adjusted life year -- as the point of incident.

9 Once again, when you look specifically at pathogen

10 reduction compared to bacterial culture and you see

11 that the ratio is not as favorable but there's a fair

12 amount less uncertainty regarding the costs and

13 consequences.

14 Okay. So, that literally is the extent of

15 what the economic evidence is available today. I want

16 to sort of just make some points regarding the

17 limitations of that effort as evidence and then a few

18 additional things to consider as we consider pathogen

19 inactivation. So, some of these studies that didn't

20 indicate which screening tests were used, that becomes

21 very important to understand, is it really reflective

1 of a good setting, for example, U.S. or not? There is
2 a lot of effort and a lot of discussion that goes on
3 about this unknown emerging pathogen. I have a
4 difference of opinion with the consensus panel about
5 the use of unknown emerging pathogens as something that
6 you would do in an analysis.
7 I think as I will make this point again in
8 just a few minutes, I think there's too much potential
9 to make the results be what you want them to be. The
10 issue that really is on the table as we look forward is
11 the question of how much can noninfectious threats
12 actually be intervened here with the use of these
13 technologies and then you definitely need to try to
14 account for the product loss.
15 So, the potential for increased transfusion
16 unit, we say that there isn't much of a bedside, still
17 want to come at it from the standpoint of a blood bank,
18 do I need more unit of platelets available and so on
19 and so forth. All right. So economic data for
20 Riboflavin light treatment and for Methylene Blue light

21 treatment are not available.

1 So, an ideal economic analysis would
2 actually in the base case compare each technology to
3 all interventions in a given setting, provide a list of
4 infectious threats known to be reduced or inactivated
5 by the technology, provide a list of the noninfectious
6 threats reduced or inactivated, importantly, provide
7 realistic uncertainty ranges for those parameters that
8 are uncertain, conduct sensitivity and scenario
9 analyses. I think this gets into the question of if we
10 can do stepwise or group deletion of interventions we
11 really need to appreciate what that impact is,
12 incrementally as we consider the various options.
13 And then sort of it's kind of the question
14 that remains out there, because there's no evidence one
15 way or another about this but would actually some sort
16 of pathogen reduction technology allow for the
17 modification of donor selection criteria, could be

18 tattoo/piercing deferrals, travel to malaria-endemic
19 areas, talk about increase of 2 to 3 percent of supply,
20 that doesn't have ramifications for availability so,
21 it's definitely important to model. However, I have to

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1 go back.
2 So then moving on, think about sort of
3 where we stand now, really this is actually
4 hemovigilance data for 2003 and 2004 so really, as we
5 all know, in terms of transfusion adverse events,
6 reaction is actually in these noninfectious issues. We
7 do get into bacterial contamination that is relevant in
8 that setting but it's like how many of these can you
9 actually prevent or what increment of these could
10 actually be prevented by the use of these technologies.
11 There is some evidence of course that you might be able
12 to prevent or minimize some TRALI, maybe even some
13 febrile or nonhemolytic reaction, so, accounting for
14 that kind of issue moving forward I think is where you

15 will see shifts in the cost-effectiveness ratio than
16 what I just presented.
17 There are limitations on estimating sort of
18 the magnitude of all current risk and potential risk
19 reduction using pathogen reduction technology are just
20 not possible. Even in a setting like Quebec, which I
21 just sort of brushed right over, everybody knows that

1 underreporting is a problem in even an active
2 surveillance system for hemovigilance, of course we
3 don't have a hemovigilance system in the same way in
4 the U.S. so it would be really hard to say, well, how
5 many of these could we actually realistically prevent
6 in this setting. Another thing that is definitely a
7 critical problem is that treatment cost data for many
8 of these conditions in the transfused population are
9 not available or not well-defined.
10 So, is the ideal analysis possible in the
11 U.S. today? That answer is no. Well-characterized

12 cost data are not available. It's a question of are
13 there unknown emerging agents, separate issue, then
14 there's this question about unknown emerging agents. I
15 just find that even if you say I want to do something
16 that's HIV-like or hepatitis C-like that those are not
17 going to be next agents that impact the blood supply.
18 We don't know what it's going to be.
19 So, we can use those as a boundary estimate
20 in something like a sensitivity analysis. That would
21 be informative for sure but I wouldn't base your

1 economic question just on unknown emerging agents, just
2 makes me uncomfortable, because I don't know what it
3 will look like. It will happen but we just don't know
4 what it will look like.
5 Analysis have to data- driven and you don't
6 have that nationwide data in transmission outcomes in
7 the U.S. at this point. So, it's going to be
8 model-based that means it's going to have assumptions

9 that some people are probably going to disagree with.
10 That's just going to be the reality.
11 So, I do want to spend just a few minutes
12 on this opportunity cost issue revisited. So it's
13 possible consequence and forgone benefits, things like
14 I'm going to put up here, some of them may make an
15 impression on you, some of them may not. What I'm
16 putting up there are things to thing about.
17 So, what if the emerging threat is a prion
18 or some agent that's highly resistant to treatment?
19 Well, we've done what we can, you obviously have to
20 make a decision to use technology or not, knowing that
21 it's not going to do everything but in the public's eye

1 when we use the term pathogen inactivation or pathogen
2 reduction would not be well-received at all. Will PRT
3 lead to less interest in screening test development?
4 Brian McDonough discussed this a little bit about the
5 market for blood screening anyway but does this create

6 an additional disincentive to screen test developers
7 and infectious disease diagnostics? And then what did
8 that mean for the countries that currently can't
9 account for those current screens, so we're looking at
10 sort of the reverberation to more resource-limited
11 countries for the adoption of the technology.
12 And, finally, I think that something that
13 we talk about when we think about removing various sort
14 of donor tests, well, actually there's a public health
15 issue here that also has to be addressed. I don't
16 think that even if pathogen reduction technology
17 exquisitely deals with West Nile virus, does that mean
18 we're going to stop testing donors for West Nile virus?
19 A donor comes in to donate, has a West Nile virus
20 infection, that's something that you probably want to
21 know and want to communicate to that donor. If we got

1 rid of that test obviously we couldn't communicate with
2 that donor and we will just never know. So, there are

3 just some tradeoffs there. And this is truly an
4 opportunity of cost in the sense of what does it mean
5 if we make some of these modifications.
6 Okay. So, in conclusion, actually,
7 pathogen reduction technology is not cost-effective
8 according to traditional thresholds but, as many people
9 have said already, and is absolutely the case, this has
10 not been applicable to blood safety; however, it is
11 likely that even a comprehensive assessment of pathogen
12 reduction technology will not produce an incremental
13 cost-effectiveness ratio that's consistent with other
14 sectors of healthcare. Pathogen reduction, the
15 cost-effectiveness ratios are highly sensitive to
16 whatever interventions are included in the analysis,
17 improvement in the overall ICER can be achieved but
18 only if the mix of currently adopted safety procedures
19 could be discontinued are included in that analysis.
20 So, the final is that just sort of this is
21 what I think things sort of stand today from available

1 research compared to current viral screens and
2 including bacterial detection where conducted for
3 pathogen reduction technologies are about $2 million
4 for quality adjusted life year, for plasma, for
5 platelets with and without bacterial culture -- but
6 let's say "with" because that's where we are -- it's $1
7 million for quality adjusted life year and, of course,
8 for red cells, no information is available for that.
9 Thank you.
10 DR. BRACEY: Thank you, Dr. Custer. I'll
11 open up the floor for questions or comments. Dr.
12 Klein?
13 DR. KLEIN: Brian, thank you very much.
14 That was nice. It was a little more than we got in
15 Canada, which is very helpful, but I wonder, there are
16 a couple of issues that I think I'd like to hear you
17 discuss a little bit more. You suggested that if we
18 developed models, say, on one end of HIV for which we
19 have a ton of data, secondary spread, cost of
20 treatment, death, disability, and on the other end West
21 Nile virus, for which there was very little, and it's

1 quite likely that the next agent will fall somewhere in
2 between, that these kind of boundary estimates are not
3 helpful but is it realistic to just ignore them?
4 DR. CUSTER: Well, I guess, as I said, I
5 don't think that you can ignore them and I think that
6 you can do them in analysis, sensitivity analysis. We
7 sort of talked about this before but I actually, I
8 challenge the Committee to really ask themselves
9 something like HIV will affect the blood supply in the
10 current world that we live in.
11 So, the amount of surveillance that's going
12 on is sort of much more aggressive and much more
13 thoughtful than it used to be. So, I would be very
14 surprised. So, maybe it's informative but I think it
15 also is a little bit disinformative because I may wrong
16 and time will tell but I would be surprised if
17 something of the level of HIV serves nothing to the
18 blood supply went unnoticed for two to four years and
19 we had massive amounts of transfusion-transmission of
20 that pathogen.
21 DR. BRACEY: Ms. Finley -- oh, Dr. Klein,

you wanted to follow-up?

DR. KLEIN: If I could just follow up, I hope you're right. I hope I'm not around if you're wrong. I also wonder about the cost that we currently give to our system because as you suggested we ought to be looking at the cost of the strategy that we're using and comparing that with the strategy that we want to put in place. And I wonder if any of the models look at the cost of the lost donors and what it requires to recruit new donors, the offsetting costs which you mentioned, and the cost of introducing the new test, which is substantial to the community, just a number of things that are changing your information systems every time and with West Nile virus changing it as the epidemic changes in various areas of the country. Do you really think that we've costed out what we're doing now accurately?

DR. CUSTER: We actually absolutely have

19 not. I think that the cost data in sort of blood
20 safety and transfusion medicine is very poor, probably
21 a question of what is the cost of truly recruiting a

1 new donor and so on. There are estimates and, you
2 know, what it costs to have a recruitment staff, for
3 example, but on a per donor basis that information has
4 not been done. So, I need to find a cadre of
5 economists who want to come and really look at some of
6 these questions.
7 DR. BRACEY: Do you have a question, Ms.
8 Finley?
9 MS. FINLEY: Thank you for your
10 presentation and I will also follow-up on the last
11 comment about really asking economists to look at this.
12 There's one very large section of costs that's never
13 addressed in any presentation that I have ever seen in
14 what is now approaching 15 years in the blood policy
15 area, which is the total cost of both hepatitis C and

16 HIV. Most of the costs of the illnesses were borne by
17 the patients who were affected, not by the blood banks.
18 There's never been any assessment of the cost to those
19 patients, cost of treatment, costs to their families,
20 lost income, et cetera. There's never been any
21 assessment as far as I've ever seen what the industry

1 spends on all of this, defense against all of the
2 litigation, all the PR firms that were on retainer, all
3 of the lawyers that are retained.
4 And when I look at opportunity costs and
5 costs for quality of life year saved that's only half
6 of the equation. If we're looking total costs we need
7 to consider all of those issues but we've never
8 included those and I would challenge the Committee and
9 the industry to take a look at that because I think if
10 anyone ever bothered even if it was on the back of an
11 envelope to sketch out what this cost, probably you
12 would look at the implementation of new testing

13 modalities in a slightly different manner.

14 DR. CUSTER: You're correct that nobody has

15 ever tried to calculate those costs. I believe we're

16 still sort of back at square one just starting with the

17 most basic question and there are some efforts, recent

18 efforts, just now getting underway saying what is

19 actually the cost of a unit of blood. So, we start

20 with that and that actually includes the adverse

21 events. So, it starts to move in that direction but

1 those sort of activity-based cost methods are just

2 starting to be used and applied in some sense.

3 MS. FINLEY: They couldn't have been

4 applied in these situations, I very firmly believe, and

5 I think the fact -- and I'm not holding you

6 accountable. I'm just saying that when we look at

7 this, especially when we're discussing implementation

8 of an expensive new technology, we have to look at the

9 whole 360.

10 DR. CUSTER: I think that that's true. I
11 think that one of the things that happens in the U.S.
12 in particular is because we have lots of
13 compartmentalized budgets, that's a really difficult
14 question, in a setting where you have actually one
15 healthcare payer, a single payer system that is saying
16 what is my liability for my blood blanks, what are my
17 patient outcomes, and so on and so forth, there might
18 be work that actually has looked at some of that stuff.
19 MS. FINLEY: I've never seen anything. If
20 you ever see it, please let me know because I'd be very
21 interested. Thank you. That was a very interesting

1 presentation.
2 DR. BRACEY: We have time for one more
3 comment or question from Dr. Triulzi.
4 DR. TRIULZI: Thank you, Mr. Chairman.
5 Brian, you made in your comment in the second to last
6 slide that the thresholds don't compare favorably to

7 general medical interventions. But, I have seen in the
8 past a comparison to general transfusion medicine
9 interventions and actually it compares pretty darn
10 favorably.
11 In fact, when we look at individual unit
12 NAT or Chagas, I would bet that they are probably on
13 the order of a log higher than these kind of numbers,
14 particularly 500,000, if bacterial culture is
15 discontinued. So, an alternative message might be that
16 in the world of transfusion medicine, it is equally
17 cost-effective to the other measures that we have
18 included or planned to include in the near term and
19 that the benefit, potential benefit as an emerging
20 pathogen protection is a bonus that we get at no more
21 cost than other things that we're planning on

1 implementing.
2 DR. CUSTER: I think that that's a
3 reasonable way of looking at it. Clearly that evidence

-- and I said specifically for plasma $2 million for quality adjusted life year is the same as -- some of the other sort of solvent-detergent treatment in Spain, 2.2. So, yeah, no, absolutely, so there are added benefits and we do get a little bit caught in whatever the added benefits versus just saying where does it stand compared to what we're compared to do right now, so.

DR. BRACEY: I think it would be a good time for us to take a short break and reconvene at quarter of to see if we can fashion together a Committee recommendation. Thanks.

(There was a break in the proceedings.)

DR. BRACEY: Well, we've certainly heard lots of data, some data with slight, well, potential differences in the end analysis. What we are faced with right now is making a decision in terms of a course of action after hearing all of that data. In

1 some preliminary discussions we've talked about whether
2 in the broad concept we feel that the Committee is in a
3 position to recommend that in this country that we
4 begin to have some action regarding the issue of
5 pathogen reduction.
6 So, I would be interested in hearing
7 discussion. I think from what I have heard -- and I
8 could be wrong -- but there is a consensus that we
9 should begin to do something to address this rather
10 than to watch passively. So, I would open the floor
11 for discussion on that. Yes, Dr. Ramsey?
12 DR. RAMSEY: Just a general small point
13 before we start and that was my thought that if there
14 was a way to eliminate the need for blood irradiation
15 in the future, red cells included, then this would be a
16 contribution to national security by eliminating the
17 need for the blood irradiators that are perceived to be
18 a security risk for the country.
19 DR. BRACEY: Dr. Holmberg?
20 DR. HOLMBERG: Yeah, that's a very
21 interesting point. And I know CAP and AABB have been

1 involved with some of this because the nuclear people
2 have made a push on the safety, and also there are some
3 words out there about the CZM, the availability of the
4 CZM in a lot of the institutions. But some of the new
5 regulations actually require specific, secure locations
6 for irradiation and I think that that's something, too,
7 that in the future we may want to tap in with people
8 like Brian Custer as far as, you know, that's an
9 additional expense, too.
10 DR. RAMSEY: To decommission the
11 irradiator, that's another one, too.
12 DR. HOLMBERG: Well, that's right. We
13 don't want to end up like what happened in Brazil.
14 But, you know, I think that those are expenses that I
15 think that when we look at the total cost of blood what
16 are we actually, what potentially could be offsetting
17 some of these costs.
18 DR. BRACEY: One of the things that we've
19 heard is the term of paradigm shift and a move away
20 from a strategy of layering on test after test after
21 test as new agents are discovered. I would be

1 interested in hearing from the Committee, is there an
2 endorsement of paradigm shift in the way that we
3 address blood safety? Dr. Klein -- oh, Dr. Epstein?
4 DR. EPSTEIN: Maybe you want to go first,
5 Harvey because I'm going to speak against. I think
6 that it's a very catchy idea but I wonder whether it's
7 fundamental. I think the real issue is that we've
8 always been proactive and reasonably precautionary.
9 We've instituted many new things when we thought that
10 they had potential significant benefit and I think
11 what's really going on here is simply that we are
12 looking at a new technology opportunity. What's novel
13 about this new technology opportunity is that it puts
14 something precautionary in place. It's a safeguard
15 against many classes of potentially emerging agents,
16 not all but many.
17 And, I think that what we are mixing up is
18 that that unique feature of this technology is then
19 being seen as a paradigm shift. I think what it really

20 is, is taking advantage of a new technology opportunity
21 in its full dimensions. You could have argued that NAT

1 was a paradigm shift. Why? Because it was, you know,
2 it was reduction of the window period with direct viral
3 detection right at a genomic level. It never did that
4 before. Was it really a paradigm shift or was it just
5 a better mousetrap? So, I just find the term a little
6 bit disquieting because I'm not sure what element of it
7 is really a paradigm shift. I know what the attributes
8 are, which people will say. They'll say that, well, it
9 can obviate introducing new tests for new agents.
10 That's certainly true, but, you know, other things
11 might do that, too.
12 DR. BRACEY: Dr. Klein?
13 DR. KLEIN: I would like to take the other
14 side of that in that I think that the difference is --
15 and you can call it a paradigm shift if you like that
16 jargon or a proactive approach but I think the

17 difference is that we've relied upon a strategy of
18 waiting for something to be identified, then hustling
19 to find a way to interdict it and whether that way was
20 a test or whether it was a geographic exclusion or
21 whether it was some other method. It really is a

1 totally different approach, in my mind, because it's
2 always reactive. It waits for something to happen and
3 then you do something.
4 Now, with the plasma fractions, I think the
5 beauty is that if you had not known that West Nile
6 virus was transmitted via blood, you would not have
7 known from plasma fractions at all, or, we're not sure
8 now what the risk is of blood transmission of almost
9 any viral agent that is common in the U.S., influenza,
10 not to mention the new strains of influenza. Perhaps
11 they're transfusion-transmitted to some extent. Maybe
12 they cause morbidity and mortality. If we look hard
13 enough we might find that. If you had almost any of

14 the pathogen inactivation technologies -- and I don't
15 endorse any specific ones -- you'd never know because
16 you'd never see it. And I think that's the strategy
17 that I would support for making the blood supply safer
18 going forward rather than waiting for something to
19 happen and hoping that we can react quickly enough.
20 And again I just point out with West Nile
21 virus, there was a test and it still took us a year. I

1 think it was a magnificent feat but it still took us a
2 year to get a test that existed implemented. Suppose
3 there hadn't been a test. Suppose it was an agent.
4 And we know there will be another one, I'm sorry, I'm
5 absolutely certain of that, I don't know what it will
6 be but there will be one. If there isn't a test
7 available, it's certainly going to take us more than a
8 year. Are we willing to take that risk?
9 DR. BRACEY: Ms. Finley?
10 MS. FINLEY: I think there is an

11 opportunity for the concept of paradigm shift to be
12 misinterpreted by the public. You know, they're very,
13 very reliant and very knowledgeable about the test
14 aspect of it so I want to propose this language and see
15 if this might bridge the gap here. We feel that this
16 focus, as a focus provided by this new technology
17 opportunity presents the first opportunity -- say what
18 this is, what you want -- to utilize pathogen
19 inactivation to, you know, to move towards a more
20 proactive approach to blood safety, or words to that
21 effect.

1 DR. BRACEY: So the key point being moving
2 from a reactive stance to a proactive stance?
3 MS. FINLEY: I'm trying to capture Dr.
4 Klein's concept, with which I agree, and address what I
5 consider to be a possible misinterpretation as well as
6 Dr. Epstein's concerns.
7 DR. BRACEY: Did you have something, Matt,

8 or --

9 DR. KUEHNERT: Yeah. Well, one thing is

10 that, you know, this, I was having trouble grasping

11 what the Committee was thinking was the paradigm shift

12 and is it just pathogen inactivation or is that a

13 larger, broader scope which is all part of a strategic

14 plan and this is just one piece of it? In other words,

15 what I was saying before about evaluating every

16 intervention on its own merit, et cetera, I mean,

17 pathogen inactivity certainly is different. I mean,

18 this is the first time in my recollection that you're

19 actually adding something to blood components as

20 opposed to taking something away.

21 And, so, that is an important difference

1 but on the other hand it is just one possible

2 intervention and, so, I guess the Committee just has to

3 think about how much emphasis they want to, where they

4 want to put this in perspective in the greater scheme

5 of improving outcomes in transfusion.

6 DR. BRACEY: Right. That's a good point.

7 Clearly, I'm not sure if the Committee wants to endorse

8 this as the end-all, but be-all rather than as an

9 element. But, is there a comment or question from Dr.

10 Sandler?

11 DR. SANDLER: I agree with Ms. Finley. I

12 think that we all understand what we want to do but by

13 introducing something, paradigm shift, we're going to

14 take a page of text to explain that we don't really

15 mean stopping what we're doing and doing a variety of

16 things. I think it's best not to bring in that simile

17 or whatever it is that could be misinterpreted. I

18 think the focus of where we could use the remaining

19 time is to pick up on Dr. Alter's recommendation that

20 we recommend to the Secretary that there be a

21 commitment to some process to move this forward from

1 where we are. I think that's something that we can get

2 our hands around in the time that's left and do a good
3 job with.
4 DR. BRACEY: Thank you. Dr. Duffell?
5 DR. DUFFELL: Yeah, the way I look at it,
6 it's a shift from testing quality into the product
7 rather than building it in. Right now that's what's
8 we're doing, is we're testing the quality into the
9 product. Pathogen inactivation builds it in right from
10 the start.
11 DR. BRACEY: Dr. Triulzi?
12 DR. TRIULZI: Yeah, I think the layers of
13 safety concept has served us well, and I think that we
14 can position this, as was I think in Roger Dodd's talk
15 that testing accounts for that much of the layer and
16 everything else is this much of the layer, that we have
17 the opportunity to add another layer of safety-net
18 complements to the existing layers. And, so, it
19 doesn't take it into that shifting paradigm or change
20 in paradigm but if it complements the existing layers
21 of safety, and it doesn't necessarily even overlap a

lot but it complements it.

DR. BRACEY: Thank you. Dr. Klein?

DR. KLEIN: I would agree with Darrell in that I think perhaps the wording I was searching for would be adding a proactive strategy to the current testing system. By the way, just for historical accuracy, this is not the first time or even near the first time we added anything to blood. If we go back to adenine, it took us 20 years to add that to blood in the United States compared to Europe. And we can go back to other examples as well. So, maybe it's the first time we added anything for infectious disease but we've added things to blood.

DR. BRACEY: What I would suggest, I'll take a comment or question from Ms. Benzinger but perhaps with the thought and the discussion that we have had, we could look at the preamble that is in a fused draft and see if we can fashion that to meet the intent of the Committee. Ms. Benzinger?

MS. BENZINGER: That's what I was going to address. You've got that in Dr. Epstein's original

1 statement. If you go past the beginning you've got,
2 the Advisory Committee on Blood Safety recognizes that
3 accumulating evidence for the efficacy and safety of
4 pathogen reduction is now sufficient to warrant a
5 transition from the current strategy of reacting to
6 infectious threats after they have caused disease in
7 blood recipients to a proactive, preemptive strategy of
8 pathogen reduction that would broadly render known
9 agents non-infectious and prevent emerging agents from
10 becoming transfusion risks. Without using --
11 DR. BRACEY: Right. And what we were
12 talking about, without using that next sentence, we
13 would strike the next sentence that says we feel that
14 this paradigm shift is advisable and achievable, just
15 scratch that. So, is everyone in favor of that? Okay.
16 So --
17 DR. EPSTEIN: No.
18 DR. BRACEY: Dr. Epstein?
19 DR. EPSTEIN: Well, I guess what's
20 bothering me, it's not that we ever chose a strategy of

21 being reactive, it's just that's what was available.

1 Okay? That's the point that I keep wanting to fix. I
2 like what Darrell has suggested, which is that we frame
3 this as adding a safeguard. In fact, I have a zillion
4 slides where I've done just that. The last line after
5 the five tiers is a sixth tear which says pathogen
6 reduction for some products, and, I think what we're
7 really talking about is something along the lines that
8 the Advisory Committee finds that accumulating evidence
9 for the efficacy and safety of pathogen reduction
10 warrants a commitment and concerted effort to add
11 pathogen reduction technology as a broadly applicable
12 safety advancement which -- and I didn't quite work on
13 these words -- which additionally will provide a
14 preparedness or a safeguard against potentially
15 emerging infectious threats.
16 DR. BRACEY: Well, let's see if we can
17 capture that then. So, we can strike what you got

18 highlighted and then, let's see, sufficient to warrant
19 addition or adding --
20 MS. FINLEY: Warrants a commitment.
21 DR. EPSTEIN: And concerted effort.

1 DR. BRACEY: Okay. Let's see, can we get
2 the, get one --
3 DR. EPSTEIN: Well, I'm suggesting this
4 first line change recognizes to finds because we're
5 actually making a determination.
6 MS. LUNNEY: I'm sorry. I couldn't hear
7 you.
8 DR. BRACEY: Finds instead of recognizes.
9 DR. EPSTEIN: Okay. So, I'm suggesting
10 that the word recognize be modified, either to finds or
11 determines that accumulating evidence for the efficacy
12 and safety of pathogen reduction, then insert the words
13 warrants, or strike "is now sufficient to," just
14 warrants, A, commitments and concerted effort to add

15 pathogen reduction technology.

16 MS. LUNNEY: Concerted effort.

17 DR. EPSTEIN: Concerted effort.

18 DR. BRACEY: Right here. That's it.

19 DR. EPSTEIN: Concerted effort to add

20 pathogen reduction technology as a broadly applicable

21 safeguard which additionally would provide a reasonable

1 precaution against potentially emerging infectious

2 diseases.

3 MS. LUNNEY: Reasonable?

4 DR. EPSTEIN: Yeah, a reasonable

5 precaution.

6 MS. BIRKOFER: A reasonable precaution

7 against --

8 DR. EPSTEIN: Potentially emerging

9 infectious disease.

10 DR. BRACEY: Well, one of the things that

11 raises the point is that we focus too much solely on

12 infectious. It's adding a layer for infectious
13 diseases but there's also other potential gain but we
14 can address that later.
15 MS. LUNNEY: Did it come out?
16 DR. BENJAMIN: Taking the sentence out?
17 DR. BRACEY: We would have to say something
18 here to the effect that this would result in a
19 proactive strategy. Let's see.
20 DR. KOUIDES: Should it be reasonable
21 precaution or reasonable protection against potential

1 emerging disease? Is precaution the right word?
2 DR. BRACEY: I think protection. Yeah,
3 protection.
4 MS. LUNNEY: Reasonable protection?
5 DR. BRACEY: Yeah, instead of precaution.
6 Okay. So, now, this would say, this would result in a
7 strategy of -- a strategy of proactive so just scratch
8 out, all this out, delete, delete the proactive --

9 strike that. So, this would result in a strategy of
10 proactive, yeah, in a proactive preemptive strategy,
11 right. And then you can scratch pathogen reduction,
12 well, because we already mentioned pathogen reduction
13 up here. In other words, this process would recognize
14 a proactive preemptive strategy that would broadly
15 render -- yeah, okay, let's, so let's try that.
16 So, the Advisory Committee on Blood Safety
17 and Availability finds accumulating evidence for the
18 efficacy and safety of pathogen reduction warrants
19 commitment and concerted effort to add pathogen
20 reduction technology as a broadly applicable safeguard
21 which additionally would provide a reasonable

1 protection against potential emerging infectious
2 diseases.
3 MS. BIRKOFER: Plural?
4 DR. BRACEY: Plural, diseases, right. So
5 this would result in a proactive preemptive strategy

6 that would broadly render known agents noninfectious
7 and prevent emerging agents from becoming transfusion
8 risks. To achieve this goal, government, industry, the
9 blood bank establishment -- there was a question about
10 the public.
11 MS. FINLEY: And the public.
12 DR. BRACEY: Okay. So, I like that term
13 public -- public stakeholders.
14 MS. FINLEY: And public stakeholders?
15 DR. BRACEY: Yes. So you just go back here
16 and strike "and the" right here. So, to achieve this
17 government, industry, comma, now, the blood bank
18 establishment, is that right, is that --
19 DR. TRIULZI: Blood bank community.
20 DR. EPSTEIN: We should say blood
21 organizations.

1 DR. BRACEY: Blood organizations, okay,
2 blood organizations, and public stakeholders need to

work in concert and need to commit the required financial and technical resources -- the question is, do we need this piece here?

DR. EPSTEIN: No.

MS. FINLEY: I would say no.

DR. KOUIDES: Blood transfusion organizations.

DR. LOPES: Blood collection.

DR. SANDLER: Blood collection and transfusion. Blood services.

DR. BRACEY: Okay. So blood services?

DR. SANDLER: Blood services.

DR. EPSTEIN: Well, it's also a trade organization. They're not for services. The trade organizations aren't the services themselves.

DR. BRACEY: Well, that's true. That's a good point. Let's just leave it as blood organizations for now. Okay. Dr. Holmberg?

DR. HOLMBERG: Is this redundant to have

1 concerted effort at pathogen reduction technology where
2 you already said pathogen reduction at the top, say
3 pathogen reduction warrants commitment and concerted
4 effort --
5 DR. BRACEY: Yeah, to add --
6 DR. HOLMBERG: -- as a broader applicable
7 safeguard.
8 DR. BRACEY: Oh, I see what you're saying.
9 It's redundant to say it here and here.
10 DR. HOLMBERG: Right.
11 DR. BRACEY: Okay. Well, I think, I don't
12 know, I don't have a major sense of it but you think it
13 is redundant?
14 DR. HOLMBERG: Yes.
15 DR. BRACEY: Okay. All right. So, the
16 Advisory Committee on Blood Safety and Availability
17 finds that accumulating evidence for the efficacy and
18 safety pathogen reduction warrants commitment and
19 concerted effort to add this technology -- this
20 technology because what we're focusing on is the
21 technology that we wanted to add -- as a broadly

1 applicable safeguard which additionally would provide a
2 reasonable protection against potential emerging
3 infectious diseases. This would result in a proactive,
4 preemptive strategy that would broadly render known
5 agents noninfectious and prevent emerging agents from
6 becoming transfusion risks. To achieve this goal
7 government, industry, blood organizations and public
8 stakeholders need to work in concert and need to commit
9 the required financial and technical resources just --
10 well, we scratched this --
11 MS. FINLEY: Period.
12 DR. BRACEY: We scratched that. Now, the
13 one thing that we don't have is broadening of the
14 impact to things like TRALI. Well, we could add a
15 statement here, furthermore --
16 DR. RAMSEY: Its under the development
17 later --
18 DR. BRACEY: It's down, well, let's go
19 down --
20 DR. RAMSEY: Potential benefits.
21 DR. BRACEY: We'll go down to potential

1 benefits. Okay. Whereas a safe and adequate blood
2 supply is an essential national resource, the Committee
3 finds the following actions are needed to address
4 safety concerns for transmissible diseases, including a
5 need for preparedness against potential emerging --
6 well, this sounds --
7 DR. BENJAMIN: That's repetition, need for
8 preparedness against potential emerging infectious
9 diseases is set up in the third, fourth line.
10 DR. BRACEY: Yeah. Do we need this? I
11 don't think we need it. I mean --
12 DR. BENJAMIN: I'd say including a need for
13 preparedness, you can probably take out against the
14 potentially emerging infectious disease.
15 DR. BRACEY: Well, I think we can put that
16 in the bottom under the benefits, or you want to
17 highlight it?
18 DR. BENJAMIN: I like the word

19 preparedness.

20 DR. BRACEY: That's what I'm thinking. Dr.

21 Sandler says we don't need the three comments,

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1 commitment, what does the --

2 DR. TRIULZI: We don't need it.

3 DR. BRACEY: Let's strike it.

4 MS. BIRKOFER: When in doubt delete.

5 DR. BRACEY: All right. Strike it. Thank

6 you. In particular, the Committee finds that A, based

7 on credible scientific assessments, current risk of

8 transmission of infectious diseases from blood

9 transfusion is very low, consistent with public

10 expectations for a reasonably safe blood supply.

11 That's true but it almost --

12 DR. TRIULZI: I think I'd put the word

13 "known" before the --

14 DR. BRACEY: Right, right, let's do that,

15 known, right, transmission of known infectious

16 diseases, right here.

17 MS. LUNNEY: I'm sorry. Where?

18 DR. BRACEY: No, where your pointer is.

19 DR. BENJAMIN: Where the pointer is, top

20 line.

21 DR. BRACEY: Right here.

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1 MS. LUNNEY: Oh, sorry.

2 DR. BRACEY: That's all right.

3 DR. DUFFELL: You know, but why is the

4 statement needed? It seems to undermine what we've

5 just said.

6 DR. BRACEY: Well, I know. That's what I

7 was thinking.

8 DR. TRIULZI: Because you can only test for

9 what you know about.

10 DR. BRACEY: But it's saying that the blood

11 is very safe.

12 DR. DUFFELL: I mean, that's the problem.

13 I've got is saying it's very safe, which just
14 undermines your opening paragraph.
15 MS. FINLEY: But that is the consistent
16 phrase that we've used coming from the Institute of
17 Medicine report.
18 DR. BRACEY: Well, and I guess the other
19 thing is item B, though, if one reads through item B, I
20 guess, so, item B reads, despite overall safety of
21 blood supply, unmet needs exist to further reduce known

1 infectious threats to blood transfusion recipients from
2 numerous agents including bacteria, certain viruses and
3 parasites and prions.
4 DR. BENJAMIN: I would take the "known"
5 out.
6 DR. KOUIDES: Take out A.
7 DR. BRACEY: So take out A?
8 DR. KOUIDES: Put B into A so it, at the
9 end of A you have however, comma, despite overall

10 safety of blood supply.

11 DR. BRACEY: You know, actually we say the

12 blood supply is very safe so actually A doesn't really

13 add.

14 DR. DUFFELL: It doesn't add because --

15 MS. FINLEY: But we say it's safe relative

16 to known risks and that is an accurate statement there.

17 DR. DUFFELL: You're lead-in there, despite

18 overall safety, just, that, I mean, you might want to

19 add some verbiage to that but that's saying what A

20 said, right, despite overall safety?

21 DR. BRACEY: Right.

1 MS FINLEY: Yeah, I don't have a problem

2 with that.

3 DR. BRACEY: So change B to A and rework B.

4 Okay. So, okay, so, the Committee -- is the consensus

5 that we delete A?

6 MS. FINLEY: Yes.

7 DR. DUFFELL: Yes.

8 DR. BRACEY: All right. Let's delete A.

9 MS. BENZINGER: What you could do is say

10 despite overall safety of blood supply, based on

11 credible scientific evidence and then go unmet needs

12 exist.

13 DR. BRACEY: That's an excellent point,

14 okay, so despite overall safety of the blood supply

15 based on credible scientific assessments.

16 DR. LOPES: Based on credible scientific

17 assessments.

18 DR. BRACEY: You have to get rid of this

19 comma here.

20 MS. LUNNEY: Comma, okay.

21 DR. BRACEY: Comma there. Thanks. Unmet

1 needs exist to further reduce -- Dr. Holmberg?

2 DR. HOLMBERG: Well, you know, this just

3 addresses the -- unmet need exists to further reduce

4 known infectious -- maybe we should say known or
5 unknown infectious threats.
6 MS. FINLEY: I agree.
7 DR. BRACEY: I think we may have the
8 "unknown" further down. Let's read down a little bit
9 more and see. The well-established strategy of
10 implementing donor screening and testing subsequent to
11 the identification of infectious agents of concern to
12 blood safety has inherent limitations based on the
13 possibility for widespread transmission of disease
14 before a new agent is recognized or can be interdicted
15 by specific methods. That's it. So that captures it.
16 The cost and complexity of agent-specific
17 screening and testing is itself becoming a barrier to
18 further blood safety innovations. At the same time,
19 business models do not appear to favor continued
20 aggressive investments in blood safety technologies in
21 the absence of mandates that would lower market risk.

DR. SANDLER: Do we need all that?

DR. BRACEY: Yeah, you know, that's a lot of inside information.

MS. FINLEY: Yeah, I think we should stop at "technology."

DR. BRACEY: Let's see. Right here?

MS. FINLEY: Yeah. The rest is sort of "inside baseball."

DR. BRACEY: Well, it's still part of, well, we know that, and, but we need to let others know that as well. Dr. Epstein?

DR. EPSTEIN: You know, why I'd put that in is that it's part of explaining to the Secretary why there has to be an advocated, committed goal. It's because if we don't set up that goal, then the resources won't necessarily get mobilized toward it.

MS. FINLEY: Okay. I have no problem with that.

DR. BRACEY: Okay. All right. Pathogen reduction technologies offer a potential alternative to agent-specific screening and testing assuring blood

1 safety against the vast majority of known infectious
2 threats, while concurrently establishing a meaningful
3 safeguard against future emerging agents.
4 DR. LOPEZ-PLAZA: Unknown -- significant --
5 DR. BRACEY: I thought we said that
6 already. Yeah, so we can delete this.
7 DR. EPSTEIN: Yeah, we said that.
8 DR. BRACEY: Because the preamble on the
9 other statement wasn't as broad as the preamble on this
10 one.
11 MS. LOPEZ-PLAZA: Okay. Thank you.
12 DR. BRACEY: D, the anticipated high costs
13 of pathogen reduction technologies likely could be
14 offset through gradual elimination of other blood
15 safety interventions such as leukocyte reduction, blood
16 irradiation, bacterial culture and current donor
17 screening and testing methods.
18 DR. RAMSEY: Current, gradual elimination
19 of current blood safety --
20 DR. BRACEY: Oh, right, right, right,
21 right. Right here, current.

1 DR. KOUIDES: Change that to current.
2 DR. LOPEZ-PLAZA: Have a question.
3 DR. BRACEY: Yeah, but you can get rid of
4 current here.
5 DR. RAMSEY: Select the current.
6 DR. LOPEZ-PLAZA: Pathogen reduction is
7 part of the process, of some of the pathogen
8 inactivation, not going to be eliminated. I mean
9 irradiation can be eliminated but not leukocyte
10 reduction, is my understanding. Please clarify that.
11 DR. BRACEY: Dr. Epstein?
12 DR. EPSTEIN: That's only
13 technology-specific. If we have pathogen reduction for
14 whole blood you won't necessarily --
15 MS. FINLEY: I'm wondering if you even want
16 to go as far as specifically naming the ones you might
17 eliminate or whether that just raises the question.
18 DR. BRACEY: That's a good point. Because,
19 yeah, at the higher level it won't have meaning.

20 MS. FINLEY: It also might inspire those
21 who might lose to get activated in an active sort of

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1 way.
2 DR. BRACEY: So gradual elimination of
3 current, of certain or some --
4 DR. EPSTEIN: Some.
5 MS. FINLEY: Of some current safety
6 interventions and then just leave out --
7 DR. BRACEY: Some, yeah, so just we just
8 put "some."
9 MS. FINLEY: That would be up to the
10 regulators anyway as to what they want to get rid of.
11 DR. BRACEY: Okay. And then scratch,
12 delete after interventions, go to interventions, and
13 then just hit delete. Delete the rest. Dr. Truilzi?
14 DR. TRIULZI: What's now currently B, we
15 actually went over very quickly, and I don't think
16 we're adequately capturing in those that the testing

17 strategy results in loss of donors due to
18 nonspecificity.
19 DR. BRACEY: Well, we've got something down
20 here in B, in a further statement.
21 DR. TRIULZI: Okay. That's fine.

1 DR. BRACEY: We'll get that. Okay. So,
2 the anticipated high costs of pathogen reduction
3 technologies likely could be offset through the gradual
4 elimination of some current blood safety interventions.
5 E, because they cannot be inactivated in blood
6 components, techniques to detect and remove prions need
7 separate consideration. We're sort of, for the prions,
8 do we need to --
9 DR. SANDLER: We want to mention vCJD,
10 should be mentioned specifically and put it in front
11 because the agent of vCJD and other prions --
12 DR. BRACEY: Oh. So, you're saying --
13 right, right, right.

14 DR. SANDLER: The agents of vCJD.

15 DR. BRACEY: All right. So you would go up

16 to scratch, because, the first two --

17 DR. SANDLER: "They" is not clear

18 because --

19 DR. BRACEY: Okay. So because the --

20 DR. SANDLER: Agents.

21 MS. FINLEY: The preamble --

1 DR. SANDLER: The agents of vCJD and other

2 prions -- and other prion diseases --

3 DR. BRACEY: Well, okay, and other prion

4 diseases, and then scratch the "why," delete "why,"

5 cannot be inactivated in blood components, techniques

6 to detect and remove prions need separate

7 consideration. Okay. That's fine.

8 DR. DUFFELL: Or you just simply saying

9 these need separate consideration.

10 DR. BRACEY: Oh, here you say --

11 DR. DUFFELL: Yeah, because you're
12 repeating it.
13 DR. BRACEY: Yeah, so just, yeah, so here
14 you would say these.
15 MS. LUNNEY: Say these?
16 DR. BRACEY: Instead of prions, these
17 agents.
18 DR. SANDLER: Infective agents.
19 DR. BRACEY: Infective agents. Oh, I'm
20 sorry. Marc? I'm sorry.
21 DR. MALTAS: I'm still missing in all these

1 points something about noninfectious risks.
2 DR. BRACEY: Right, right. We have some
3 benefits below that we'll also get to. So, what we
4 have here following are some statements of potential
5 benefits. So, development of this new system or
6 strategy, say strategy, development of this new
7 strategy --

DR. LOPEZ-PLAZA: I mean is it development, or implementation --

DR. BRACEY: Sure, sure, implementation of this new strategy, addition, addition, addition, addition.

DR. EPSTEIN: Well, again is a new strategy or a new technology? See, I think the underlying strategy is the same. It's just that we've always taken advantage of available technology.

DR. BRACEY: Well, how about addition of this technology?

DR. HOLMBERG: It's not a new strategy. You're adding I like the idea what you said, adding the sixth layer and I think that that's --

DR. BRACEY: So really we'll treat this as an addition because this isn't just another layer.

DR. KOUIDES: Addition and refinement.

DR. BRACEY: Well, the problem is that

5 currently -- so, addition and refinement of this
6 technology. Addition and refinement of this technology
7 and then scratch this new strategy piece here. Oh,
8 sorry. Ann?
9 MS. BENZINGER: How about implementing new
10 technologies offer the following potential benefits?
11 DR. BRACEY: Well, part of the issue is
12 that it may not be considered, it's not all new, so --
13 MS. BENZINGER: I realize it's not new but
14 I think that it's implementation into the U.S. system.
15 DR. LOPEZ-PLAZA: Development.
16 DR. BRACEY: Right. Implementation but I'm
17 not sure, it's addition versus implementation, I'm not
18 seeing that one is that much better than the other. I
19 don't know. What's the Committee feel. Dr. Bowman?
20 DR. BOWMAN: Mr. Chairman, why don't we say
21 pathogen reduction? I mean, that's what we're talking

1 about.

DR. BRACEY: Yeah, that' a good point. We don't have to worry whether implementation or addition, it's technology.

MS. BENZINGER: You're limiting it to that technology, too.

DR. BRACEY: So, pathogen reduction, just leave it as that.

MS. BENZINGER: If you're able to inactivate the prion, adding the layer, talking about --

DR. BRACEY: Right. We're just, all the bullets that follow below won't address prions. We're just addressing pathogen reduction. So then pathogen reduction offers the following potential benefits. This may be, we talked about it, avoiding obligate blood recipient infectious risk before emerging infectious diseases are detected and new assays are developed as previous infections, HIV, HCV, WNV. I mean, we mentioned that already so I think we can scratch that.

1 MS. FINLEY: I would leave it.
2 DR. BRACEY: Well, you leave it --
3 MS. FINLEY: For a couple of perception
4 reasons.
5 DR. BRACEY: Number two, avoiding
6 unnecessary loss of potential blood donors -- or we can
7 just say, scratch potential, just blood donors -- as an
8 undesirable outcome attributable to false-positive
9 infectious disease tests and donor screening
10 strategies. I don't know that we need all the rest.
11 Just scratch, after "strategies" scratch. Potential
12 economic gains associated with adoption of a strategy
13 to need -- you know, we talked about this above.
14 DR. KOUIDES: Yeah, we have to be careful
15 to --
16 DR. BRACEY: No, not the whole thing.
17 MS. LUNNEY: Sorry.
18 DR. BRACEY: Scratch number three.
19 MS. LUNNEY: Okay.
20 DR. BRACEY: And really number four is
21 captured above anyway. This is a melding of the two.

1 What we're talking about is you're not going to be
2 reliant upon the diagnostic assay. We talked about
3 that before.
4 MS. FINLEY: Where does it talk about that?
5 I would want to leave that spelled out because,
6 challenge facing the, you know, the blood community.
7 DR. KLEIN: It's really avoidance of the
8 need to develop new screening assays, isn't it, whether
9 it's convincing manufacturers or --
10 DR. BRACEY: Yeah, so avoidance of the
11 need --
12 MS. FINLEY: Yeah.
13 DR. KLEIN: -- to develop new screening
14 assays.
15 MS. FINLEY: Right.
16 DR. BRACEY: Yeah, because that's a big
17 outlay, and resource requirement. So avoidance of the
18 need to --
19 MS. FINLEY: Develop.
20 DR. SANDLER: Develop.

21 DR. BRACEY: -- develop new diagnostic

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1 assays.

2 DR. SANDLER: For emerging infections.

3 DR. BRACEY: Yeah, for emerging infections.

4 That's true.

5 DR. BENJAMIN: Should it say emerging or

6 localized infections because one of the problems --

7 DR. BRACEY: Yeah, right, exactly.

8 Emerging or localized infections.

9 DR. BENJAMIN: And/or.

10 DR. BRACEY: And/or.

11 DR. SANDLER: Probably infectious agents.

12 DR. BRACEY: Yeah, infectious agents.

13 DR. SANDLER: Infectious --

14 DR. BRACEY: Agents, okay. If you could

15 scratch the rest then. Now, here's where we get to the

16 point, mitigation of non-viral threats that represent

17 the leading residual fatality risks associated with

18 blood transfusion, e.g., TRALI, bacterial
19 contamination.
20 DR. HOLMBERG: Do we want to say non-viral
21 or noninfectious?

1 DR. BRACEY: Noninfectious.
2 DR. BENJAMIN: Well, no, you've got
3 bacterial then.
4 DR. BRACEY: Well, yeah, that's right.
5 Well, we're talking about the leading, if one of the
6 things that we had to think about is, you know, what
7 are the -- how would we rank the risks and so we've
8 got, you know, two major ones here.
9 DR. BRACEY: The reason, yeah, the reason
10 is the Norway experience. And, if one uses, yeah, this
11 is the Norway experience.
12 DR. BRACEY: Dr. Epstein?
13 DR. EPSTEIN: Well, yeah, it's a
14 consequence of pooling, not actually that you're

15 inactivating bad antibodies. It's simple a byproduct
16 of pooling. You have different things operating, you
17 have, you know, removing plasma from platelets --
18 DR. BRACEY: True.
19 DR. EPSTEIN: -- if you use additive
20 solutions for removal of the plasma and then for the
21 pooled plasma product it's because of the pooling

1 process which is part of the inactivation. If you had,
2 you know, single unit, the antibodies would still be
3 there.
4 DR. BRACEY: Well, true, but still it's a
5 side effect or side benefit.
6 DR. KLEIN: One could argue that HAL
7 antibodies aren't the only cause of TRALI, since only
8 50 percent of the case have been associated with it.
9 So if in fact other people are correct in the
10 non-antibody mediated on the second hit theory so maybe
11 we shouldn't be quite so specific. I mean, probably

12 adding, this technology, however, might mitigate,
13 whether it's by pooling or by inactivating leukocytes
14 or by some other method, who knows. I think the point
15 is that they don't see it. No.
16 DR. EPSTEIN: I'm just a little
17 uncomfortable --
18 DR. KLEIN: Whatever, maybe it is pooling,
19 maybe it is pooling plus something else.
20 DR. EPSTEIN: But tomorrow's pathogen
21 reduction technology may not reduce TRALI. It's just

1 the things we're looking at now which we may or may not
2 be the things we end up implementing.
3 DR. KLEIN: I think that's true but I think
4 one of the potential added values, maybe now, maybe not
5 next year but I think that's the potential added value,
6 whatever the mechanism.
7 DR. BRACEY: Although, I mean, our goal is
8 really to get by it rather than to have a specific

9 proven mechanism. I don't know.

10 DR. RAMSEY: We can, I don't know if you

11 want to throw in graft-versus-host. It's maybe not a

12 leading fatality but do you want to put in

13 graft-versus-host disease somewhere?

14 DR. LOPEZ-PLAZA: High fatality might not

15 be --

16 DR. BRACEY: I mean, we would have to

17 probably scratch "leading" to make it more factual --

18 well, but I know that there are statements that in

19 other words, some feel that if, that we're really

20 missing a current opportunity, there's great debate

21 right now about how to reduce these noninfectious

1 hazards of transfusion.

2 DR. KLEIN: So one could say potential

3 mitigation of nonviral threats such as TRALI --

4 DR. BRACEY: We don't know --

5 DR. KLEIN: -- bacterial contamination,

graft-versus-host disease.

DR. BRACEY: Okay. So, let's do that. Nonviral threats such as --

DR. LOPEZ-PLAZA: Mediation of nonviral threats --

MS. LUNNEY: Take this all out?

DR. KLEIN: You might keep "associated."

DR. BRACEY: Associated with blood transfusion, yeah, associated with --

DR. EPSTEIN: Associated with blood transfusion such as --

DR. BRACEY: So scratch, yeah. Okay. Mitigation of non-viral threats associated with blood transfusion such as TRALI, bacterial contamination.

DR. RAMSEY: And GVHD.

DR. BRACEY: And GVHD. So put

graft-versus-host disease.

DR. HOLMBERG: GVHD.

DR. BRACEY: And alloimmunization. Yeah. Okay. HLA alloimmunization. Yeah, A-L-L-O -- double L -- okay.

DR. EPSTEIN: Do you want to add the word potential as part of it?

DR. KLEIN: I like potential.

DR. BRACEY: Okay. So put potential in front of mitigation then.

DR. SANDLER: You already have "potential" in the lead, top lead, top line.

DR. BRACEY: Good point. It's already there. So, we're comfortable with number four then? "Such as," take the comma out after "as," good point, right here. All right. Mitigation of non-viral threats associated with blood transfusion, such as TRALI, bacterial contamination, GVHD and HLA alloimmunization. Five, eliminating loss of valuable platelet and plasma donations as a consequence of historical screening -- screening based on history and

1 testing strategies currently used for TRALI-risk
2 mitigation.
3 DR. KLEIN: It's the same as 2.
4 DR. BRACEY: Take that out.
5 DR. LOPEZ-PLAZA: You have to have two
6 into --
7 DR. BRACEY: Okay. Yeah, you can take that
8 out.
9 DR. LOPEZ-PLAZA: Only refers to infectious
10 diseases and you might want to add a comma over there,
11 known noninfectious or --
12 DR. BRACEY: False-positive infectious
13 disease test, well, we have, and other donor, and donor
14 screenings and strategies, so, I think it's captured.
15 Then the next would be shielding -- well, here's this,
16 well, shielding the nation from intentional
17 introduction of biological threats into our blood
18 supply. The "bioshield." Well, I mean, you know you
19 can, okay, that's a stretch. Okay.
20 MS. FINLEY: You might want to take the
21 word intentional out because maybe the intention wasn't

to introduce it into the blood supply but rather to knock out a city so if you took it out, I think it's an important point.

DR. BRACEY: So how does the Committee feel on this?

DR. DUFFELL: I'd just say just shielding from biological threats. Why wouldn't you just leave it at that and strike the middle portion:

DR. HOLMBERG: I think it's an important point. I think that I like what Bill said but I think this supports also the President's Directive 21.

MS. FINLEY: Yeah, I would just take out "intentional," and leave the rest in there, spelling it out for people who may not be familiar with this, it is important.

DR. BRACEY: So shielding the nation from --

DR. DUFFELL: Biological threats.

DR. BRACEY: From biological, from introduction of --

MS. FINLEY: Yeah. I mean, I don't need it

1 to fall on introduction so if you want it take it
2 out --
3 DR. KLEIN: You may want to put that last.
4 I think it has some currency right now.
5 MS. FINLEY: Yes, definitely.
6 DR. KLEIN: You know, the first and last
7 sometimes is what people remember.
8 DR. BRACEY: Okay. Yeah, that's a good
9 point. So, can you do that, Jennifer? Thank you. All
10 right. So, we've shifted that and so, ah, so, we get
11 to class two which was mentioned yesterday, in terms of
12 protecting immunocompromise -- because look in
13 commonalities to transplant tissue recipients.
14 Protecting immunocompromised transplant recipients from
15 serious viral infections due to -- that's redundant --
16 viral agents of high prevalence in the normal
17 population, e.g. --
18 DR. SANDLER: You can just say patients and

19 not transplant --

20 DR. BRACEY: Yeah, well, I was trying to

21 catch the -- I was trying to link it to tissue, you

1 know, we have this responsibility for tissue and

2 transplant safety but you're right, maybe that's too

3 specific. Dr. Epstein?

4 DR. EPSTEIN: Well, I think we're missing a

5 certain logic here, which is that there's a principal

6 benefit of reducing the risk from currently known

7 agents, then there's the benefit of a safeguard against

8 potential emerging agents and then there are other

9 potential benefits. I think what this section is

10 really about is other potential benefits and we're

11 diluting out a statement of the principal benefit by,

12 you know, busting it up into little pieces and putting

13 a little here and a little there. Again, there's a

14 principal benefit.

15 DR. BRACEY: Yes.

16 DR. EPSTEIN: It's eliminating many
17 residual risks.
18 DR. BRACEY: Right.
19 DR. EPSTEIN: It's adding protection
20 against potentially emerging risk and it has potential
21 additional benefits. So, I just think we need to

1 capture the, you know, the eliminating residual risks
2 because, for example, the issue of CMV and
3 immunocompromised patients, well, we eliminated I think
4 at least about 98 percent of that risk in what we now
5 do. Leukocyte reduction and CMV testing does that very
6 thing. It's just this may do it better.
7 DR. BRACEY: So what if we put, offers the,
8 say, your statement put up here in the examples include
9 or you think we don't need the examples?
10 DR. EPSTEIN: Where are you?
11 DR. BRACEY: In other words, the principles
12 could be put up at the lead and then specific examples

13 include? Such as?

14 DR. EPSTEIN: I'm not sure exactly how you

15 want to frame it but I think point one should be, you

16 know, reduction of existing residual risk, or, yeah,

17 reduction or elimination of current risks of known

18 infectious agents, of known infectious agents.

19 DR. BRACEY: Of known infectious agents.

20 DR. EPSTEIN: And then if you wanted to say

21 there, you know, including protecting immunocompromised

1 patients from serious infections from agents common in

2 the blood supply but again I think that's very, very

3 particular.

4 DR. BRACEY: Yeah, that's a little too

5 detailed, I think.

6 DR. EPSTEIN: Yeah.

7 DR. BRACEY: Okay. The point I think of

8 having number five and number six was trying to find

9 commonalities.

10 DR. KLEIN: But then number two you want
11 protection against emerging agents or, you know, first
12 the, what we have, second is what we might get and then
13 the other added values, avoiding loss of blood donors,
14 et cetera.
15 DR. EPSTEIN: And I would bundle the
16 concept of, you know, bioterror in number two because
17 it's avoiding potential risks from emerging infectious
18 agents including -- and you could say pandemic,
19 influenza and bioterrorism agents. You can be explicit
20 because we know there's a precautionary value there.
21 DR. BRACEY: So let's take, why don't we

1 take, we don't need this word "obligate," right?
2 DR. EPSTEIN: No, no. I think number two
3 is a whole different point.
4 DR. BRACEY: That's a whole different --
5 yeah, yeah, so reduction of current risks of known
6 infectious agents.

7 DR. EPSTEIN: Then number two.

8 DR. BRACEY: A new number two?

9 DR. EPSTEIN: Correct.

10 DR. BRACEY: New number two, reduction of

11 risk of emerging --

12 DR. EPSTEIN: Well, it's protection against

13 the risk.

14 DR. BRACEY: Protection against the risk of

15 merging infectious agents.

16 DR. KOUIDES: Shielding the nation from

17 introduction --

18 DR. BRACEY: What's that now?

19 DR, KOUIDES: Number nine --

20 DR. BRACEY: Yeah, yeah, yeah, put number

21 nine, right, shielding the nation from introduction of

1 biological threats --

2 DR. DUFFELL: Well, but we wanted to keep

3 that one separate to highlight.

DR. BENJAMIN: It becomes number three.

DR. BRACEY: Well, I think we moved away from that, though. It's just confusing -- so you can move nine to -- okay. And then --

DR. EPSTEIN: Just add the word "and," and "shield" or "including."

DR. BRACEY: Okay. Dr. Holmberg, comment?

DR. HOLMBERG: Down on number five now --

DR. BRACEY: Number five.

DR. HOLMBERG: To develop new diagnostic assays.

DR. BRACEY: Screening.

DR. HOLMBERG: Should we change that to screening?

DR. BRACEY: Should that be screening assays instead of diagnostic?

MS. FINLEY: Yeah.

DR. KLEIN: Yeah.

1 DR. BRACEY: So, new screening assays. So,
2 this is the avoidance of the need four to develop new
3 screening assays, okay. So then we don't need number
4 seven. Scratch number seven. You can scratch number
5 seven, too. You can scratch that seven, too.
6 Okay. Now, let's get down to point of
7 action. Based on these findings -- and we have really
8 two points of action. Based on these findings, the
9 Committee recommends that the Secretary, A, adopt as a
10 high priority the development and implementation of
11 safe and effective pathogen reduction technologies for
12 all blood transfusion products. There's a difference.
13 In one recommendation in order to still take this
14 endeavor we recommend immediate steps of a task force
15 or working group, so.
16 DR. KLEIN: You know, I think that's very
17 specific, and I'm not sure how helpful that is. I
18 mean, I would let the Secretary or whoever is acting
19 for the Secretary decide how to do that. I would hate
20 to see the outcome being another large committee that
21 will, you know, deliberate for four or five years, meet

1 three times or four times a year. I would be very
2 careful about that.
3 DR. BRACEY: Dr. Holmberg?
4 DR. HOLMBERG: I think we already
5 established that in the top part. You know, we said
6 that we need to pull together a group, so, I think that
7 this is really redundant.
8 DR. BRACEY: Okay. So it's redundant. So,
9 we'll just have A, adopt as a high priority the
10 development and implementation of safe and effective
11 pathogen reduction technologies for all blood
12 transfusion products. Is the Committee okay with that?
13 Dr. Lopez?
14 DR. LOPEZ-PLAZA: Again, we already have
15 something that I think is driving here, is to be able
16 to implement it and then we have other areas that we
17 need to develop. And I don't know if we should be very
18 specific because one of the things we're discussing
19 here is to implement what already has been developed
20 and has completed clinical trials, plus recognize that
21 there are other areas that we need to develop such as

1 red cell pathogen inactivation.
2 DR. BRACEY: Dr. Epstein?
3 DR. EPSTEIN: Well, I think the problem
4 with that is that it preempts the FDA decision-making
5 process. We have not licensed technologies for
6 platelet pathogen reduction but we have historically
7 licensed -- some of these are approved devices, I'll
8 use the term approved -- you know, solvent-detergent
9 treated pool plasma was voluntarily withdrawn from the
10 market. So, the point is we shouldn't preempt the FDA
11 review and approvals process by saying we're going to
12 implement because what are you implementing? You have
13 no approved technologies in the U.S.
14 DR. BRACEY: So, what we're saying the
15 point is it's not already -- the development piece -- E
16 really seems to be unnecessary, it's too specific so we
17 just drop E, is that, in its entirety?
18 MS. BIRKOFER: Well, if the issue is
19 specifying the members, you could just say after the

20 word "immediate," you could just say immediately,
21 should recommend the immediate charting of a course and

1 then establishment of mechanisms. You could just --
2 you know what I mean? You could just stop with the
3 word "immediate," delete down to number one but I think
4 what Dr. Holmberg said is that at point there was that
5 it --
6 DR. BRACEY: Yeah, it's embedded above.
7 That's why I think we could probably strike it. Dr.
8 Epstein?
9 DR. EPSTEIN: You could add the word
10 "urgent" in A. Adopt as a high priority urgent
11 development.
12 DR. BRACEY: Yeah. Because we want a sense
13 of immediacy. Yeah, scratch immediate then?
14 MS. BIRKOFER: Yeah.
15 DR. BRACEY: Sound fair? Okay. B, provide
16 funds to overcome current barriers to development and

17 validation of pathogen reduction technologies and
18 methods for the detection and removal of prions.
19 DR. KLEIN: Is it funds or resources?
20 DR. BRACEY: Resources, I think is a
21 better -- change funds to resources?

1 DR. RAMSEY: Oh, okay. This is the way --
2 the way I heard it at first was this was all talking
3 about prions but --
4 DR. BRACEY: Oh, no.
5 DR. RAMSEY: -- there's two separate parts
6 to this.
7 DR. BRACEY: There are two separate parts.
8 And I think one of the questions will be whether to
9 leave the prion piece in or take the prion piece out.
10 Dr. Triulzi?
11 DR. TRIULZI: I think it is elevating it to
12 the same level of urgency as pathogen reduction.
13 DR. BRACEY: That's a good point. So why

14 don't we strike that.

15 DR. TRIULZI: Because we did include it

16 elsewhere.

17 DR. BRACEY: Well, but I think we still

18 need to watch and observe but I don't think it warrants

19 it in here. So can we strike "and removal of prions"?

20 DR. SANDLER: Dr. Epstein, there are

21 special words that mean "new money." What are the

1 words that mean "new money"?

2 DR. BRACEY: All right.

3 DR. SANDLER: Taking money from NIH, moving

4 it here, shifting it around but what's the word for new

5 money?

6 MS. FINLEY: But that would be interactions

7 with Congress to appropriate.

8 DR. BRACEY: So we would say provide

9 resources to overcome current barriers to the

10 development of validation of pathogen reduction

11 technologies. Period. That's it.

12 DR. DUFFELL: It's earmark, that what it is

13 earmark. That's what you're looking for. Earmark

14 money, seed money.

15 DR. BRACEY: C, coordinate efforts of the

16 public health agencies to identify and, where

17 appropriate, eliminate current blood safety measures

18 that would add no significant benefit in conjunction

19 with effective pathogen reduction.

20 MS. FINLEY: Again are we putting the cart

21 before the horse? I mean, really that's something that

1 will flow out of the pathogen reduction. It's really a

2 matter for the regulators to decide and this Committee

3 and BPAC in the future. So, while our expectation is

4 to eliminate it, I'm not sure that we get anything or

5 help the Secretary by putting that in there.

6 DR. BENJAMIN: I think take it out.

7 DR. BRACEY: Okay. So let's scratch that.

8 The Committee recommends that the Secretary ensure
9 adequate safety monitoring, yeah, yeah, yeah, of
10 pathogen reduction blood products postmarketing, using
11 an active national hemovigilance system similar to
12 those in European countries.
13 DR. EPSTEIN: I would strike "similar to
14 those in European countries."
15 DR. BRACEY: Strike "similar" -- yeah.
16 DR. BENJAMIN: Yeah. Yeah.
17 DR. EPSTEIN: There's a thought that we had
18 mentioned but not incorporated in the draft which is
19 strategies for gradual rollout.
20 DR. BRACEY: Right.
21 DR. EPSTEIN: I think it's related to C in

1 that you want close monitoring but it's a separate idea
2 because we don't currently have mechanisms to do that.
3 DR. BRACEY: What if we, in A of all blood
4 products in a gradual -- no. Yes?

5 MS. FINLEY: The concept of gradual rollout
6 would create an inequity in the country if one region
7 had access to a technology that another didn't have. I
8 think at this point our goal is to try and get the
9 Secretary to recognize this is a priority and to put
10 the resources behind it. That really gets into the
11 implementation.
12 DR. BRACEY: Yeah, okay. That's a good
13 point.
14 DR. HOLMBERG: But I think the issue here
15 was not to gradually roll it out into different regions
16 of the country but not to wait until we have the entire
17 package of whole blood, pathogen reduction.
18 MS. FINLEY: Then the way you phrase if
19 would be better for public perception and palatability.
20 DR. BRACEY: So, perhaps if one -- oh, Dr.
21 Epstein?

1 DR. EPSTEIN: Well, I think there are two

2 different concepts going on, neither of which is
3 elaborated yet in the text. One would be clear
4 recommendation of the Canadian Consensus Conference
5 with which we seem to all agree not to wait until we
6 have all three major components but that if we have
7 safe and effective technology for platelets and plasma,
8 go with it. So that's one idea. And maybe that's a
9 finding or I don't think it's a specific recommendation
10 to the Secretary necessarily. FDA moves to approve or
11 not approve those technologies.
12 But then the second idea really had to do
13 with the observation that we want these technologies to
14 be safe at a level that can't be determined in the
15 clinical trials that may lead to their approval. And,
16 you know, do you really want a very rapid
17 implementation whereby for argument's sake over a
18 period of six months all 3 million platelets are
19 treated this way and then we discover that lo and
20 behold there's a 1 in 100,000 risk? And the idea up
21 here is that we would like to have a system analogous

1 to what we heard from Dr. Heiden exists in Germany and
2 France where it can actually be implemented gradually
3 center by center.
4 Now, what's been pointed out is that our
5 culture -- this comes back to, you know, the discussion
6 we had about ethics -- our culture rejects that. Our
7 culture says that if it's available here, we want it
8 available everywhere. And by gosh, if it's not
9 available and it's billed as a safety advancement, you
10 know, you're legally liable, where you have
11 competitiveness issues with your neighborhood blood
12 center and you have legal liability. And, so, I think
13 that there's a big unsolved problem here, which is that
14 we really would like it to be rolled out gradually but
15 we can't accomplish that by deciding who gets it and
16 who doesn't.
17 DR. BRACEY: But I think that's one of the
18 issues where the -- and this would perhaps resolve the
19 dialogue component.
20 MS. FINLEY: Yeah, I think that's a valid
21 -- Jay's got a point but it's a complicated point and

it's an implementation issue. And I think if we are trying to float the concept of this, you know, I don't think we need to get into that level of detail. The regulatory matter, as we discuss the impact will be discussed here. We've got a lot of time before that we go down that road.

DR. BRACEY: Well, yeah. I mean, I see basically what we're doing is a call to action.

MS. FINLEY: Right.

DR. BRACEY: And then following the call to action, the details will get resolved.

MS. FINLEY: Yeah. Yeah. I think there's a big risk of that point, the second point being misinterpreted.

DR. BRACEY: Well, let's take a look at this.

DR. KLEIN: I don't think it's necessary to get into it. I mean, I think we all recognize that probably we need a pilot just as they said in Canada before you -- for a lot of reasons, for logistic

21 reasons, for phase four reasons, for a whole host of

1 reasons.

2 MS. FINLEY: I'm not disagreeing with you

3 but at this level --

4 DR. KLEIN: No, that's exactly what I'm

5 saying.

6 MS. FINLEY: Okay.

7 DR. KLEIN: I don't think -- I think that

8 that's implementation. That's probably more than what

9 we need at this point.

10 MS. FINLEY: Right.

11 DR. DUFFELL: Yeah, I think it can be done

12 through labeling. I mean, you could slowly broaden the

13 application starting with the highest risk patients and

14 that way it is fair. It's across the board but you're

15 limiting it at least initially to those who are at the

16 highest risk because of multiple transfusions or

17 something.

18 DR. KLEIN: But again, I don't think we
19 need to -- we don't need to address that.
20 DR. DUFFELL: Yeah, we don't. I agree. I
21 think it's an FDA thing later.

1 DR. BRACEY: So the last piece that's
2 listed here, which is not a bulletin but says that the
3 Committee further recommends that efforts to further
4 reduce the infectious risks of transfusion should not
5 be undertaken to the exclusion of efforts to reduce
6 noninfectious risks such as TRALI, hemolysis from blood
7 incompatibility and transfusion associated circulatory
8 overload. That's, I mean, we're saying noninfectious
9 risks are important. I don't know if we need to have
10 that much detail.
11 MS. FINLEY: It's awkward. It's hard to
12 read.
13 DR. BRACEY: Yes.
14 DR. KOUIDES: To go back to what Dr. Klein

15 mentioned yesterday, should we also add inappropriate
16 use --
17 DR. BRACEY: Blood utilization?
18 DR. KOUIDES: Yeah, inappropriate blood
19 utilization.
20 DR. LOPEZ-PLAZA: You would have to state
21 more than you said that there if you want to look

1 at complications and risks.
2 DR. BRACEY: Well, why don't we just say, I
3 mean, I don't know that -- do we need to specify all
4 the noninfectious risks?
5 DR. LOPEZ-PLAZA: I don't think so.
6 DR. BRACEY: Why don't we just leave it at
7 that.
8 MS. FINLEY: Do we need it at all? I mean,
9 I don't know that that gets us any further on this.
10 DR. BRACEY: Yeah, part of the problem --
11 well, we certainly want a balance.

12 MS. FINLEY: Yeah, but I think it's open to
13 significant misinterpretation.
14 DR. KLEIN: Well, I think then we probably
15 have to get it right. Because, again, certainly in
16 Canada and all we heard from Brian today, there's a
17 concern, a real concern is if you say okay, this is a
18 very expensive thing so let's forget about barcoding to
19 identify patients and blood components because we can't
20 afford everything and let's forget it. And I think the
21 point is that there are other technologies that address

1 safety that could be implemented or could be developed
2 and implemented and you hate to say that if you do this
3 you're not going to do anything else.
4 MS. FINLEY: Yeah, I like the way you say
5 it. I think that one looks like, you know, you have to
6 sacrifice the infectious disease risk, which is a
7 political minefield to these other things and I don't
8 think that's really what you're trying to say.

DR. BRACEY: Well, actually, there was a good point made by Dr. Holmberg and that is, can we move this up to the higher section?

MS. FINLEY: But I still don't like the wording of that. I think --

DR. BRACEY: Well, reword would be to strike all the specifics --

MS. FINLEY: Efforts.

DR. BRACEY: You want to leave it specifics?

DR. HOLMBERG: That's what I was hearing.

DR. KOUIDES: When you think that TRALI and hemolysis are the first two leading causes --

DR. BRACEY: That's a good point. So then just copy that and let's see if we can move it up.

MS. FINLEY: But I still think it needs some reworking to look like what Dr. Klein said.

MS. LUNNEY: Where?

DR. BRACEY: Up to the preamble. Now, where would it fit?

DR. TRIULZI: You know, the avoidance of inappropriate transfusions is important because it may be years between platelet, plasma and the red cells actually having the technology and that may be the strategy you have to use.

DR. BRACEY: So how about, can we just put it right here at this point?

DR. HOLMBERG: After the --

DR. BRACEY: Right here.

DR. DUFFELL: Second paragraph.

DR. BRACEY: Or separate paragraph, separate paragraph, okay. So --

DR. DUFFELL: Don't need the word "further."

MS. FINLEY: Committee recommends?

DR. BRACEY: Committee recommends. But the

3 line is not right. The Committee recommends that
4 efforts -- the Committee recommends -- recommends is
5 the wrong place, yeah.
6 DR. RAMSEY: I think it's recognizes, also
7 recognizes.
8 DR. BRACEY: The Committee recognizes that
9 efforts to further reduce the infectious risks of
10 transfusion should not be undertaken to the exclusion
11 of efforts to reduce noninfectious risks such as --
12 MS. FINLEY: That's not what you really
13 mean. It's what Harvey said, which is that in the
14 interim while we're waiting for this technology to
15 become utilized, we don't want to miss the opportunity
16 to further reduce risk in all of these other areas by
17 implementing technologies that may be available in the
18 interim. So, it's a positive statement here. That
19 comes across very negatively and I think it has a lot
20 of opportunity --
21 DR. EPSTEIN: Yeah, concurrently --

1 DR. RAMSEY: Say the need to also reduce
2 noninfectious risks.
3 DR. BRACEY: It doesn't seem to fit.
4 DR. SANDLER: After the other
5 recommendations have been declined, then you --
6 DR. BRACEY: It's a final statement, it
7 says don't throw out the baby with the bathwater.
8 Yeah, so let's take it to the end.
9 MS. FINLEY: Looks like a tradeoff between
10 the two, say it more positively.
11 DR. BRACEY: So take it down to the bottom
12 again. Sorry.
13 MS. LUNNEY: Okay.
14 DR. BRACEY: So the Committee recognizes
15 that --
16 DR. SANDLER: Further recommends.
17 MS. FINLEY: No --
18 DR. EPSTEIN: What if it said something
19 more along the lines of concurrent efforts to further
20 reduce noninfectious risks of transfusion should be
21 undertaken?

1 DR. BRACEY: Okay. Yeah, that's the word.
2 So, concurrent efforts to reduce noninfectious risks --
3 you could scratch all that. You want to go all the way
4 to noninfectious risks.
5 MS. LUNNEY: Oh.
6 DR. BRACEY: Yeah, in the backspace.
7 DR. KLEIN: Or you could even have little D
8 there, concurrent efforts to introduce technologies
9 should not be neglected or should not be abandoned or
10 whatever.
11 DR. KOUIDES: Yeah.
12 DR. BRACEY: So make it a D.
13 DR. SANDLER: Ensure that -- you need a
14 verb to start.
15 DR. BRACEY: Yeah, that's a good point.
16 Ensure that -- so D.
17 DR. HOLMBERG: Just go back up and make a
18 D.
19 DR. BRACEY: Make a D.
20 MS. LUNNEY: Oh, I see. Okay.
21 DR. HOLMBERG: Bring it up as a D.

1 DR. BRACEY: All right. Ensure that -- and
2 then scratch everything. Go right to concurrent.
3 Dr. EPSTEIN: Maybe this is a chance to get
4 in the availability point. Ensure that other efforts
5 to assure blood safety and availability are not
6 compromised including efforts to review noninfectious
7 risks --
8 DR. BRACEY: Ensure that other efforts to
9 improve blood safety and availability.
10 DR. EPSTEIN: And availability not
11 compromised.
12 DR. BENJAMIN: To improve.
13 MS. FINLEY: Right.
14 DR. BRACEY: To improve blood safety and
15 availability.
16 DR. BENJAMIN: Are not compromised.
17 DR. BRACEY: Are not compromised, yes.
18 DR. BENJAMIN: By these efforts.

19 DR. BRACEY: And scratch "concurrent."
20 That's it. You can go here and strike everything else
21 after "efforts."

1 DR. LOPEZ-PLAZA: Why do you have to keep
2 the examples?
3 DR. BRACEY: No, we're going to strike it.
4 We're striking it. Okay. So --
5 DR. HOLMBERG: Can we go back into the
6 preamble?
7 DR. BRACEY: To the preamble, please.
8 We're almost there.
9 DR. HOLMBERG: We drop the stakeholder and
10 the Committee work in concert, do we need that second,
11 and work in concert to commit, it should be work in
12 concert to commit if, and need, and the next to last
13 line, to work in concert to commit.
14 DR. LOPEZ-PLAZA: Yeah.
15 DR. BRACEY: Oh, in concert.

16 MS. FINLEY: Yeah.

17 DR. BRACEY: That's good, cut that out.

18 DR. HOLMBERG: Cut that out.

19 DR. BRACEY: To commit, okay. All right.

20 Correct. All right. Let's go to the preamble. The

21 Advisory Committee on Blood Safety and Availability

1 finds that accumulating evidence for the efficacy and

2 safety of pathogen reduction warrants a commitment and

3 concerted effort to add this technology as a broadly

4 applicable safeguard which additionally would provide a

5 reasonable protection against potential emerging

6 infectious diseases. This would result in a proactive,

7 preemptive strategy that would broadly render known

8 agents noninfectious and prevent emerging agents from

9 becoming transfusion risks. To achieve this goal,

10 government, industry, blood organizations and public

11 stakeholders need to work in concert to commit the

12 required financial and technical resources. Do you

13 want to spell it out or just say needed resources?

14 MS. FINLEY: No.

15 DR. BRACEY: Okay. That's fine. In

16 particular the Committee finds that A, despite overall

17 safety, despite -- how about the overall safety or --

18 MS. FINLEY: Yeah, the overall safety --

19 DR. BRACEY: Despite the overall safety of

20 the blood supply based on credible scientific

21 assessments unmet needs exist to further reduce known

1 infectious threats to blood transfusion recipients from

2 numerous agents, including bacteria, certain viruses

3 and parasites -- what does it say, parasites and

4 prions, yeah. So scratch "and."

5 MS. LUNNEY: After viruses?

6 DR. BRACEY: Yeah, and just put a comma

7 there.

8 DR. SANDLER: Take out infection. They're

9 all infectious.

10 DR. BRACEY: Right. So this would be
11 infectious.
12 MS. FINLEY: You can take out certain under
13 viruses.
14 DR. BRACEY: Take out what now?
15 MS. FINLEY: Take out "certain" in front of
16 "viruses." It doesn't add anything.
17 DR. BRACEY: Yeah, right. Right, so --
18 DR. SANDLER: How about infectious for
19 numerous? Take out numerous and put in infections.
20 They're all infectious.
21 MS. BIRKOFER: You could take out "certain"

1 under viruses.
2 DR. BRACEY: Right. So this would be
3 infectious agents. Strike "certain" after bacteria.
4 Well, make that infectious agents.
5 MS. BIRKOFER: And then finish.
6 DR. BRACEY: Infectious agents including

7 bacteria, viruses and prions. The well-established
8 strategy of implementing donor screening and testing
9 subsequent to the identification of infectious agents
10 of concern to blood safety has inherent limitations
11 including the possibility for widespread transmission
12 of disease before a new agent is recognized or can be
13 interdicted by specific methods. Sounds good. The
14 cost and complexity of agent-specific screening and
15 testing is itself becoming a barrier to further blood
16 safety innovations. At the same time, business models
17 do not appear to favor continued aggressive investments
18 in blood safety technologies in the absence of mandates
19 that would lower market risk.
20 DR. SANDLER: Technology period.
21 DR. BRACEY: Technology period. Scratch

1 everything after technologies. Jennifer, you got the
2 hardest job. Okay. Okay. Moving on, the anticipated
3 high costs of pathogen reduction technologies likely

4 could be offset through the gradual elimination of some
5 current blood safety interventions.
6 DR. SANDLER: Good.
7 DR. BRACEY: E, because the agents of vCJD
8 and other prion diseases cannot be inactivated in blood
9 component techniques to detect and remove these
10 infectious agents need separate consideration.
11 DR. SANDLER: Good.
12 DR. BRACEY: Pathogen reduction offers the
13 following potential benefits: One reduction of current
14 risks of known infectious agents; two, protection
15 against the risk of emerging infectious agents
16 including shielding the nation from introduction of
17 biological threats into our blood supply; three,
18 avoiding obligate blood recipient infectious risk
19 before emerging infectious diseases are detected and
20 new assays are developed as occurred with previous
21 infectious agents, e.g., HIV, HCV, WNV.

1 DR. EPSTEIN: Delete the examples?
2 DR. BRACEY: Okay.
3 DR. EPSTEIN: Delete everything after "are
4 developed," what about we, stop after --
5 MS. LUNNEY: After developed?
6 DR. BRACEY: Yeah, right, stop after
7 developed, yeah. So, go all the way to developed.
8 Great. So, avoiding obligate blood recipient
9 infectious risk before emerging infectious diseases are
10 detected and new assays are developed. That's great.
11 Four, avoiding unnecessary loss of blood donors as an
12 undesired outcome attributable to false-positive
13 infectious disease tests and donor screening
14 strategies.
15 DR. SANDLER: Nonspecific?
16 DR. BRACEY: Nonspecific donor screening
17 strategies, okay. Okay. Five, avoidance of the need
18 to develop new screening assays for emerging and/or
19 localized infectious agents; six, mitigation of
20 nonviral threats associated with blood transfusion,
21 such as TRALI, bacterial contamination, GVHD and HLA

1 alloimmunization.

2 DR. SANDLER: Why not spell the words out

3 so that a nontechnical person who may get this has some

4 idea what we're talking about?

5 DR. BRACEY: Right. We'll do that.

6 DR. SANDLER: Okay.

7 DR. BRACEY: We'll spell them out. Based

8 on these findings the Committee recommends that the

9 Secretary, A, adopt as a high priority the urgent

10 development and implementation of safe and effective

11 pathogen reduction technologies for all blood

12 transfusion products; B, provide resources to overcome

13 current barriers to development and validation of

14 pathogen reduction technologies; C, ensure adequate

15 safety monitoring of the pathogen reduced blood

16 products postmarketing using an active national

17 hemovigilance system and D, ensure that other efforts

18 to improving blood safety and availability are not

19 compromised by these efforts. Two comments. Okay.

20 Ms. Benzinger?

21 MS. BENZINGER: The one comment I had and

1 I'll go back to what I said in the beginning, I think
2 that we should in the beginning at the preamble just
3 mention availability and a donor pool be increased.
4 And I know that has nothing to do with the pathogens
5 but this is about availability.
6 DR. BRACEY: Okay. Comments from the
7 Committee?
8 DR. KLEIN: Do we have a line in there
9 about availability --
10 DR. BRACEY: Well, we speak about
11 availability indirectly through the decreasing loss of
12 donors.
13 MS. FINLEY: But that doesn't get to the
14 heart of the fact that 95 percent of eligible donors,
15 whatever incredible number it is, aren't donating.
16 DR. BRACEY: But that's another topic.
17 MS. FINLEY: Okay. But at our meeting we
18 did have a considerable discussion about the platelet
19 shortage.

20 DR. BRACEY: Well, I know but this is
21 another topic. I mean, we're mixing --

1 MS. FINLEY: Well, then, maybe we can throw
2 another recommendation together quickly that just
3 addresses that other topic since we did discuss it?
4 DR. BRACEY: Well, I mean, I think we
5 addressed that other topic at our last meeting. We
6 need the information and the basis, we gave that
7 recommendation --
8 MS. FINLEY: It appears to be getting worse
9 so maybe in the letter that we sent to summarize this
10 we can point out that we feel that the situation is
11 getting worse, we need some specific evidence to be
12 collected or something.
13 DR. BRACEY: Dr. Benjamin?
14 DR. BENJAMIN: I would argue that we stick
15 to today's topic. Clearly it does appear to be getting
16 worse. This is the middle of January, where every year

17 it gets worse. So, rather than responding to something
18 that is seasonal, in a Committee recommendation, we
19 should stick to what we're trying to achieve here.
20 MS. FINLEY: It's not seasonal when I'm
21 getting calls in August about it. We're not talking

1 about something that happened here. Well, what I'll
2 say is if we would make this an agenda item for our
3 next meeting that would be perfectly fine with me.
4 DR. BRACEY: Okay. That's fine. It's a
5 separate --
6 MS. FINLEY: I agree. I agree.
7 DR. BRACEY: And this is very important and
8 we need to close.
9 MS. FINLEY: It's a shortage --
10 DR. BRACEY: No, I understand. Dr.
11 Epstein?
12 DR. EPSTEIN: A small point but when we say
13 would broadly render known agents noninfectious, it

14 should say most or nearly all known agents because it's
15 not all known agents.
16 DR. KLEIN: That's true. Most.
17 DR. BRACEY: So, most. Ms. Birkofer?
18 MS. BIRKOFER: Dr. Bracey, can you scroll
19 down? Because, isn't there a line that addresses the
20 importance of donors, that these pathogen reduction
21 technologies do not impact donors?

1 DR. BRACEY: Yeah, we talked about that.
2 MS. BIRKOFER: Where is that?
3 DR. BRACEY: That line is IN the second
4 set, number four.
5 MS. BIRKOFER: Okay. Because I think what
6 Ms. Benzinger -- I think we just have to be sensitive.
7 She's coming at things from a consumer perspective and
8 not a technical, not a scientific, not a medical, just
9 a person.
10 DR. BRACEY: Right.

11 MS. BIRKOFER: And what she is trying to
12 say is that availability from her perspective is
13 paramount. So, could you just weave in the word
14 somewhere in that line and then I think that would be,
15 you know, at least acknowledging her views as a
16 Committee member as being valid?
17 DR. BRACEY: So avoiding unnecessary loss
18 of blood --
19 MS. BIRKOFER: Put in the word
20 "availability" then.
21 DR. KLEIN: I mean, I would just think, and

1 I'm certainly the one that's always said that
2 availability is a safety issue and I believe that 100
3 percent but I think from a strategic standpoint I think
4 you want to drive this home and stay on target. And
5 then I think we need to have as an agenda item the
6 whole issue of availability and have an entire document
7 like this that just addresses availability for what the

8 Secretary should do about it.

9 MS. FINLEY: Harvey, at our next meeting if

10 that's an agenda item I would like to formally request

11 that there's a shortage of platelets and that we get

12 some hard facts behind that.

13 DR. BRACEY: We can do that. Again --

14 MS. FINLEY: That would be fine with me.

15 DR. KLEIN: It's not just platelets --

16 MS. FINLEY: The "other Ann" can speak for

17 herself but for me that would be okay.

18 DR. SANDLER: Number four, I suggest we

19 add, increase the availability of blood by avoiding --

20 DR. BRACEY: Increase the availability of

21 blood donors -- no, increase availability of blood

1 supply by avoiding, okay. That's it.

2 DR. KLEIN: Sorry. I have two comments.

3 If we could go back up to D, I'm concerned -- right up

4 above D, D is barely visible at the top of the screen.

5 Okay. I am concerned that one could read that and say,
6 gee, what they're going to do is eliminate some of the
7 current safety measures by introducing someone's
8 technology. And I think what we really mean by that is
9 eliminate some current blood safety interventions that
10 are rendered redundant. I mean, that's what we really
11 need, something to that effect.
12 MS. BENZINGER: Could or would be offset?
13 DR. KLEIN: Likely would be offset.
14 DR. BRACEY: Likely would be offset.
15 DR. KLEIN: Of some current blood safety
16 interventions that are rendered redundant or something
17 to that effect.
18 DR. BRACEY: Okay. So the anticipated high
19 cost of pathogen reduction technologies would be offset
20 by the elimination of redundant --
21 DR. KLEIN: I would say what you really

1 mean is when you introduce pathogen reduction

technology, depending upon what it is, some of these things are going to be redundant.

DR. BRACEY: Right. Likely offset through the gradual reduction of current blood safety interventions that would be rendered redundant.

DR. KLEIN: Yes, we maybe able to word it better than that but I think that's the concept.

DR. BRACEY: So, right here, rendered redundant, that would be rendered redundant. Now, we are getting very close. We have a comment from the floor. Dr. McCullogh?

DR. McCULLOUGH: I think it's the last item, C, that refers to postmarket follow-up through a national hemovigilance system and I wonder if that could prove to be complicated by specifically saying a national hemovigilance system that is clearly, there are a lot of interest in setting it up, but who knows how long it will take to get that up and running and how it will function. And I wonder if wording more like appropriate postmarketing studies or something

1 like that wouldn't be better because that would provide
2 the FDA quite a wide latitude to require how they
3 wanted appropriate follow-up post-licensure and not be
4 hung up on the specific national hemovigilance system.
5 DR. BRACEY: What does the Committee think?
6 MS. FINLEY: No, I think we need a national
7 hemovigilance system, that is the recommendation of the
8 Committee and that, you know, issues like
9 postmarketing, that's FDA's purview and that's not an
10 application --
11 DR. BRACEY: Okay. So, how does the
12 Committee feel, national hemovigilence system or
13 postmarketing --
14 MS. FINLEY: National.
15 DR. BENJAMIN: Postmarketing.
16 DR. KOUIDES: National.
17 DR. BRACEY: All right. Let's take a vote.
18 All in favor of the national hemovigilance system?
19 One, two, three, four.
20 DR. EPSTEIN: You don't vote, Harvey.
21 DR. KLEIN: I can't vote. You're right.

DR. BRACEY: Those in favor of -- three, okay. National wins.

MS. FINLEY: Thank you.

DR. BRACEY: Okay. We need to vote on this. We need to close.

DR. KLEIN: Can I make just one more comment, because again I think there's something we may miss and we do have, I think, a little further down about recommending that we develop and implement something for all blood components or all blood products.

DR. BRACEY: Yes. All blood products.

DR. KLEIN: Again I think I would not like to lose the idea that if you get something for one blood product you ought to put it into effect immediately.

DR. BRACEY: So why don't we just strike "all" and say "blood products"?

MS. FINLEY: As they become available.

DR. KLEIN: As they become available.

21 DR. BRACEY: For blood products as they

1 become available. Okay. So, it's further down. For
2 -- where is that? No, here it is, under A. For blood
3 products --
4 DR. KLEIN: Well, how about the urgent
5 development of safe and effective pathogen reduction
6 technologies for all blood transfusion products and
7 implementation as each one, as they become available?
8 MS. FINLEY: As they become available.
9 DR. SANDLER: Exactly.
10 DR. BRACEY: Okay. And implementation as
11 they become available.
12 DR. KLEIN: And implementation as they
13 become available.
14 DR. BRACEY: And implementation as they
15 become available, okay. So, we were trying to get a
16 call to action. We need to close on this so we will
17 get a call to action. Are we ready for a vote?

18 PARTICIPANTS: Yes.

19 DR. BRACEY: First I need a motion.

20 MS. FINLEY: I would be happy to make a

21 motion.

1 DR. BRACEY: Okay. Second?

2 DR. DUFFELL: I second.

3 DR. BRACEY: Okay. Is there discussion?

4 We've had lots of discussion.

5 MS. BIRKOFER: No further discussion.

6 DR. BRACEY: All in favor?

7 PARTICIPANTS: Aye.

8 DR. BRACEY: All opposed?

9 (No affirmative response)

10 DR. BRACEY: Yea! We have a product!

11 Thank you.

12 DR. HOLMBERG: Okay. Just a couple

13 comments. I again would like to thank Dr. Sandler for

14 his years of service and you will be getting something

15 I hope hand-delivered to you, so, unfortunately I don't
16 have it now. But I also would like to make a comment
17 on regards to the next topic and I know that the issue
18 of availability came up and was a desired topic. I
19 also want to remind you that at the last meeting we
20 talked about availability and the implication from the
21 blood supply was that we have no problem. So --

1 MS. FINLEY: Again, again, we're getting
2 anecdotal evidence so perhaps the Department can take a
3 look at this in more detail. I'm sure we'd be happy to
4 help you but I think there's a problem when I'm getting
5 told --
6 DR. BENJAMIN: Ann, could I ask you, when
7 you say we, are you talking referring to Celgene -- who
8 is "we"?
9 MS. FINLEY: No, no, we're talking to the
10 Committee. The Committee in this forum three times
11 said that there were serious shortages.

DR. BRACEY: I think we need to, we'll explore that. I can tell you that the issue I think largely is resource sharing because there are regions where there are, yes.

MS. FINLEY: Yes, I've heard that, too.

(Meeting concluded at 5:24 p.m.)

State of Maryland.

Baltimore County, to wit:

I, ROBERT A. SHOCKET, a Notary Public of the State of Maryland, County of Baltimore, do hereby certify that the within-named proceedings personally took place before me at the time and place herein set out.

I further certify that the proceedings were

recorded stenographically by me and this transcript is a true record of the proceedings.

I further certify that I am not of counsel to any of the parties, nor in any way interested in the outcome of this action.

As witness my hand and notarial seal this 22nd day of January, 2008.

_____

Robert A. Shocket,

Notary Public

My Commission Expires:

November 1, 2010