UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

MEETING

Thursday, August 16, 2007

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This meeting came to order at 8:00 a.m. in the Doubletree Hotel and Executive Meeting Center, 8120 Wisconsin Avenue, Bethesda, Maryland. Dr. Frederick Siegal, M.D., presiding.

PRESENT:

FREDERICK SIEGAL, MD, CHAIR
DONALD W. JEHN, MS, EXECUTIVE SECRETARY
MARK BALLOW, MD, MEMBER
HENRY M. CRYER, III, MD, MEMBER
ADRIAN DI BISCEGLIE, MD, MEMBER
WILLARDA V. EDWARDS, MD, MEMBER
MAUREEN A. FINNEGAN, MD, MEMBER
SIMONE A. GLYNN, MD, MEMBER
KEITH C. QUIROLO, MD, MEMBER
GEORGE B. SCHREIBER, SCD, MEMBER
IRMA SZYMANSKI, OV, MD, MEMBER
DONNA S. WHITTAKER, PHD, MEMBER
JUDITH R. BAKER, MHSA, CONSUMER REPRESENTATIVE
LOUIS M. KATZ, MD, NON-VOTING INDUSTRY REPRESENTATIVE
MELVIN BERGER, MD, PHD, TEMPORARY VOTING MEMBER
RICHARD A COLVIN, MD PHD TEMPORARY VOTING MEMBER
JAMES R. ALLEN, MD, MPH, NON-VOTING TEMPORARY MEMBER

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1 P-R-O-C-E-E-D-I-N-G-S
2 8:05 a.m.
3 EXECUTIVE SECRETARY JEHN: Let's go ahead
4 and get started. Mr. Chairperson, Members of the
5 Committee, invited guests, temporary voting members
6 and public participants, I would like to welcome all
7 of you to this 90th meeting of the Blood Products
8 Advisory Committee. I'm Donald Jehn, the Executive
9 Secretary for this meeting.
10 This meeting will be completely open to
11 the public. At this time, I would like introduce the
12 individuals seated at the head table for today. To my
13 immediate left is our BPAC Chairperson Dr. Frederick
14 Siegal, Medical Director of Comprehensive HIV Center,
15 St. Vincent's Catholic Medical Centers, New York.
16 To my right and going down the table is
17 Dr. James Allen, Medical Advisor, American Social
18 Health Association; Dr. Mark Ballow, Chief Division of
19 Allergy and Immunology, SUNY New York and Women's and
20 Children's Hospital of Buffalo; Dr. Richard Colvin,
21 Clinical Assistant in Medicine, Center for Immunology
22 and Inflammatory Diseases, Massachusetts General
23 Hospital East; Dr. Henry Cryer, Chief of Trauma and
24 Clinical Care at UCLA; Dr. Adrian Di Bisceglie, Chief
25 of Hepatology, St. Louis University School of

1 Medicine; Dr. Willarda Edwards, President and Chief
2 Operating Officer of Sickle Cell Disease Association
3 of America; Dr. Maureen Finnegan, Associate Professor,
4 Department of Orthopedic Surgery, University of Texas
5 Southwestern Medical Center; Dr. Simone Glynn, Branch
6 Chief Transfusion and Medicine and Therapeutics
7 Branch, NHLBI.
8 And then on my left side going down, Dr.
9 Keith Quirolo, Clinical Director, Apheresis Program,
10 Department of Hematology, Children's Hospital at
11 Oakland; Dr. George Schreiber, Vice President of
12 Health Studies, Westat; Dr. Irma Szymanski, Professor
13 of Pathology, Emerita, University of Massachusetts
14 Medical Center; Dr. Donna Whittaker, Chief Department
15 of Clinical Support Services, U.S. Army Medical
16 Department Center and School, Fort Sam, Houston; and
17 Ms. Judith Baker, our Consumer Rep located at UCLA;
18 and, finally, our Industry Rep, Dr. Louis Katz,
19 Executive Vice President, Medical Affairs, Mississippi
20 Valley Regional Blood Center.
21 Committee members not in attendance are
22 Drs. Cooner, Kulkarni, Manno and Quinn. Dr. Allen is
23 at the table for the discussion of the response of the
24 Office of Blood, Research and Review Office Level Site
25 Visit for Research. I would like to thank all of you

1 for attending this meeting.

2 Now if I could have Dr. Goodman. We have

3 four retiring members after this meeting and we would

4 like to recognize them. Dr. Szymanski.

5 (Applause.)

6 EXECUTIVE SECRETARY JEHN: Dr. Donna

7 Whittaker.

8 (Applause.)

9 EXECUTIVE SECRETARY JEHN: Dr. Keith

10 Quirolo.

11 (Applause.)

12 DR. WHITTAKER: And Dr. George Schreiber.

13 (Applause.)

14 EXECUTIVE SECRETARY JEHN: We thank them

15 all. Thanks very much.

16 Okay. Before we start the meeting, I do

17 have a conflict of interest statement to read. It's

18 rather lengthy, so please bear with me.

19 The Food and Drug Administration, FDA, is

20 convening today's meeting of the Blood Products

21 Advisory Committee under the authority of the Federal

22 Advisory Committee Act, FACA, of 1972. With the

23 exception of the Industry Representative, all

24 participants of the Committee are special government

25 employees, SGEs, or regular federal employees from

1 other agencies and are subject to the Federal Conflict
2 of Interest laws and regulations.
3 The following information on the status of
4 this advisory committee's compliance with Federal
5 Ethics and Conflict of Interest laws including, but
6 not limited to, 18 USC Section 208 and 21 USC Section
7 355(n)(4) is being provided to participants in today's
8 meeting and to the public. FDA has determined that
9 participants of this advisory committee are in
10 compliance with Federal Ethics and Conflict of
11 Interest Laws including, but not limited to, 18 USC
12 Section 208 and 21 USC 355 (n)(4). Under 18 USC 208
13 applicable to all government agencies and 21 USC
14 355(n)(4) applicable to certain FDA committees,
15 Congress has authorized FDA to grant waivers to
16 special government employees who have financial
17 conflicts when it is determined that the Agency's need
18 for a particular individual's services outweighs his
19 or her potential financial conflict of interest,
20 Section 208, and where participation is necessary to
21 afford essential expertise, Section 355.
22 Members of the Committee who are special
23 government employees at today's meeting including
24 special government employees appointed as temporary
25 voting members have been screened for potential

1 financial conflicts of interest of their own as well
2 as those imputed to them, including those of their
3 employers, spouse or minor child related to the
4 discussion of (1) FDA's response to the Officer of
5 Blood Research and Review Office Site Visit held on
6 July 22, 2005 and (2) measles antibody levels in U.S.
7 immune globulin products. These interests may include
8 investments, consulting, expert witness testimony,
9 contracts, grants, CRADAs, teaching, speaking,
10 writing, patents and royalties and primary employment.
11 Today's agenda also includes several
12 updates. In accordance with 18 USC Section 208(b)(3),
13 waivers were granted to Dr. Mark Ballow and Dr. Melvin
14 Berger for the discussion of topic two on Measles
15 Antibody Levels in U.S. Globulin Products. A copy of
16 the written waiver may be obtained by submitting a
17 written request to the Agency's Freedom of Information
18 Office, Room 12A-30 of the Parklawn Building.
19 With regard to the FDA's guest speakers
20 for Topic two, the Agency has determined that the
21 information provided by these speakers is essential.
22 The following information is being made public to
23 allow the audience to objectively evaluate any
24 presentation and/or comments made. Dr. Donald Baker
25 is employed by Baxter Healthcare Corporation. Dr.

1 Baker has financial interests in his employer. Dr.
2 William Moss is employed by Johns Hopkins Bloomberg's
3 School of Public Health as an Associate Professor in
4 the Departments of Epidemiology, International Health
5 and Molecular Microbiology and Immunology. Dr. Jane
6 Seward is employed by CDC as a Deputy Director,
7 Division of Viral Disease, National Center of
8 Immunization, Respiratory Diseases. Dr. Toby Simon is
9 representing Plasma Protein Therapeutics Association.
10 He is employed by ZLB Plasma as the Corporate Medical
11 Director. Dr. Simon has a financial interest in his
12 employer. Dr. Othmar Zenker is employed by CSL
13 Behring. As guests, they will not participate in the
14 Committee deliberations. Nor will they vote.
15 In addition, there may be regulated
16 industry and other outside organizations' speakers
17 making presentations. These speakers may have
18 financial interests associated with their employer and
19 with other regulated firms. The FDA asks in the
20 interest of fairness that they address any current or
21 previous financial involvement with any firm whose
22 product they may wish to comment upon. These
23 individuals were not screened by the FDA for conflicts
24 of interest.
25 Dr. Louis Katz is serving as the Industry

1 Representative acting on behalf of all related
2 industry and is employed by the Mississippi Valley
3 Regional Blood Center. Industry Representatives are
4 not special government employees and do not vote.
5 This conflict of interest statement will
6 be available for review at the registration table. We
7 would like to remind members that if the discussions
8 involve any other products or firms not already on the
9 agenda for which an FDA participant has a personal or
10 imputed financial interest, the participants need to
11 exclude themselves from such involvement and their
12 exclusion will be noted for the record. The FDA
13 encourages all other participants to advise the
14 Committee of any financial relationships that you may
15 have with any sponsor, products, direct competitors
16 and firms that could be affected by the discussions.
17 Before I turn the microphone over to the
18 Chair, I would like to request that everybody take a
19 moment and check to make sure they have their cell
20 phones and pagers set to silent or turned off. Thank
21 you. Dr. Siegal, I'll turn it over to you.
22 CHAIRMAN SIEGAL: Thank you, Don. I would
23 like to welcome you all to this glorious summer
24 meeting of the Blood Products Advisory Committee.
25 Fortunately, we don't have a lot of controversial

1 topics, but we have a fair amount to cover. I
2 particularly want to welcome back Jim Allen, an old
3 friend from the AIDS wars. Can you not hear me?
4 Well, it's not really important anyway.
5 (Laughter)
6 CHAIRMAN SIEGAL: But Jim was, of course,
7 my predecessor on this committee and we've known one
8 another since about 1981 maybe.
9 Our first set of topics are the Committee
10 updates and we're going to start with Jerry Holmberg
11 who is going to review and summarize the meeting of
12 the DHHS Advisory Committee on Blood Safety and
13 Availability. Jerry.
14 DR. HOLMBERG: While we are waiting to get
15 that up on the screen, I'll just give you a little
16 disclosure. I do have financial interests in my
17 company, the Federal Government, and that financial
18 interest is not only receiving a salary, but paying
19 taxes.
20 (Laughter.)
21 DR. HOLMBERG: And if anybody would like
22 to know, I have had my annual financial review with
23 the Ethics Office.
24 What I would like to do today is to give
25 you an update on the Advisory Committee on Blood

1 Safety and Availability and the Office of Blood Safety
2 and Availability and also primarily give you a summary
3 of the May 10 and 11, 2007 meeting.
4 First of all, I would like to note that we
5 have some staff changes. The biggest staff change
6 that I would like to mention that is not on the slide
7 here is that Dr. Aquinobi, the Assistant Secretary for
8 Health, has resigned from the Administration and that
9 resignation is as effective as of September 3rd. In
10 my office, we do have Lt. Commander Rich Henry who has
11 moved up to the Deputy Director position and we have a
12 new Public Health Officer, LTjg Jennifer Lunney who is
13 our Senior Health Preparedness Advisor.
14 At the May 10th and 11th meeting, Dr.
15 Aquinobi asked the committee to review several
16 commonalities between transfusion and transplantation
17 safety. The reason for that is in October the charter
18 for the Advisory Committee on Blood Safety and
19 Availability was modified to include interests or
20 concerns of transfusion and transplantation safety.
21 This sort of opens up the scope of issues that we can
22 deal with at the committee and Dr. Aquinobi was
23 looking to see are there areas of commonality.
24 So the first question was is there a
25 process, an opportunity, to lay out a process for

1 transfusion and transplantation safety for the future
2 and the committee overwhelmingly said that, yes, there
3 is a need to develop a process to enhance the quality
4 and improvement in transfusion medicine and
5 transplantation medicine.
6 Is there scientific evidence to support a
7 need for a master strategy? In this particular area,
8 the committee really struggled as far as finding
9 scientific evidence, but based on surveillance
10 evidence there is a limited reports of infectious
11 disease transmission and therefore, substantiate the
12 need for a master strategy and you can read on there
13 as far as the differences in the risk/benefit profiles
14 between transfusion tissue and transplantation
15 recipients but that all these patients have the
16 potential for acquiring life-threatening infections if
17 an infectious disease screening is flawed or emerging
18 or unknown diseases evolve unchecked over time.
19 So another question that was asked was
20 what should be the scope of a master strategy and the
21 number one issue that came out was a recipient outcome
22 surveillance or a biovigilance system to identify all
23 donors using common identification numbers linked to
24 biological products that are uniquely identified;
25 mandatory adverse event reporting process for tissues,

1 organs and blood therapy through appropriate
2 mechanisms to designated public health authorities and
3 to recipients and donors and timely and efficiently
4 trace all biological products to the clinical user,
5 recipient, and donor and to recognize transmissible
6 events resulting in adverse outcomes including
7 infectious agents, malignancies and toxins; also to
8 build communication and education networks to
9 disseminate data to users; to develop informatics to
10 support surveillance, process, involvement,
11 improvement and evidence-based research; and to
12 include other strategic plan elements as needed such
13 as donor recruitment, donor screening, research
14 coordination and emergency preparedness.
15 What are the areas of commonality of blood
16 products, cohort progenitor cells and bone marrow
17 tissues and organs? Key elements in common with
18 transfusion required for ensuring high quality include
19 donor recruitment; donor screening; and, of course,
20 eligibility; collection; infectious disease testing;
21 transportation; storage; processing; labeling;
22 traceability; good manufacturing practices; good
23 tissue practices. I would also say probably good
24 transplantation practices; outcome analysis; adverse
25 event reporting. And in addition, there needs to be a

1 way to evaluate the differences between the different
2 transfusion and transplantation products, modalities.
3 How best should this be done with the
4 stakeholders and how do we begin? The recommendation
5 was that HHS should convene a forum of stakeholders to
6 include public health agencies, accrediting agencies,
7 manufacturers, clinicians, consumers and endusers and
8 HHS should be responsible for implementing a master
9 strategy with appropriate resources based on input
10 from stakeholders.
11 And what are the resources needed and what
12 are the estimated costs? The committee really do not
13 get to that area and had a difficult time trying to
14 put a price tag on what this would mean.
15 Let me just go back to that slide there.
16 As an outcome of the recommendations, Dr. Aquinobi has
17 sent a letter to Dr. Bracey who is the Chairman of the
18 Advisory Committee on Blood Safety and Availability.
19 In that letter, he does recognize the recommendations
20 and the answers to the questions and also reassures
21 Dr. Bracey that the Department has already moved
22 forward in various aspects on bioviligence and we have
23 already put resources towards those bioviligence
24 endeavors through not only the recipient side but also
25 through the donor side of surveillance and also CDC is

1 supporting a collaborative effort with the TTSN for
2 tissues and transplantation.
3 Our next meeting is next week. The two
4 issues that we're primarily looking at ethical
5 considerations and risk benefits for ensuring
6 transfusion and transplantation safety during focal
7 periods of shortages. Those focal periods of
8 shortages could be seasonal shortages, preparation for
9 pandemic, disasters both manmade or natural and then
10 also to review and discuss the elasticity of the blood
11 supply to support transfusion and transplantation
12 safety as well as strategies and barriers to those
13 strategies.
14 And that's all I have. If there are any
15 questions, I'll be happy to entertain those.
16 CHAIRMAN SIEGAL: Questions from the
17 Committee?
18 DR. FINNEGAN: One of my questions and I
19 realize I'm a little bit naive about what the
20 infrastructure for IT is within this environment, but
21 would you consider having IT infrastructure as one of
22 the stakeholders? Because it would seem to me if you
23 had a good IT infrastructure, that the cost long term
24 would be much less.
25 DR. HOLMBERG: Absolutely. We have

1 already initiated some of those discussions primarily
2 using some of the infrastructure that is already in
3 place within the Federal Government and outside the
4 Federal Government. Also within the Department of
5 Health and Human Services is a health information
6 technology office that is personally -- that reports
7 directly to Secretary Leavitt. They've done case
8 studies analysis for electronic health records and
9 also for laboratory surveillance.
10 So we're moving in that direction, but,
11 yes, definitely in our stakeholder meetings, we will
12 consider IT so that there are stakeholders, there are
13 placeholders, I should say, for future systems that
14 are developed that we can mine the data down into.
15 The other thing that I want to emphasize
16 there is that we are really looking at this as a
17 quality system in such a way that this will be a
18 system to develop or to get data that we can analysis
19 in hopes of being able to share it throughout the
20 entire community and not to be punitive against a
21 stakeholder. So it's trying to be very open in the
22 way we collect the data and for that reason, we have
23 already involved many of the stakeholders such as the
24 AABB and the UNIS and the various -- the American
25 Association of Tissue Banks. Yes. Dr. Ballow.

1 DR. BALLOW: So is this to include all
2 fractionated blood banks as well?
3 DR. HOLMBERG: Well, we do have them --
4 DR. BALLOW: Coagulation products, IV, IG,
5 etc.?
6 DR. HOLMBERG: We do have them as one of
7 the stakeholders and we have not had the meeting yet,
8 but they are on the list to participate.
9 The other thing I want to draw the
10 attention to is that we do have a federal registry
11 notice out that came out on July 30th seeking
12 nominations to the Advisory Committee on Blood Safety
13 and Availability. I would like to take this
14 opportunity to draw your attention to that and to
15 remind people that nominations are due by August 31st.
16 Thank you.
17 DR. SZYMANSKI: I had one more question.
18 I notice an interesting word "malignancy" and how are
19 you going to screen for that? In donors or in the
20 recipients? Is that something new that is not being
21 done now when you screen donors?
22 DR. HOLMBERG: I didn't understand the
23 word that you were referring to.
24 DR. SZYMANSKI: You said you are going to
25 not only worry about infectious diseases, but

1 transmission or something with malignancy and I was
2 wondering. Do you have any other approaches than what
3 are used right now when you screen donors for blood
4 donation?
5 DR. HOLMBERG: As far as blood donations,
6 we do not have a mechanism to be able to track that.
7 However, in the organ community they do have the
8 adverse event reporting and that does get passed back
9 to UNIS. But it's open. We're the point right now of
10 just developing this and, of course, as we move
11 forward in bioviligence, I'm sure there will be other
12 avenues that we want to investigate. I think that
13 what he want to do is to not only look at what we know
14 today but also to look towards the future and to be
15 able to look beyond the horizon for anything that may
16 potentially affect the blood organ or tissue products.
17 CHAIRMAN SIEGAL: Are there any other
18 questions for Dr. Holmberg? Okay. If not, Jerry,
19 thank you. The next speaker will be Jennifer Scharpf
20 who is going to review the FDA workshop from last
21 April on immune globulins for primary immune
22 deficiency disease referencing antibody specificity,
23 potency and testing. Dr. Scharpf.
24 DR. SCHARPF: Thank you, Dr. Siegal, and
25 good morning. This morning I will provide the

1 Committee on the FDA's workshop on immune globulins
2 for primary immune deficiency diseases and the
3 workshop was officially titled "Immune Globulins for
4 Primary Immune Deficiency Diseases; Antibody
5 Specificity, Potency and Testing." And the workshop
6 was held on April 25 through 26 of this year at the
7 National Institutes of Health. FDA is grateful to The
8 Immune Deficiency Foundation, The Plasma Protein
9 Therapeutic Association and Dr. Holmberg and the
10 Office of the Secretary, Office of Public Health and
11 Science at HHS for their sponsorship of the workshop.
12 And we thank the sponsors not only for their
13 financial support but also their scientific
14 contributions to the program. Additionally, I would
15 like to recognize Dr. Dorothy Scott for her role as
16 organizer and chair of the program.
17 The goals of the workshop were fourfold:
18 (1) to assess the current potency testing of immune
19 globulins. The potency tests currently required are
20 for antibodies to measles, polio and diphtheria and at
21 the workshop, we wished to examine the potential for
22 potency tests for antibodies against pathogens most
23 commonly associated with infection in PIDD patients;
24 (2) to list antibodies needed to protect primary
25 immune deficient patients from infections; (3) to

1 identify candidate antibody specificities for potency
2 testing of immune globulins for treatment of PIDD;
3 and, finally, on the second day, our goal was to
4 address approaches to diminishing measles antibody
5 levels in currently licensed products.
6 So on the first day of the workshop, our
7 goal was to identify the most clinically relevant
8 antibody specificities for PIDD patients.
9 Epidemiology and surveillance data was reviewed and
10 there was a description of patient registries in
11 Europe and the United States. The registries which
12 are supported by the European Society for
13 Immunodeficiencies and, the United States,
14 Immunodeficiency Network, have the potential to gather
15 long-term perspective clinical data on these patients.
16 We then reviewed data on antibody levels in currently
17 licensed products and both of these datasets were
18 taken to then address the question of which antibody
19 specificities would be useful and relevant to measure
20 with respect to clinical importance and to assure lot
21 to lot manufacturing consistency.
22 The first question we addressed to the
23 panel of experts and the workshop audience was which
24 pathogens are of greatest concern in immune globulin
25 treated and untreated patients. And to address this

1 question, data on infectious diseases and PIDD, both
2 patients with humeral and cellular immunodeficiencies
3 was presented by clinicians.
4 The workshop participants identified Strep
5 pneumococcus and Haemophiles influenzae as the most
6 important bacterial infections for this patient
7 population. Several viral infections were also
8 mentioned as pathogens of concern including Epstein-
9 Barr Virus, Cytomegalovirus, echoviruses, Varicella
10 Zoster, adenovirus and Coxsackie.
11 Representatives from the FDA, the Paul-
12 Ehrlich-Institut in Germany and two IGIV fractionaters
13 then presented data on antibody levels in currently
14 licensed products. The presentations revealed that
15 multiple antibody specificities have been studied,
16 trends in antibody levels over time, across products
17 and variations with the plasma source whether
18 recovered or source were observed and regarding
19 emerging diseases, West Nile Virus antibody titers,
20 have been measured in U.S. products, although as one
21 would expect both seasonal and locational variations
22 are observed.
23 So at the end of the first day of the
24 workshop, it was proposed that pilot testing of immune
25 globulins for Strep pneumonia and H. influenza should

1 be conducted and we believe this type of study is
2 feasible since assays have been validated for the
3 specificities in serum and who reference labs already
4 exist to which samples could be sent for testing.
5 In the proposed studies, manufacturers
6 would voluntarily send blinded samples to their
7 reference lab for testing antibody levels to determine
8 the feasibility, antibody levels and function, and
9 several manufacturers have expressed their willingness
10 to send samples. And finally, we would like to
11 measure the trough titer level antibodies to these
12 bacterial pathogens in patients receiving the product
13 to determine the relationship between in vitro potency
14 and in vivo levels. And we anticipate that by working
15 with manufacturers, samples from clinical studies
16 would be available for this type of testing.
17 On the second day of the workshop, we
18 discussed the current lot release tests for measles
19 antibodies and measles antibody levels are a standard
20 lot release measure of potency in the United States
21 products and this was a historically important
22 specificity due to measles epidemics. There has been
23 declining antibody levels observed in products over
24 the past several years and this is attributed to the
25 decline of titers in the donor population.

1 The regulatory impact of declining measles
2 titers is that the product could fail the lot release
3 specification and the specific lots must be rejected
4 and rejection of lots could lead to an obvious
5 negative impact on the availability of the product for
6 the primary immune deficient patients.
7 Presentations at the workshop revealed
8 data on the measles epidemiology in the United States,
9 decreasing measles titers in the donor population,
10 immune globulin products and primary immune deficient
11 patients and the estimated protective level of
12 antibody in these patients. I won't expand on these
13 presentations since the data will be presented to the
14 Committee later this afternoon.
15 Following those presentations, we asked
16 the following questions to the expert panel and the
17 audience: is measles infection of current clinical
18 concern for primary immune deficient patients, how
19 much measles antibody is needed to attenuate or
20 prevent measles in this patient population; what is
21 the potential clinical impact of diminishing anti-
22 measles titers in immune globulin products; and
23 finally, what are the possible approaches to address
24 the decline of anti-measles antibodies in immune
25 globulins with respect to clinical efficacy in

1 prevention of measles infection as well as with
2 respect to utility of a test for lot-to-lot
3 consistency.
4 So the possible approaches identified by
5 the discussants at the workshop included: (1)
6 gathering relevant data relating product titers to
7 patient trough levels and estimated protective levels
8 and (2) the option that CBER can potentially change
9 the recommendation on antibody potency, however, this
10 change in level must be scientifically and clinically
11 justifiable and this is the issue that will be before
12 the Committee today.
13 So in summary, the next steps identified
14 at the workshop are to (1) design and implement
15 testing protocols to assess levels of antibodies in
16 immune globulins to H. Influenza and Strep pneumonia
17 pathogens commonly associated with infection in
18 primary immunodeficient patients and the study will
19 evaluate the feasibility of using these specificities
20 as potency tests; (2) implement a study to measure
21 measles antibody trough levels by neutralization
22 assays in patients to better ascertain the
23 relationship between product dose and trough level;
24 and finally, CBER will deliberate on solutions to
25 address the diminishing measles antibodies titers and

1 immune globulins weighing, of course, the scientific,
2 clinical and supply considerations.
3 And finally, information is available on
4 the CBER website including the transcript and all of
5 the workshop presentations. Thank you for your
6 attention.
7 CHAIRMAN SIEGAL: Thank you, Dr. Scharpf.
8 Are there questions from the Committee? I actually
9 do have a question which is that since we will discuss
10 this later but is it feasible to change the licensure
11 requirements entirely so that measles antibody which
12 may not really be relevant is simply not part of the
13 criteria for approval of the product.
14 DR. SCHARPF: I think we can look at
15 examining changing the titer and that's what we will
16 present later this afternoon to the Committee.
17 CHAIRMAN SIEGAL: Because it certainly
18 would be more relevant to look at representative
19 pneumococcal antibody titers for the PIDD population.
20 DR. SCHARPF: And that was some of the
21 conclusions of the workshop.
22 CHAIRMAN SIEGAL: Anybody else?
23 DR. GOLDING: Yes, I'll just help to
24 answer that question. I mean we are looking very
25 actively at changing this, the relevant titers, and

1 what Jennifer mentioned is that we're looking at H.
2 influenzae and also at Strep pneumoniae as being much
3 more important and relevant pathogens. But I don't
4 think we have any plans in the near future to drop
5 measles because as you will hear later, we still think
6 this is a pathogen we need to worry about even though
7 it's much rarer these days. But also in terms of
8 consistency of lot-to-lot testing, it's important to
9 have tests in place that have the history and the
10 ability to show differences between batches.
11 CHAIRMAN SIEGAL: Okay. Let's move on.
12 Finally, Lore Fields from FDA is going to summarize
13 the FDA workshop just yesterday on licensure of
14 apheresis blood products.
15 MS. FIELDS: Good morning. Yesterday we
16 had a workshop on the licensure of aphersis blood
17 products at Lister Hill Auditorium at NIH.
18 In keeping with the vision of CBER to
19 protect and improve public health and to approve safe
20 and effective blood products, we planned a workshop to
21 help educate industry on how we approve apheresis
22 submissions at the Blood and Plasma branch. We
23 estimate that currently appropriately 40 percent of
24 the submissions coming into the Blood and Plasma
25 branch are on apheresis products. We did have 175

1 places available yesterday for the workshop and we did
2 fill the entire auditorium.
3 The goals and objectives for the workshop
4 were to educate industry on the licensure process for
5 apheresis platelets, red blood cells and plasma for
6 transfusion. We wanted to discuss the managed review
7 process as it applies to the Blood and Plasma branch,
8 discuss and review the required documents needed for
9 submission, review the comparability protocol and what
10 is required to obtain one and review the requirements
11 for an apheresis instrument. Additionally, we asked
12 speakers from industry to give examples on how they
13 successfully submit their FDA's licensure submissions.
14 We also asked Dr. Katz from the Mississippi Valley
15 Regional Blood Center to talk on his recently
16 published paper, "Frequent Platelet Apheresis Does Not
17 Clinically Significantly Decrease the Platelet Counts
18 in Donors" by Dr. Katz, et al.
19 The workshop was developed and cosponsored
20 by CBER, the Department of Health and Human Services,
21 AABB and America's Blood Centers and we would like to
22 thank AABB, ABC and HHS for their contributions to the
23 workshop.
24 During the workshop, we had several
25 presentations. I'm going to go over just very brief

1 overviews of what was discussed. Dr. Goodman did open
2 the workshop for us.
3 Dr. Williams provided an informative
4 presentation on the statutes and regulations that we
5 use to do licensure submissions. Dr. Williams also
6 covered licensing, changes to an approved application,
7 alternative procedures and how managed review is
8 applied to the Blood and Plasma branch.
9 Ms. Ciaraldi did a comprehensive
10 presentation that described how we perform reviews.
11 This presentation included the documents, regulations,
12 guidance and operators' manuals references that we
13 frequently use when we are doing our reviews.
14 Ms. Nesbitt did a top ten pitfalls with
15 submissions presentation and what we did with this was
16 he got together in the Blood and Plasma branch and we
17 came up with the top ten reasons that we find errors
18 in submissions and she went through them. Hopefully,
19 the blood centers will then be able to apply this to
20 their submissions before they send them in and it will
21 facilitate the process of getting licensure done in a
22 timely manner.
23 The next two presentations were given by
24 representatives of the American Red Cross and Blood
25 Systems. We are always being asked for examples of

1 acceptable submissions. So we asked these two blood
2 centers to provide the attendees with an overview of
3 their processes.
4 Steve Kassapian who is the Director of
5 Regulatory Affairs at American Red Cross reviewed his
6 processes and included some of the examples and forms
7 that his group has put together over the last couple
8 of years that they use to facilitate their process.
9 Ms. Kathleen Hopping from BSI reviewed how
10 they have standardized their platelet Apheresis
11 licensure process. She also provided the attendees
12 with timetables on how the process improvement has
13 reduced the time of the licensure or the approval for
14 licensure at their blood centers.
15 I went over a brief review of the current
16 guidance for platelet Apheresis and the 2005 draft
17 guidance.
18 We did have an unexpected presentation
19 yesterday that is unfortunately not on your slides. A
20 direct final rule was actually displayed yesterday as
21 well. So we had a surprise presentation by Ms.
22 Elizabeth Callahan who is the Acting Director of the
23 Division of Blood Applications and in this is the
24 changes that will allow a storage period of seven days
25 for platelet Apheresis and also the increase for the

1 minimum pH from 6.0 to 6.2 for platelet Apheresis
2 quality control.
3 Dr. Katz put on a presentation based on
4 the comments to the 2005 draft guidance. His group
5 did a study to determine what the impact is on
6 platelet counts and donation intervals. This is the
7 data that was previously presented to you in March of
8 2006. The paper was recently published and so we
9 asked him to present the data to the attendees.
10 The failure investigation presentations
11 covered the regulations behind the investigations by
12 Ms. Hoi-may Wong and also one example of how a
13 structured investigation process is working at a major
14 blood center.
15 Ms. Faye Kugele described how the ARC has
16 standardized their failure investigation processes and
17 how the standardized procedures have improved their
18 investigation of failed products.
19 We did something a little different at our
20 workshop and one of the things is we spent a lot of
21 time talking to the regulatory people at the blood
22 centers, but they never actually see our faces. So we
23 spent about 30 minutes at our afternoon break kind of
24 introducing ourselves to them so they had a face to go
25 with the person that they talked to.

1 The Device Manufacturers Forum was an
2 opportunity for the manufacturers to provide the
3 attendees with pertinent information from their
4 operators' manuals, package inserts and other
5 documents that should be included with their
6 submission. They also provided updates on recent
7 changes on their cleared devices and this was done by
8 Merilyn Wiler from Gambro, Dr. Orton from Fenwal and
9 Sue Finneran from Haemonetics.
10 The final session was a question and
11 answer sessions. Questions were actually provided to
12 a docket in advance and we discussed the answers as
13 our final session. There were 17 questions submitted
14 and discussed.
15 Overall, we received excellent feedback on
16 the workshop. The Regulatory Affairs staff from the
17 blood centers who attended said they learned a lot and
18 they were provided an excellent resource to help them
19 with their next submission to CBER.
20 The workshop planning committees contains
21 six people from industry: Celso Bianco, Sue Finneran
22 from Haemonetics, Joe Giglio from AABB, Steve
23 Kassapian from American Red Cross, Dr. Orton from
24 Fenwal and Merilyn Wiler from Gambro BCT. In
25 addition, there were seven people from FDA on the

1 planning workshop. Thank you.
2 CHAIRMAN SIEGAL: Thank you. Are there
3 questions from the Committee or anybody else?
4 (No response.)
5 CHAIRMAN SIEGAL: All right. Thank you
6 very much. In view of that, let's go onto the
7 Informational Presentations on WHO Biological
8 Standards. The first presentation will be by Paul
9 Mied from FDA talking about the WHO meeting and
10 Collaborating Centers for Biological Standards and
11 Standardization to Support the Development of WHO
12 Biological Reference Preparations for Blood Safety-
13 related in vitro Diagnostic Tests. Dr. Mied.
14 DR. MIED: Thank you, Dr. Siegal.
15 This morning I would like to present a
16 summary of the January 29th and 30th WHO meeting with
17 the WHO Collaborating Centers for Biological Standards
18 and Standardization. Now this two day meeting was
19 held at CBER in Bethesda and the three WHO
20 Collaborating Centers for Biological Standards and
21 Standardization that participated in the meeting were
22 NIBSC in the U.K., PEI in Germany and CBER.
23 The meeting was convened by WHO,
24 specifically the Quality Assurance and Safety Blood
25 Products and Related Biologicals Team and the

1 Department of Medicines, Policies and Standards of the
2 World Health Organization. The objective of the
3 meeting was to foster cooperation among the WHO
4 Collaborating Centers in the development of WHO
5 international biological reference preparations for
6 the control of in vitro diagnostic tests related to
7 blood safety.
8 Now the WHO is establishing a five year
9 strategic plan to prioritize development of these
10 reagents. These biological reference preparations are
11 used for the validation, quality control, assessment
12 of comparability and regulation on a global basis of
13 blood safety related in vitro diagnostic tests. This
14 contributes to a harmonized regulation of blood and
15 blood products. Specifically, these reagents are used
16 to provide an indication of the analytical sensitivity
17 of in vitro diagnostic test kits.
18 Now the meeting, the two day meeting,
19 covered the following agents which have an impact on
20 blood safety: HAV, HBV, HCV, Parvo B19, HTLV 1 and 2,
21 CMV, West Nile Virus, Dengue Virus, HHVA, prion
22 agents, bacteria and the causative agents of syphilis,
23 malaria, Chagas and Leishmaniasis. The existing
24 established WHO biological reference preparations were
25 discussed at length along with several new proposals

1 for development of international standards and
2 reference panels and the priority projects identified
3 were, first of all, the replacement of four existing
4 WHO biological reference preparations and I'll briefly
5 describe for you some of these highest priorities.
6 One of the highest priorities identified
7 was a proposed second international reference
8 preparation for anti HBS immunoglobulin to replace the
9 first international reference preparation that was
10 established back in 1977 and it's now close to
11 exhaustion. NIBSC will be the coordinator of the WHO
12 collaboration study to demonstrate the usefulness of
13 candidate materials for use with a wide range of assay
14 kits and the report of the WHO collaborative study is
15 expected to be submitted to the Expert Committee on
16 Biological Standardization or ECBS in October 2008.
17 For HCV RNA, there is an ongoing
18 collaborative study that NIBSC is coordinating that
19 was begun in 2006 to replace the second international
20 standard of HCV RNA with the proposed third
21 international standard. Two lyophilized candidate
22 materials generate from anti HCV-negative window
23 period genotype 1A donations have been distributed to
24 32 laboratories covering the main commercially-
25 available NAT tests for HCV RNA. It's expected that

1 the proposal for the establishment of this standard
2 will be submitted at the meeting of the ECBS in
3 October 2007.
4 The first international standard for Parvo
5 B19 DNA which was established in 2000 will be nearly
6 exhausted by 2009. A small collaborative study was
7 proposed by NIBSC to demonstrate the comparable
8 potency of a freeze-dried candidate replacement
9 material to this standard. NIBSC will present an
10 update of discussions from the SoGAT meetings to the
11 ECBS in 2007 and the Collaborative Centers agreed to
12 submit the report of the WHO collaborative study to
13 the ECBS in 2008 for establishment of the second
14 international standard.
15 Now there was some discussion at the
16 meeting that what was really needed is a genotype
17 reference panel for Parvo B19 DNA and a consensus was
18 reached to identify source plasma materials of
19 genotypes 2 and 3 and to present an update to the ECBS
20 about that in 2007. Regulators want to be sure that
21 all three genotypes 1, 2 and 3 with two subgroups are
22 detected by various NAT assays worldwide for the
23 testing of plasma pools and that appropriate plasma
24 standards are available to validate those NAT tests.
25 There will be future discussion about the

1 establishment of a Parvo B19 genotype reference panel.
2 The current anti syphilitic reference here
3 and the first international standard was established
4 way back in 1957 and it has assigned unitage and it's
5 used by reference laboratories, diagnostic labs and
6 manufacturers of diagnostic immunoassays. NIBSC is
7 the coordinator of an WHO international collaborative
8 study that is already underway to evaluate two freeze-
9 dried plasma pool preparations, one representing
10 active syphilis IGG and IGM and the other latent
11 syphilis for IGG that had been selected as replaced
12 candidates for this first international standard for
13 T. palladum particle agglutination tests and
14 cardiolipin assays and various immunoassays. The data
15 are currently being analyzed and the study report will
16 be submitted to the ECBS meeting in October.
17 Now a second set, as a second set, of
18 priority projects, there was agreement among the
19 collaborating centers that several new WHO biological
20 reference preparations are needed. First of all, an
21 HIV-1 genotype panel is needed to assess the impact of
22 new HIV variants on test sensitivity.
23 The first international reference panel
24 for HIV-1 RNA genotypes was established by the ECBS in
25 2003. Now this was a set of ten HIV-1 genotypes A, B,

1 C and D, CRF 01AE, F and G, AGGH and Group N and Group
2 O. But CBER and NIBSC will be collaborating to
3 identify representatives of the less common subtypes
4 such as G, H, J and K and a range of circulating
5 recombinant forms such as CRF 01AE and CRF 02AG to be
6 used in a panel that's an extension of this reference
7 panel and CBER and NIBSC will develop a plan and hold
8 a discussion at a WHO workshop and report on the WHO
9 collaborative study to ECBS in 2009.
10 For an HIV-2 RNA standard, CBER and NIBSC
11 are collaborating to exchange information on available
12 candidate HIV-2 strains. These are cultured subtypes
13 A and B and there will be a discussion of a plan at a
14 WHO workshop and a report of the WHO collaborative
15 study to ECBS in 2009.
16 The proposed second anti HIV international
17 reference panel will be an extension of the
18 established first panel for anti HIV-1/2 antibodies.
19 This first panel was a six member panel established by
20 the ECBS in 2006 and it consists of subtypes A, B, C,
21 CRF 01AE, Group O and HIV-2. This panel is needed for
22 the control of the HIV EIA tests, rapid tests and
23 combo antigen antibody tests. Samples from CBER
24 comprised of different HIV-1 and HIV-2 subtypes from
25 different geographical regions will be provided as

1 candidate materials. The project proposal is to be
2 submitted to ECBS for endorsement by 2008.
3 Eight different genotypes are known for
4 HBV, A to H, representing different subtypes related
5 to A determinant of HBsAG. The current WHO biological
6 reference preparations for HBsAG and HBV DNA both
7 generated from genotype A2, subtype ADW2 represent
8 only one percent of worldwide HBV infected population.
9 So there is a need for the development of HBV
10 genotype reference panels to evaluate surface antigen
11 tests and HBV DNA NAT tests in terms of their ability
12 to detect those other genotypes or subtypes prevalent
13 in the regions where the tests are on the market.
14 The aim here is to develop two genotype
15 panels, one for HBsAG tests and one for NAT assays and
16 PEI is coordinating efforts to collect plasma units
17 worldwide that represent these different genotypes and
18 is conducting a feasibility study to characterize and
19 assess candidate panel members and by September 2007,
20 PEI will develop protocol for the collaborative study
21 to investigate the impact of the different genotypes
22 on the sensitivity of surface antigen and NAT tests.
23 The report of the collaborative study will be
24 submitted to ECBS in 2008.
25 The standardization of anti Hepatis-B core

1 testing using WHO international standard and the
2 assessment of the sensitivity of anti-core assays is
3 important to ensure the detection of true low level
4 reactive samples. PEI in cooperation with NIBSC and
5 CBER is evaluating for the international collaborative
6 study the candidate material which is a low anti-core
7 positive without any other detectable HBb markers.
8 After the international collaboration
9 study the statistical analysis will be done at PEI by
10 March 2008 and they'll submit the study report to ECBS
11 in 2008.
12 An anti HCV reference panel containing
13 antibodies directed against single HCV antigens is
14 needed for the quality control of anti-HCV tests.
15 This would be a reference panel for each of the four
16 major antibodies detectable by commercial anti-HCV
17 test kits, anti-core and antibodies to the
18 nonstructural proteins NS3, NS4, NS5. Now Chiron
19 offered to help by preparing mono-specific anti-HCV
20 antibodies and these are from pooled HCV Genotype 1A
21 positive plasma units with high titers against each of
22 the four Reba-3 antigens. A feasibility was conducted
23 by the WHO collaborating centers using these candidate
24 materials. But because of the limited quantity of
25 these materials that was available, this panel was

1 considered useful for regulatory authorities to
2 determine the potencies of the tests rather than to be
3 used for the control of batch consistency by
4 manufacturers. PEI will finalize the analysis of all
5 data from the feasibility study and will present the
6 progress report to the ECBS in October 2007 and the
7 WHO collaborative study will start in 2008.
8 As you know, there is now mandatory
9 screening for antibodies to HTLV-1 and -2 in many
10 countries around the world. These agents pose
11 significant risks to the blood supply in specific
12 areas such as Africa, South America, the Caribbean and
13 Japan. CBER proposed that an anti HTLV-1/2 reference
14 panel be developed because the current lack of
15 reference panels hinders the ability to evaluate new
16 tests which have improved sensitivity and to assure
17 that they are detecting the antigenic variance. Some
18 HTLV-2 subtypes, we know, may escape detection by
19 currently available technology.
20 The collaborating centers felt that for
21 the development of a reference panel the candidate
22 material should include samples from HTLV infected
23 individuals, from areas where HTLV-1 and -2 are
24 endemic including special samples that represent the
25 HTLV-2 subtypes and CBER will coordinate the

1 feasibility study by collecting and testing samples
2 from these diverse geographical areas.
3 For Plasmodium, there is a need for an
4 antibody reference panel to define the sensitivity and
5 specificity of serology assays to detect malaria
6 infection. The panel would be useful for the
7 validation of EIA test kits and to compare the
8 efficacy of commercial test kits by regulatory
9 agencies and by the user. Additionally, these
10 antibody standard preparations would be a useful tool
11 for assays to measure safety and efficacy in the
12 development of malaria vaccines.
13 It was decided that the panel should
14 include sera from individuals who were exposed to only
15 one species of Plasmodium and should cover the
16 recognition of all species of Plasmodium. NIBSC will
17 send samples from positive donors to CBER to determine
18 their reactivity to different mono-specific
19 recombinant antigens and CBER and NIBSC will select a
20 pilot panel of sera and develop a protocol for the
21 collaborative study that would be reported to the
22 ECBS.
23 Several countries in Latin America
24 representing the highest endemic region for Chagas
25 disease, the U.S. and Spain, have implemented testing

1 of the blood donors for antibodies to T. cruzi.
2 However, serological tests are of variable sensitivity
3 and there is no global reference material. Reference
4 preparations are needed for both screening and
5 clinical diagnosis. Although variability in the
6 antibody response throughout the endemic range does
7 not appear to be a large problem, there is enough
8 concern in the field that a reference panel of
9 reactive sera should have representatives of multiple
10 geographical areas.
11 CBER proposed the development of an
12 international reference panel for anti T. cruzi
13 antibodies and WHO will form a working group that will
14 discuss issues related to the development of this WHO
15 anti T. cruzi panel including the need for the
16 establishment for the panel of reactive sera
17 representing multiple geographical areas. Now at the
18 WHO Chagas meeting in July, it was agreed that the
19 panel would include antibody-positive plasma units
20 from Mexico, Columbia, Bolivia and Brazil.
21 Now in addition to these priorities, there
22 were several other biological reference preparations
23 that were proposed that need further discussion by the
24 collaborating centers, an HIV-2 RNA genotype panel, an
25 HCV genotype panel, as I mentioned earlier, a Parvo

1 virus B19 genotype panel, an anti CMV standard, a West
2 Nile Virus RNA preparation or a Pan panel for
3 arthropod born flavivirus RNA, an HCV core antigen
4 preparation, anti-HHV8 and HHV8 DNA preparations, TSE
5 blood preparations, a blood-borne bacteria panel and
6 anti Leishmania panel. So there will be additional
7 discussion among the WHO collaborating centers in
8 future meetings about those various panels.
9 Now there were some additional agreements
10 among the WHO collaborating centers such as a need for
11 collection and exchange of epidemiological information
12 which has an impact on blood safety. It was agreed
13 that the established WHO biological reference
14 preparations and those to be developed in the future
15 are suitable to cover new technologies such as
16 microarray and nano particle assays for the detection
17 of infectious agents.
18 They recognized a need for improved
19 collaboration among WHO collaborating centers and with
20 the WHO. Annual face-to-face meetings and
21 teleconferences are necessary to monitor progress on
22 all of these priority projects I talked about and
23 there is a need to establish a network of WHO
24 collaborating centers for IVD-related biological
25 standardization representing all WHO regions to ensure

1 complimentary and focused expertise at the global
2 level.
3 So what's the plan of action? Well, the
4 priority projects to establish WHO biological
5 reference preparations, to support international
6 regulations for blood and blood products safety.
7 We'll form a five year in vitro diagnostic strategic
8 plan and this plan will be submitted to the ECBS for
9 endorsement in October 2007.
10 Thank you for your attention.
11 CHAIRMAN SIEGAL: Thank you, Dr. Mied.
12 Are there questions?
13 DR. DI BISCEGLIE: I have a question
14 please. With regard to the standard for HCR RNA, you
15 said that the standard that was being reworked was for
16 genotype 1. Are there other existing standards for
17 other genotypes and, if not, why not, I guess?
18 DR. MIED: I think they're very hard to
19 get. I know that what they have has been generated
20 from a genotype 1A donation or several genotype 1A
21 donations.
22 DR. DI BISCEGLIE: The issue being this
23 that I think it's well known that the genotype may
24 affect the sensitivity of assays to detect HCV RNA.
25 DR. MIED: Yes.

1 DR. DI BISCEGLIE: And, for example,
2 genotypes 3 and 4 are emerging in Europe at the
3 moment. We haven't seen that in this country yet.
4 But can we be reassured about the sensitivity of NAT
5 assays to detect these other genotypes if we don't
6 have standards?
7 DR. MIED: Yes. That's one thing we
8 really -- Mei-ying, go ahead.
9 DR. YU: I would like to comment about
10 this. Usually, the primers and the approach should be
11 situated in the very conserved region. So whatever
12 you are detecting you should detect all genotypes at
13 least for HCV. I mean, yes, I understand there are
14 mutants and there are some nearly evolved isolates,
15 but in essence for HCV NAT, they are selected. But I
16 understand your issue.
17 DR. DI BISCEGLIE: No, I understand that
18 and I think those of us with longer memories will
19 recall that the very first assay that was developed
20 for measurement of HCR RNA was found within a few
21 months to have very discrepant ability to detect
22 various genotypes despite the primer selection. So I
23 am somewhat concerned about this.
24 DR. MIED: Yes, it is a concern. But I
25 think that the assays that are licensed for use in the

1 United States for screening, the NAT assays, some
2 limited numbers of the different genotypes have been
3 tested and there hasn't seemed to be a problem because
4 of conserved region in the primers and probes that are
5 used. But it remains to be seen, you know, on a
6 global basis with other HCV NAT tests how well they
7 detect these other genotypes.

8 DR. DI BISCEGLIE: Sorry to be persistent.
9 I accept that. I did see, for example, there was a
10 plan to develop an HBV genotype panel for similar
11 reasons. I would have thought the reasons to develop
12 an HCV RNA standard of different genotypes would be
13 more compelling than that for HBV DNA and at this
14 stage, I'll just -- I won't comment anymore.

15 DR. YU: May I just add one more thing?
16 Actually, NIBAC has HCV genotype panels that there is
17 a panel that contained all six genotypes of HCV and
18 you can obtain that from NIBAC and again, during that
19 collaborative studies, there were using the primers
20 and, of course, those all six genotypes were
21 calibrated against the first international standard of
22 HCV and again, in that study, yes, there are some.
23 They are less sensitive, one of the genotypes and so
24 forth. But again, primers and probes should be
25 situated in the conserved regions in order to get the

1 maximum sensitivity.

2 CHAIRMAN SIEGAL: Dr. Katz.

3 DR. KATZ: Yes. Paul, on your next to the
4 last slide, you had the very tantalizing category,
5 blood-borne bacteria. Would you enlighten me?

6 DR. MIED: The blood-borne bacteria were
7 discussed. I think that PEI has six different
8 standards that they're willing to contribute to a
9 feasibility study. The need here, of course, is for
10 methods and platelet bacteria screening and also
11 pathogen reduction of cellular blood components.
12 These standards, bacterial standards, could be of
13 value in evaluating those methods. So a feasibility
14 study is needed to see if there are standards, if
15 there are strains that PEI has will be useful in that
16 regard.

17 DR. KATZ: So this is some, I presume,
18 relatively arbitrary clinical samples from blood or
19 platelet contamination spiked into something?

20 DR. MIED: I'm not sure what they actually
21 are. I don't know. I'll have to check on that.

22 CHAIRMAN SIEGAL: Dr. Epstein.

23 DR. EPSTEIN: I could just comment on
24 that. The Paul-Erhlich-Institut, Miesha Kneubbling,
25 has actually published on this. They have developed a

1 candidate panel. The source of the isolates, of
2 course, is from clinical cases, but the isolates are
3 selected for very reproducible growth conditions and
4 resistance to serum killing so that they can then be
5 spiked into samples that others wish to study and then
6 the presumption is then you have a level playing field
7 for assessing the capability of detect assays and
8 obviously they are designed to span a range of
9 bacterial groups and types. So that's the underlying
10 concept because right now, if a manufacturer wants to
11 validate a bacterial detection assay you simply have
12 to engage in a conversation on where they get their
13 isolates and which ones they choose instead of having
14 any kind of standard array.
15 DR. MIED: Yes. The PEI standards were
16 prepared from different blood-borne bacteria. They're
17 offering six defined stable and shippable bacterial
18 standards, Staph epidermidis, Staph aureus, Staph
19 pyogenes, Klebsiella pneumoniae, E. coli and B. cereus
20 for a feasibility study.
21 MS. BAKER: Thank you for the
22 presentation. I know that the World Federation of
23 Hemophilia has held near annual meetings about blood
24 safety, the next being in September, I believe, in
25 Montreal. Are you aware of any efforts to communicate

1 this information, the summary, with the World
2 Federation of Hemophilia or other similar
3 international consortia?
4 DR. MIED: No, I'm not aware of those
5 efforts.
6 MS. BAKER: Okay.
7 DR. MIED: There may be some on the part
8 of WHO. I don't know what the plans are there.
9 MS. BAKER: Thank you.
10 DR. COLVIN: I just want to go back to the
11 hepatis C issue again in that from a infectious
12 disease point of view it seems to me that we could
13 almost treat the different HVC genotypes as almost
14 different infectious agents because they act so
15 differently and, yes, there are obviously conserved
16 sequences.
17 But I agree with Dr. Di Bisceglie that we
18 may not be looking at the same thing. Yes, in some
19 panels, they may work. But especially if we're
20 setting an international standard, it seems that we
21 should look at each one individually.
22 DR. EPSTEIN: Let me just say that this is
23 an issue that has been recognized by the WHO and there
24 have been consultations and certainly it's open for
25 additional discussion and we go to this meeting.

1 We're members of the panel. We hear you. We can
2 pursue this further. But the bottom line here is
3 whether the reagents that are available do or don't
4 work as generalizable standards and that can be
5 determined at the laboratory level.

6 And as it's been said, each of these
7 reagents is evaluated in a large collaboration of
8 multiple laboratories. So we will get the right
9 answers through the studies and the question is how do
10 we approach the problem up front. But, yes, we can
11 bring this discussion to Geneva.

12 DR. MIED: The plasma samples that NIBSC
13 has, they've procured HCV genotypes 2 through 6
14 specifically, 2B, 3A, 4A, 5 and 6A. These were
15 calibrated against the first international standard
16 for HCV RNA in a collaborative study and they have
17 been set at 1,000 International Units per mil for each
18 genotype. The problem is that the expression of these
19 genotypes 2 through 6 in International Units should be
20 taken with caution due to the genetic variability of
21 the virus and the fact that the calibration had been
22 made against the International Standard representing
23 the genotype 1A.

24 So it was agreed that this panel didn't
25 have the status of the WHO international reference

1 panel, but it is suitable for use in NAT assay
2 validation. So we'll just have to see. We need
3 scientific studies to assess the global variation of
4 HCV and evaluate the impact of these variants on the
5 sensitivity of various NAT tests around the world.
6 CHAIRMAN SIEGAL: Thank you, Dr. Mied.
7 Next we'll hear from Dr. Mei-ying Yu from FDA on the
8 potency and safety standards for plasma derivatives.
9 DR. YU: My talk will be potency and
10 safety standards for plasma derivatives. The outline
11 of my talk, first I will briefly give the introduction
12 and then I will describe the available potency
13 standards for clotting factors, potency and safety
14 standards for immune globulin and albumin products,
15 safety standards for in process control and finally
16 standards under development.
17 The Division of Hematology in CBER FDA has
18 the primary responsibility for the scientific
19 evaluation of manufactured biological products derived
20 from blood or plasma and their analogs from
21 recombinant DNA technology. To ensure their safety
22 and effectiveness, DH personnel have actively
23 participated in developing and establishing CBER
24 FDA/WHO global potency and safety standards through
25 close collaboration with WHO collaborative centers,

1 EDQM and industry.

2 Now the global potency standard means that
3 it's not only a WHO standard but also is European
4 Pharmacopeia standard as well as CBER standard. So
5 CBER FDA standards are available to IND sponsors of
6 licensed manufacturers. These standards are for
7 setting minimum potency requirements or maximum limits
8 of final container products and it's for lot release
9 testing of final container products and it's for in-
10 process control testing as well.

11 So the next few slides will be the potency
12 standards for clotting factors. The first one is
13 Factor 9 potency standards. These are for Factor 9
14 products like Factor 9 Complex, Coagulation Factor 9,
15 Coagulation Factor 9 that's recombinant. Now this
16 standard is called WHO 3rd International Standard for
17 Factor 8 Concentrates, but it's also European
18 Pharmacopeia standard and as well a CBER standard. So
19 this standard is a global standard.

20 It has an assigned unitage, 10.7 IU/vial.
21 This is based on the international collaborative
22 studies. It was formulated from a Coagulation Factor
23 9 product that is manufactured by using monoclonal
24 antibody chromatography. It was available since 1996.
25 Now there is a need to develop a new replacing

1 standard because of the low inventory.

2 This one is a potency standard for Factor
3 8 products. The Factor 8 product assays are
4 antihemophilic factor and the recombinant
5 antihemophilic factor. The standard is CBER Mega 2
6 from European Pharmacopeia Biological Reference
7 Preparation Batch 3 for Factor 8.

8 Again, based on the international studies,
9 the assigned unitage is 11.4 per vial. This is based
10 on a one stage clotting assay. If it's based on the
11 chromogenic assay the unitage has been assigned as 8.6
12 IU/vial. It was formulated from a plasma-derived high
13 purity Factor 8 preparation provided by CBER and
14 CBER/FDA.

15 This standard was available since 2001 and
16 this is after the potency calibration against four
17 Factor 8 concentration standards. That's there were
18 Mega 1 from European Pharmacopeia BRP Batch 2, WHO
19 Fifth International Standard and Sixth International
20 Standard in a collaborative study.

21 This is a potency standard for von
22 Willebrand Factor. The product assays, antihemophilic
23 factor, von Willebrand Factor Complex (Human). This
24 standard is the first international standard for von
25 Willebrand Factor Concentrate and the unitage has been

1 assigned as 9.4 IU von Willebrand Factor. This is
2 based on the Ristocetin co-factor assay. It contains
3 9.4 von Willebrand Factor per ampoule.
4 It was formulated from a von Willebrand
5 concentrate product by NIBAC, and it has been
6 available since November 2001 after potency
7 calibration against the WHO Fourth International
8 Standard for Factor 8 von Willebrand plasma in a
9 collaborative study.
10 This one is a potency standard for
11 Thrombin-containing products. The product assays are
12 Fibrogen sealant and bovine thrombin. This standard
13 is WHO Second International Standard for Thrombin and
14 also it's called CBER Lot K. The unitage is 110 IU
15 Human Thrombin per ampoule. It was formulated from a
16 human plasma derived thrombin by NIBSC. It has been
17 available since 2003 after potency calibration against
18 a First International Standard for Alpha Thrombin and
19 the U.S. Standard Thrombin Lot J in a collaborative
20 study.
21 The next few slides I will show you this
22 potency and safety standards for immune globulins and
23 albumin. CBER referenced immune globulin for measles
24 and poliomyelitis antibody levels. This standard is
25 to be used for setting the minimum requirement for

1 measles and polio antibodies and the product assays
2 are all the immune globulin products. Here I listed
3 immune globulin, immune globulin intravenous, immune
4 globulin subcutaneous and so that this standard is
5 called CBER Lot 176. It was 2 mL fill per vial and
6 stored liquid frozen.
7 It was formulated from one immune globulin
8 lot as 16.5 percent IGG solution in 1991 and made
9 available since 1992 after a collaborative study with
10 IG and IGIV manufacturers. It was calibrated against
11 Lot 175. Again, it's for the purpose of meeting
12 potency requirements of product lots for anti-measles
13 and anti-polio levels when compared at the same IGG
14 concentration. So the requirement for anti-measles
15 antibody levels is not less than 0.6 times the level
16 of the Lot 176 when determined by hemagglutination
17 inhibition or by neutralization. And the requirement
18 for a polio antibody level is not less than 0.28 for
19 Type 1, 0.25 for Type 2, or 0.20 for Type 3. Again,
20 it's by neutralization assay.
21 Now this standard will be discussed
22 further. It will be mentioned in this afternoon's
23 session.
24 And now this standard, Lot 176, was
25 recently calibrated against the Second International

1 Standard for Anti-Measles Serum (Human). So the
2 consensus titer was 42 IU anti-measles per mL of the
3 Lot 176 and the data has been published by Audet,
4 Suzette et al. in *Journal of Infectious Disease,* 2006.
5 Again, this 42 IU anti-measles per mL is based on a
6 neutralization assay.
7 It was calibrated -- Lot 176 also was
8 calibrated against the first WHO international
9 reference preparation for anti-HAV and also the CBER
10 reference, Hepatitis B Immune Globulin Lot 2 for use
11 as a reference for anti-HBs and anti-HAV level in
12 immune globulin. So it was determined to contain 2 IU
13 anti-HBs or 95 IU of anti HAV per mL of this
14 particular lot. And again, in this collaborative
15 study, all immune globulin manufacturers participated.
16 Now there is a need to develop a
17 replacement standard, Lot 177, because of low
18 inventory. A candidate 10 percent IGIV preparation is
19 now available and is kindly provided by Baxter
20 Bioscience.
21 CBER Reference Hepatitis B Immune Globulin
22 for Anti-HBs Potency Assay is used to assay products
23 such as hepatitis B immune globulin or hepatitis B
24 immune globulin intravenous. The current lot is Lot
25 2. It contains 220 IU of anti-HBs per mL. Again,

1 this standard is stored liquid frozen and it was
2 formulated from an HBIG product which was a 17 and a 3
3 percent of IGG solution and made available in 1977
4 and, in fact, this product was also further diluted
5 and freeze dried for establishing the first
6 international reference preparation for anti-HBs
7 immune globulin that Dr. Paul Mied just mentioned
8 earlier.
9 And there is a need to develop the second
10 international standard for anti-HBs immune globulin
11 and also that will serve as a CBER Lot 3 as well in
12 collaboration with NIBSC and Paul-Ehrlich-Institut
13 because of depleted supplies of the First
14 International Standard and CBER Lot 2. Now a
15 candidate HBIG preparation is available and it is
16 kindly provided by Nabi.
17 CBER Reference Prekallikrein Activator,
18 this is a safety standard and the product's assays are
19 albumin product IGIV, IGSC and some specific IGIVs.
20 This standard is called, current standard is CBER Lot
21 3. It contains 100 IU PKA per mL and it's a liquid
22 frozen preparation. It was formulated from a highly
23 purified PKA. It actually contained 26 nanogram per
24 mL Beta Factor 12A in a 5 percent albumin solution.
25 It was calibrated against Lot 2 in 1987 and found to

1 be equivalent. So Lot 2 and Lot 3 have equivalent
2 potency. Lot 2 was calibrated against the First
3 International Standard for PKA and it was calibrated
4 and the unitage assigned was 100 IU per mL.
5 Now we have a maximum PKA level in plasma
6 protein fraction. So the upper limit is no more than
7 35.7 percent of Lot 3. So that means not more than
8 35.7 IU per mL of the PKA.
9 Again, since this reference material was
10 prepared, was made available very early, now the
11 inventory is very low. So we need to replace CBER Lot
12 3 and we have recommended to use Second International
13 standard for PKA, and that is 29 IU per ampoule.
14 Global potency standard for anti-D immune
15 globulin, this standard is used to assay Rhi(d),
16 Rho(d)IG, or Rho(d)IGIV. These are anti-D immune
17 globulin products. The standard is WHO Second
18 International Standard, but it's also a European
19 Pharmacopeia first BRP or CBER Lot 4. The assigned
20 unitage is 285 IU per ampoule and when reconstituted,
21 it's 285 IU per mL. It was formulated in NIBSC from
22 two Rho(d)IG products licensed in the U.S., one
23 acquired by the FDA and the other kindly provided by
24 Talecris and formerly, Bayer Corporation.
25 And this standard was calibrated against

1 the WHO first international reference preparation for
2 anti-D immune globulin and along with two other
3 reserve candidate preparations that is by European
4 Pharmacopeia and also CBER Lot 3 in a collaborative
5 study co-sponsored by NIBSC, EDQM and CBER FDA. It
6 was established and available since 2003.
7 Now the standard dose for use in
8 preventing hemolytic disease of the new bone, this is
9 by the FDA, should be not less than 15 IU per dose or
10 equivalent to 300 microgram per dose. Now the detail
11 of the study please reference to Susan Foab's paper in
12 Vox Sanguinis 2003 or in Pharmacopeia -- I mean
13 Pharmeuropa Bio 2003.
14 International reference reagents for anti-
15 D to standardize hemagglutination testing, now this is
16 a safety standard obviously and the product to be
17 assay is IGIV, IGSC, and some specific IGIV. It was
18 after the collaborative study the WHO recognized this
19 as international reference reagents and it's to
20 standard hemagglutination testing.
21 This standard was formulated by NIBSC by
22 spiking an anti-D free 5 percent IGIV kindly provided
23 by Bio Products Laboratory with the WHO Second
24 International Standard for anti-D immunoglobulin and
25 the spike, the total amount that had been spiked, was

1 0.475 IU anti-D per mL and the negative, it's just 5
2 percent IGIV and we call this the positive -- there is
3 a positive international reference reagent as well as
4 the negative international reference reagent. The
5 positive international reagent is also called CBER Lot
6 1A and so forth. So anyway, these international
7 reference reagents are kindly shared with CBER by
8 NIBSC. Again, all papers are published in Vox
9 Sanguinis 2005. This is by Susan Thorpe, et al.
10 Briefly in that international
11 collaborative study, the sample assay were those
12 positive and negative international -- those are
13 positive and negative reference reagents along with
14 four IGIV samples with varying levels of anti-D by a
15 proposed reference method which is a so-called direct
16 hemagglutination test. So the direct hemagglutination
17 test was carried out by 19 of the 20 laboratories.
18 But then six of the 20 labs also assay
19 these materials with an in-house indirect anti-
20 globulin test that's called IAGTs. And based on the
21 collaborative study by the direct method, the positive
22 reference reagents has a nominal titer of 8. However,
23 with those indirect methods in the collaborative
24 study, it shows that it has in fact about six of the
25 laboratories, only one of them show up that has the

1 same titer as the direct method. Some of them could
2 not even detect any titer at all. So anyway, indirect
3 method shows why inter-laboratory variability and less
4 sensitivity.
5 So there is a need for using positive
6 international reference reagents to define the maximum
7 level of anti-D in immunoglobulin products and to
8 ensure sufficient sensitivity of hemagglutination
9 testing.
10 Now the results were presented to the
11 European at the Group 6B meeting and it was
12 recommended by the Group 6B to revise the appropriate
13 monograph and to include the specification and to use
14 the direct test. CBER also adopted the same limit and
15 the direct test after CBER's preliminary findings that
16 only one of nearly 140 lots of the all-licensed
17 immunoglobulin products failed the proposed
18 specification.
19 Now since the international reference
20 reagents, the stocks are limited. So larger fills
21 were carried out by NIBSC and this larger fill is
22 called reference preparation and this is for anti-D
23 immunoglobulin. And because it's larger fill, more
24 vials were available. So it's going to be -- it's
25 being used to control the level of anti-D in Europe as

1 well as in the U.S. for all the licensed
2 immunoglobulin products.
3 Now the reference, so it's this reference.
4 These reference preparations are called European
5 Pharmacopeia BRP Batch 1 or CBER Lot 1B. That's for
6 positive reference standard and the negative, there`s
7 also a negative standard. Now the positive standard,
8 as I say, is very similar to the previous one. It
9 also was spiked with 0.0475 IU of the anti-D per mL
10 and based on the collaborative study in which all U.S.
11 manufacturers also participated in using the direct
12 methods and that has the nominal titer of 8 as well
13 and I already mentioned that.
14 So the standards were shared with EDQM and
15 CBER and, as I mentioned already, that it was
16 calibrated against international reference reagents
17 with the proposed direct method and found to be
18 nondistinguishable, at least, this is for the positive
19 reference reagents. So now, the maximum anti-D titer
20 for five percent IGG for lot release is not more than
21 the level in positive reference preparation by a
22 direct method.
23 The next few slides will be the safety
24 standards for in-process control. First is CBER
25 Papovirus B19 DNA standard. Now this standard later

1 on was sequenced and found to be genotype 1 of B19.
2 This standard is to be used, it's used for validating
3 in-process powers B19, not methods, for plasma for
4 further manufacturing as analytical procedures which
5 are viewed and approved under biologic licensing
6 applications called BLAs and all their supplements for
7 plasma derivatives and this is based on the September
8 1999 BPAC recommendation.

9 This B19 standard is to use for screening
10 plasma minipool to exclude B19 DNA positive donation
11 is used as a standard and it's to monitor the level of
12 B19 DNA in manufacturing pools destined for plasma
13 derivatives to ensure that the level does not exceed
14 10^4 IU/mL which is the FDA's proposed limit.

15 Now this standard has a unitage of 10^6 IU
16 or genome equivalent of B19 DNA per mL and it's 1 mL
17 per vial. And it was formulated from a window period
18 plasma unit and diluted with a cryo-poor-anti-B19
19 negative plasma pool and it was provided as one of the
20 candidate preparation for the WHO collaborative study
21 to establish an international standard for B19 DNA.
22 And the results of that collaborative study is shown
23 in this slide and it's freeze-dried preparation by
24 NIBSC and CC is the CBER reference preparation, and
25 since AA was recognized as a WHO First International

1 Standard for B19 DNA in October 2000 and the unitage
2 was assigned as actually it's 5 X 10^5 IU per vial. But
3 when reconstituted, it's 10^6 IU per mL and based on
4 because from the collaborative study AA, BB, CC are
5 indistinguishable statistically. So CC has
6 international units of 10^6 IU/mL.
7 And now because AA soon will be depleted,
8 the proposed Second International Standard will be BB
9 preparation and it will be NIBSC who will soon carry
10 out the collaborative study to make sure that BB can
11 used as a second international standard for B19 NAT.
12 Another in-process control is CBER
13 hepatitis A virus RNA standard. This is used for
14 validating in-process HAV nucleic acid testing method
15 for plasma for further manufacturing and it's for
16 minipools and meant to screen minipools and for
17 manufacturing pools. And these are since -- HAV NAT
18 is considered as -- is validated as an analytical
19 procedure which are reviewed and approved under BLAs
20 or supplements for plasma derivatives. Now this is
21 based on the recommendation of the June 2000 BPAC.
22 The standards contain 6 X 10^3 IU or 10^4
23 genome equivalent of HAV RNA and again it's a 1 mL
24 fill. It was formulated from a window period plasma
25 unit and diluted with with a cryo-poor, anti-HAV

1 negative plasma pool and again this standard was
2 provided as one of the candidate preparation for the
3 WHO collaborative study to establish the international
4 standard for HAV RNA.
5 And the data is shown in this slide.
6 There are quite few preparations, candidate
7 preparations, and EE is the CBER preparation and so
8 forth and then AA that is a freeze-dried preparation
9 was then later on based on the collaborative study it
10 was recognized as the WHO First International Standard
11 that contained 5 X 10^4 IU/mL or 10^5 IU/mL when
12 reconstituted and it was established in the --
13 recognized as the WHO First International Standard in
14 February of 2003. So AA was 10^5 IU/mL. So EE when
15 calibrated against AA it was 3.79 which means 6,000
16 IU/mL. Now again, all these studies are being
17 published for B19 as well as HAV NAT is referred to J.
18 Saldanha's paper in Vox Sanguinis.
19 Now the next few slides will describe the
20 potency and safety standards under development. First
21 is the WHO Second International Standard for anti-HBs
22 immunoglobulin CBER Lot 3 in collaboration with Dr.
23 Morag Ferguson of NIBSC. Dr. Paul Mied already
24 mentioned about this. Now I already mentioned that a
25 candidate five percent HBIG preparation is available

1 and kindly provided by Nabi Biopharmaceuticals.
2 And the second is CBER Reference Immune
3 Globulin Lot 177. Again, a candidate 10 percent IGIB
4 preparation is available and is kindly provided by
5 Baxter Bioscience.
6 The third standard under development is
7 Global Reference Preparations for Anti-A and Anti-B
8 Hemagglutinins to control the levels in immune
9 globulin products and to standardize hemagglutination
10 testing in collaboration with Dr. Susan Thorpe of
11 NIBSC and Dr. Marie-Emmanuelle Behr-Gross of EDQM.
12 Now again, a candidate negative five percent IGIV
13 preparation derived from type AB plasma donation is
14 available kindly provided by Baxter BioScience. And
15 Dr. Susan Thorpe is formulating a candidate positive
16 IGIV preparation.
17 Last one. The Papovirus B19 Genotype
18 Panel containing all three B19 genotypes in
19 collaboration with Dr. Sally Baylis of NIBSC. There
20 is a need to detect all B19 strains which are recently
21 classified into three genotypes because of genetic
22 diversity by B19 NAT and the higher titer window
23 period donation of both genotypes 2 and 3 are
24 available kindly provided by Baxter BioScience and
25 Talecris Biotherapeutics to NIBSC and CBER. Negative

1 plasma donations totaling 20 liters not detectable by
2 all kinds of NAT procedures is kindly provided by NGI
3 and so we will have to formulate a negative plasma
4 pool and then that would be used as a negative member
5 as well and also as a diluent for high viral stocks.
6 The last one that I would like to mention
7 is the WHO Fourth International Standard for Factor IX
8 Concentrate. This is in collaboration with Dr. Elaine
9 Gray of NIBSC.
10 Now the very last slide, this is the
11 conclusion. So DH personnel in CBER/FDA will continue
12 active collaborations and participation in developing
13 biological standards when needed and in testing
14 candidate material in collaboration with WHO
15 collaborative centers, EDQM, and industry to ensure
16 the safety and effectiveness of plasma-derived
17 products and their analogs.
18 Thank you for your attention.
19 CHAIRMAN SIEGAL: Okay. Thank you, Dr.
20 Yu. Are there any questions? If not, anybody? Yes.
21 DR. SZYMANSKI: I'm asking for
22 clarification. Your slide which says "Reference
23 Preparation to Control the Level of Anti-D in Immune
24 Globulin Products" you say you are titering the anti-D
25 by direct method.

1 DR. YU: Yes.

2 DR. SZYMANSKI: What do you mean with

3 that? Do you mean that there is IGM anti-D there?

4 DR. YU: No. This is an IGG anti-D.

5 DR. SZYMANSKI: Okay. So what is the

6 direct method?

7 DR. YU: Yes, it's by preparing treated

8 red blood cells. So you don't really need a second --

9 DR. SZYMANSKI: Thank you.

10 DR. SCHREIBER: I have one naive question.

11 I was noticing in your slides that Lot 176 is 16.5

12 IGG. The standard that you're proposing is 10 percent

13 IGG, and it looks like from the presentation we're

14 going to see later that the most common preparation

15 out there is five percent IGG. How do you decide what

16 the concentration is when you're deciding on your

17 standard, and why wouldn't the standard be more attune

18 to what the most common preparation on the market

19 appears to be?

20 DR. YU: Actually, it's very common. IGIV

21 is prepared as 10 percent IGIV, as a ten percent

22 formulation. In fact, many of the five percent IGIV I

23 know when it was infused that you usually like to

24 reconstitute two ten percent IGIV and then use

25 clinically.

1 Now again, why back in 1991, that's the
2 only product available. It's intramuscular
3 immunoglobulin which is a 16.5 percent IGG
4 concentration and you are right. Nowadays it's five
5 percent or ten percent IGIV. There are more such
6 preparations and we can dilute the ten percent to five
7 percent if needed. But it's ten percent. Actually, I
8 would like to say the assays, when you compare it, you
9 have to assay under the same IGG concentration anyway
10 and it's available, donated by the manufacturer.
11 DR. SCHREIBER: Well, I had just noticed
12 that on your slides some of your standards that you
13 are proposing are five percent, in five percent and
14 some are ten.
15 DR. YU: Yes, you are correct.
16 DR. GOLDING: Can I just -- I think for
17 clarification when the assays are done, they dilute it
18 down to one percent so that the standard and the
19 product are both at one percent. So when the assay is
20 done, they have the same concentration in terms of
21 immunoglobulins. So I think there's a way of taking
22 that into account.
23 DR. YU: Besides 16.5 percent IGG really
24 cannot freeze well. We were surprised that it lasts
25 for so long since the 1991 until now.

1 CHAIRMAN SIEGAL: All right. Well, we
2 should probably move along because we are way over
3 time unfortunately.
4 Dr. Kochman, please, is going to talk
5 about minimum potency standards for certain blood
6 grouping reagents.
7 DR. KOCHMAN: This is just a brief summary
8 to clarify what minimum potency standards are
9 available for some of the blood grouping reagents that
10 CBER regulates. The list that has been available up
11 until very recently includes Anti-A, Anti-B. There
12 are two Anti-Ds listed here. The second one should
13 actually say Anti-CD although it is intended as a
14 standard for Anti-D. Two standards for Anti-C, one
15 for Anti-c, two standards for Anti-E, one for Anti-e,
16 one standard for the Anti-IgG portion of any anti-
17 human globulin reagent and one standard for the Anti-
18 C3d portion of any anti-human globulin reagent and
19 interestingly, you can sort of get a sense for what
20 order these were prepared in by their lot numbers
21 because the lot numbers were pretty much assigned
22 sequentially.
23 These were all manufactured in the early
24 1970s. So they're getting quite old. They are all
25 polyclonal material, and we've always recognized that

1 they were all potentially biohazardous.
2 Why would we want new standards? There
3 has been a lot of question as to whether or not
4 they're actually relevant to current reagents since
5 most of these reagents in particular are available in
6 monoclonal form. We also recognized diminishing
7 stocks both here at FDA and in WHO.
8 The European Union's In Vitro Diagnostics
9 Medical Device Directive No. 98/79/EC was recently
10 implemented, and you may ask if it's European Union
11 directive why should FDA care. There are two reasons
12 we care. One is that many of our licensed
13 manufacturers wish to be able to manufacture a product
14 for distribution in Europe, and they would like to not
15 have to worry about juggling different sets of
16 standards, and we also have a number of foreign
17 manufacturers who are expressing interest in becoming
18 licensed so that they can distribute product here in
19 the United States. So it's best for both worlds if we
20 can come to some sort of agreement on these things.
21 And, lastly, and most unfortunately, some
22 of the CBER standards have been found to be reactive
23 for some of the tests for hepatitis. This isn't
24 totally unexpected because at the time the tests for
25 HCV were implemented, they found that a number of

1 source plasma donors with blood grouping reagent
2 antibodies or even other entities of interest in use
3 for controls in the reagent industry were found to be
4 reactive in some of the tests for HCV. So while we
5 weren't surprised, we weren't real happy about it
6 either.
7 Why did you choose to collaborate? As I
8 mentioned just before, to encourage international
9 harmonization. Maybe more importantly, to elicit
10 input from a larger pool of experts in the area. The
11 collaborating centers included NIBSC, the
12 International Blood Group Reference Laboratory in
13 Bristol, CLB, CBER, and WHO, and this was helpful
14 because it allowed us to replace both the FDA and WHO
15 standards at the same time.
16 For materials and methods, I should
17 preface this by saying a method, a very specific
18 method, was developed, put down on paper, and provided
19 to all centers who chose to participate, and there
20 were standardized worksheets for them to report their
21 instructions on. We recognize that hemagglutination
22 testing is extremely variable. So we wanted to
23 standardize as much of the process as we could.
24 Part of that standardization was to
25 include only potency testing. We didn't want to know

1 specificity or avidity or anything like that. We just
2 wanted to focus on potency testing. This was done
3 with serial two-fold dilution titrations again in a
4 hemagglutination test and most importantly in manual
5 tube tests. We recognize that reagents can be used in
6 various other forms these days, but the manual tube
7 test needed to be the baseline on which we
8 standardized things.
9 The participants were asked to test as
10 many commercial reagents and/or reference standards as
11 were available to them and the result was that there
12 were 45 low protein anti-D reagents in the study.
13 There were only ten high protein anti-D reagents in
14 the study, 22 anti-As and 23 anti-Bs, and we did not
15 ask them to distinguish whether these reagents were
16 monoclonal or polyclonal. We normally were able to
17 figure that out though.
18 The anti-D study was done first. There
19 were 20 laboratories in 13 countries that
20 participated. U.S. licensed manufacturers did
21 participate. Those included the American Red Cross's
22 Diagnostics Manufacturing Division, Gamma Biologicals,
23 Immucor, Medion, Millipore, which was formerly
24 Serologicals, and Ortho Clinical Diagnostics.
25 The anti-A and -B studies were done later.

1 The participants were fewer. We had only 17 in nine
2 countries, perhaps because they found out it was so
3 much work. Again, the same licensed manufacturers
4 participated in these studies. So the good thing is
5 that all of the currently licensed manufacturers at
6 the time of the study were participating in it. As we
7 expected the results were very widespread in
8 variability. Endpoint titer results varied by between
9 four and eight tubes and the endpoint titer across the
10 laboratories for both the standards and the reagents.
11 There were only few outliers, predominantly a few
12 that were extremely low titers and a few that were
13 extremely high titers. So very few datapoints were
14 believed to be incorrect.
15 But because of the extreme variability and
16 the huge number of tests involved, it was an extremely
17 complex analysis of the data that would have been far
18 too complicated to go into here. So if you really,
19 really care, the results of the analyses are published
20 in these two articles in Vox Sanguinis. I believe the
21 Committee received copies of both of these.
22 The conclusions from the studies were that
23 for Anti-D reagents, the Anti-D standard which is now
24 designated as 99/836 for manufacturers who are making
25 a low protein Anti-D reagent, they are to reconstitute

1 the standard because it's provided freeze dried. They
2 are to reconstitute it as described in the insert that
3 comes with it and then prepare a 1:3 dilution. This
4 standard replaces FDA's standard Anti-CD and as I said
5 before, this is actually a standard for Anti-D. It
6 just happens to also contain Anti-C, number 9.
7 For high protein Anti-D reagents, the
8 manufacturers are to again reconstitute it according
9 to the directions provided and then make a 1:8
10 dilution, and this replaces FDA standard Anti-D 4A1.
11 The difference in dilution is not anticipated to be a
12 significant problem. The high protein reagents are
13 rapidly disappearing from the market in favor of the
14 low protein monoclonal antibodies and so in reality,
15 most of the products will be at that higher potency
16 level.
17 The Anti-A standard 03/188 results in a
18 1:8 dilution after reconstitution and this replaces
19 the FDA's Anti-A Standard 6A. The Anti-B Standard
20 03/164 is used at a 1:4 dilution after reconstitution
21 and replaces FDA Anti-B 7A1. I would like to point
22 out that these are minimum potency standards and that
23 is the only thing they're good for. Manufacturers can
24 make their products a little bit stronger,
25 significantly stronger, if they choose to, but they

1 have to balance that increased potency with the other
2 written standards for specificity, avidity, and other
3 characteristics.
4 The reason that we go with a minimum
5 potency standard rather than sort of a what the market
6 would love to see standard is that we want to make
7 sure that reagents are not going to waste or that they
8 aren't so strong that they start causing difficulty in
9 differentiating some of the blood groups from each
10 other as frequently happens with the monoclonals. It
11 was less common with polyclonal antisera that you were
12 confused as to the true status of a donor or patient.
13 But with the monoclonal antibodies, they can be so
14 potent that they appear to be nonspecific or they're
15 picking up extremely small amounts of the opposite
16 antigen.
17 And anyone who wishes to request any of
18 these standards including the new ones, I included the
19 address to send the request, and I wanted to mention
20 also that this address is stated in the CFR. That's
21 it.
22 CHAIRMAN SIEGAL: Any questions from the
23 audience?
24 (No response.)
25 CHAIRMAN SIEGAL: Okay. At this point, we

1 will take a break. Let's take only a ten minute break
2 so we can try to get back on track. Thank you all.
3 (Whereupon, at 10:10 a.m., the above-
4 entitled matter recessed and reconvened at 10:26 a.m.
5 the same day.)
6 CHAIRMAN SIEGAL: Could we please
7 reassemble, ladies and gentlemen? Okay, our first
8 topic for the later morning session is the response of
9 the Office of Blood Research and Review Office Level
10 Site Visit for Research, July 22, 2005. Kathy Carbone
11 will introduce this. Dr. Carbone.
12 DR. CARBONE: Thank you. Today I would
13 like to start with sort of an overview of CBER
14 research, CBER's research mission, and some of the
15 research management initiatives that have been
16 initiated in the past few years as an overview and
17 then I'll turn it over to the Office to respond
18 directly to the site visit comments.
19 But let me start by thanking everyone for
20 their efforts in doing the first, at least, in my
21 history at CBER, the first office level research site
22 visit. The site visit was valuable, provided
23 wonderful information in the report and gave us a lot
24 of good things to respond to.
25 Basically, I'll start with a little

1 introduction about CBER in managing the research to
2 program goals. The important part about the research,
3 it has to cover like many of the regulatory bases we
4 have to cover, it has to cover the gamut. We have to
5 provide and maintain a long-term programmatic,
6 scientific expertise base to be able to respond to the
7 variety of challenges that reach us. But similarly,
8 we have to be prepared to respond to crisis and I
9 should say actually try to be prepared to respond in
10 advance and prepare for the crisis because as you all
11 know, research is the Titanic. You can't turn on a
12 dime. So you have to be very forward thinking and get
13 out of the old crystal ball.
14 Clearly, in our job, the FDA has a clear
15 job to do and, therefore, we are driving research
16 management to continue to be outcomes driven. In
17 other words, there are specific high priority
18 challenges that are holding up product evaluation that
19 are making product prediction of risk and benefit
20 difficult and these are the scientific challenges that
21 have to rise to the top to be resolved.
22 We focus on the critical gaps and
23 scientific tools and knowledge for product evaluation.
24 There's been a tremendous investment in product
25 discovery, biomedical discovery, and unfortunately,

1 the same investment in the ability to develop the
2 evaluation tools and knowledge to regulate those
3 discoveries has not been forthcoming. That's changing
4 with the Critical Path Initiative through the Office
5 of the Commissioner, but we really need to recognize
6 that evaluation science is a special needs science and
7 has been under supported and not given enough
8 attention along with the biomedical discovery boom.
9 So basically, our goal is to support
10 product development for critical unmet public health
11 needs. CBER's products in general, the vaccines, the
12 bloods, the cell tissue gene therapy, all have major
13 public health impacts.
14 CBER research solutions. We've approached
15 this and I think in many ways I'm very proud of the
16 staff at the Center because we've achieved something
17 which given our disease orientation and public health
18 orientation is critical and that is multidisciplinary
19 type research. We use coordinated teams for
20 regulatory challenges. Everybody has a piece of the
21 elephant to grab onto but we all are talking about our
22 piece and keep in communication and must support that
23 and facilitate that in the Center. In addition, the
24 external communication piece is very important and
25 part of this discussion is -- and this discussion is

1 part of that initiative.
2 CBER research quality initiative is
3 important because obviously, the work that's done in
4 the Center needs to be communicated to the outside,
5 evaluated by the outside scientific community,
6 confirmed or refuted in the scientific process because
7 the science that we use to do product evaluation must
8 be the soundest science possible. And, therefore,
9 peer review journals, external arbitrary site visits
10 and this kind of input is critical and we appreciate
11 your time.
12 It's also important to increase CBER
13 research impact by providing more visibility because
14 what we do to help promote and facilitate product
15 evaluation should benefit all products and all classes
16 of products and that's one of the benefits of being a
17 nonconflicted government group but doing research is
18 that what we do can provide benefit for every product
19 and every sponsor.
20 Funding these efforts is always a
21 challenge. It's a challenge for everybody and working
22 with the Office of the Commissioner for Intramural
23 Funding as well as partnerships for leverage funding
24 is a critical part of our goal. And providing core
25 research support, it's not always possible to give a

1 complete and thorough introduction of every scientific
2 issue at CBER, but I do want you to know that, having
3 been an extramural scientist for many years, we do
4 internally at CBER have a very good support system for
5 the staff including animal facilities, core
6 facilities. We have a flow cytometry core. We have
7 proteomics core. So all these and sort of
8 cooperatively across the offices facilitate the
9 research at CBER.
10 The research management initiative, this
11 is one slide in a nutshell and I'm going to walk you
12 through it in a little more detail and that is the
13 first thing to do when you're trying to figure out
14 what to do is you have to figure out what the job is.
15 And so we initiated a regulatory and public health
16 portfolio analysis which is done on a yearly basis and
17 updated and the bottom line is by taking a
18 quantitative look at the applications, for example,
19 that come into the Center as well as the pre IND
20 meetings, we actually get a quantitative view of the
21 scientific base of the issues that are coming to the
22 Center.
23 One can track documents, of course, and
24 they must be tracked through PDUFA, etc. in terms of
25 where they go, which office, whose doing the review,

1 is the review done in a timely fashion. This is a
2 different kind of tracking. This is tracking based on
3 the scientific challenges within those particular
4 applications. In addition as the public health
5 center, if you will, we also must scan the horizon,
6 look outside, deal with the Department and other
7 organizations, CDC and NIH, to get a good feel for the
8 public health issues that are coming down the pike as
9 well as the ones that are here. And that analysis
10 basically gives us the universe of needs which is
11 tremendous obviously.

12 From that universe of needs, we set the
13 specific CBER research priorities. This is a cross-
14 office effort including the Office of Compliance and
15 Biologics Quality which has been very, although they
16 do not actively do research at CBER, they've been very
17 contributory to this process and this research
18 priority setting includes the regulatory scientists,
19 the regulatory scientists leaders, the research
20 regulator scientist and the research regulatory
21 scientist leaders. This is a common effort across
22 CBER.

23 And what this does and I'll show you in a
24 little more detail how we set this, this basically
25 tells us what specifically we're going to be working

1 on because clearly we can't work on the universe.
2 From that, each office then derives its specific plans
3 for the year. They propose that over the year they
4 will be working on these issues and they will be
5 listing their deliverables as well as in this office
6 research plan reporting on their achievements. But the
7 main purpose of the office research plan is to talk
8 about in the coming year what is the research plan for
9 that office. Those are all, again, shared across the
10 Center. It's a combined sort of CBER research plan
11 and then off we go.

12 At the end of the fiscal year after the
13 research has been done, there's a careful scientific
14 program review, both of the individual scientists as
15 well as the offices, and a report is prepared. In
16 fact, we've just completed the individual research
17 program reporting on our web-based system this week.

18 Then this become the effort we are doing
19 right now that at least one year we commit to coming
20 to the advisory committee, talking about the research
21 priorities, talking about some of the achievements,
22 talking about the research plans coming up for the
23 future, and getting the advisory committee and the
24 public input in these plans. We, of course, seek
25 input throughout the year and, in fact, as one of our

1 deliverables we're encouraging staff to provide with
2 every research program or research proposal the
3 communication deliverable that goes along with that.
4 How are they going to communicate the results and get
5 feedback as well as communicate the design and get
6 feedback.
7 So in terms of the portfolio analysis, as
8 I was saying, we talked to the policy leadership about
9 key policy activities. There are prioritization lists
10 of guidances that need to be put out and the
11 scientific dilemmas and challenges that come with
12 those guidances that we can sometimes help resolve
13 through our intramural and collaborative research
14 program, the regulatory workload analysis as I
15 mentioned, what kinds of scientific challenges are
16 coming in and what's coming in in the future with the
17 early as well as current issues and, of course, the
18 public health.
19 The research priorities are a complicated
20 activity done jointly across the Center. But
21 basically, we take into account the regulatory
22 workload which may or may not come with scientific
23 challenges. Sometimes there's an area of large
24 regulatory activity but it's fairly standard, fairly
25 historically accurate, a comfortable level of

1 workload. Then there might be even a small area,
2 relatively speaking, where the challenges are enormous
3 and the science is simply not there to do the
4 regulation which we would like to do it science-lead.
5 We look at product quality issues that are
6 either anticipated to come down the pike or are there.
7 Safety and efficacy issues, the public impact of what
8 needs to be done, the unique expertise we have
9 available to do it. Obviously, we want to be able to
10 set priorities that are achievable with our given
11 resources and given staff and also in seeking out the
12 right collaborators to have and then the impact on
13 product success. Sometimes the high priority research
14 items are not what you would call major impact, new
15 discovery type. They're often sometimes very
16 standard, assays as you've heard, the standards.
17 These are sometimes critical elements that get the
18 products through. So we obviously look for things
19 that will be high impact and things that aren't being
20 done in the outside world.
21 This is just a massive list of the `07
22 research priorities, and keep in mind these are sort
23 of the areas that we think are important to work on.
24 Each office will then take these priorities and then
25 work down and say "And this specifically is what we're

1 going to do within these priorities." And now since
2 this is a blood review, I won't take up a lot of time.
3 You have this in your book. But the Office of Blood
4 will be talking specifically about their priorities in
5 detail in the next talk.
6 So the research plan as I mentioned is
7 misspelled. I apologize. My spell checker missed
8 that. But the research plan is actually a combined
9 plan for all the offices, and as you notice, the
10 leverage research projects which we have several
11 working with NIH and Cell Substrates, etc., are
12 incorporated within this research program plan. It's
13 not done separately. In addition, it's incorporated
14 as a separate element in the research program
15 reporting. So we track that as well.
16 Not to get into too much detail, but we
17 have an administrative process, for example, that
18 before a grant or a partnership is made in the outside
19 world, it has to be circulated and approved for issues
20 of relevance, etc., within the office leadership
21 before the application is even permitted to go outside
22 the Center.
23 Communication piece. Since in the last
24 four years, five years, since I've been the Associate
25 for Research, we've managed to get up on the website,

1 the research program summaries for all our research
2 programs. They include a, if you will, sort of
3 public, plain language summary of the research efforts
4 within that program, the issue of relevance, the
5 public health issue, the outcomes and how research is
6 solving these problems followed by a list of
7 publications for the more scientifically inclined, and
8 through this mechanism we're able when we go out to
9 talk to other agencies and partners and stakeholders
10 and people want to know who to talk to about what
11 issue, we direct them at the website and similarly
12 with collaborations. We direct them at the website.
13 But in addition to the office by office
14 because our researchers are also direct regulators,
15 they have product expertise, they are sorted by
16 administrative lines within the product, we also
17 recognize though that there's scientific expertise
18 across the Center. The greatest example I like to use
19 is retrovirology in blood. It's retroviral
20 contamination of blood. In vaccines, it's HIV
21 vaccines and in cell tissue and gene therapy, it's
22 retroviral vectors. So we have product experts in
23 each of those areas who all happen to be
24 retrovirologists, and to facilitate communication
25 within the Center and in speaking with the regulatory

1 scientists leaders who all were delighted to hear
2 about this to be able to have a resource to go within
3 the Center to find out who your compatriots are, these
4 individual teams are -- currently we call them the
5 Virtual Teams because they're outside the
6 administrative lines. But, in fact, the plan is to
7 bring these people together as teams for communication
8 efforts and appoint team leaders who won't be
9 responsible necessarily for the administration of
10 budget issues, but for bringing the scientists
11 together in critical mass and keeping everybody
12 communicating.
13 So research program evaluation, it's
14 critical when you make changes. When you're doing
15 these sort of management, do a follow-up to see how
16 well you're doing. And we try and do that on several
17 levels. One level is as I mentioned, we have a web-
18 based extensive research program reporting which
19 includes research achievements from the past year.
20 Research achievements include publications, guidances,
21 policies, etc., workshops held. They also list future
22 plans. So they're rated on an individual basis, what
23 somebody achieved and how, what their future plans are
24 for that coming year. We also use this web base to do
25 sort of laboratory management, freezer database,

1 staffing models, etc. So it's quite a utilitarian
2 web-based reporting.
3 But, in addition, at the next level up
4 from the view, maybe the 15,000 foot view, every four
5 years, each laboratory program consisting of several
6 PIs undergoes an external site visit, and this is
7 through the advisory committee and chaired by a member
8 of the advisory committee, actually two members, along
9 with bringing in the expert scientists based on each
10 of the individual lab's expertise, and that report is
11 generated. It's sort of, if you will, a small version
12 of the office site visit, and every staff member gets
13 reviewed every four years.
14 This also feeds into our Promotions,
15 Conversions and Evaluations Committee, internally the
16 peer review which is composed of research
17 regulators/scientists and regulatory scientists who
18 will be doing cyclical reviews. FDA has just
19 established these cyclical reviews every four years of
20 all staff members, so even if a promotion or a
21 conversion issue is not at hand. These are very
22 helpful and, in fact, just like this site visit where
23 we're responding back to the site visit -- the
24 advisory committee, the four year research program
25 laboratory site visits will also be generating a

1 written response back to the advisory committee based
2 on the suggestions given, and from this, every year we
3 formulate as part of the annual program report the
4 successes and future plans for research.
5 The web based reporting is reviewed
6 internally by leadership and by achievements. Let me
7 give you a little more detail, with achievements, a
8 return on research resources expanded, the direct
9 impact of the research on the regulatory challenges,
10 the quality of the research which is critical
11 obviously, the contribution to guidances, policies and
12 workshops. So we're not talking simply counting
13 papers here. We're talking about the whole ball of
14 wax for the regulatory impact.
15 Future research plans. We do short-term,
16 yearly basis. The long-term are proposed in every
17 four year research assessment research site visit, and
18 it's similar sort of criteria.
19 This slide is in your book, and I won't go
20 into this in great detail. But the bottom line is
21 this describes how we do the site visits for each of
22 the laboratories.
23 And then the four year cycle internal
24 review and I was talking about the cyclical
25 assessments. We have formal operating procedures for

1 all of these because when staff come in on day one we
2 want them to know what's expected of them as they come
3 in. So all of this is formalized and done with as
4 much communication. We have a website internally to
5 communicate to the staff.
6 So stakeholder input, that's what we're
7 doing today. This is part of our external input. We
8 ask for input into all levels, all, the entire circle
9 of research management at CBER, and today Blood will
10 be responding to the office site visit that was kindly
11 provided by many of these Committee members.
12 So I just want to quickly review some of
13 the things that were said in site visits which these
14 are a compilation of all the office site visits that
15 we had, all the three major laboratory research
16 offices and the Office of Biostatistics and
17 Epidemiology were planning their first office site
18 visit soon.
19 Basically, we had actually an individual
20 on one of the office site visits who also sat on the
21 1998 CBER Scientific Review, and this was a quote from
22 that individual who felt "there's been a striking
23 improvement since that time and focus in relevance and
24 quality." That was very kind to hear. The site
25 visits as a rule, the Site Visit Committee, strongly

1 supported the FDA's research on -- the emphasis on the
2 importance of research and also gave suggestions for
3 the importance of maintaining support.
4 The strengths and summary from the
5 multiple site visits, productivity, scientific merit,
6 mission relevance. They well recognized the staff for
7 the outreach efforts that they do, the complimentary
8 cross office expertise, success of recruitment and
9 retention, core facilities, and then leveraging and
10 collaboration.
11 However, the concerns were numerous. Some
12 of the concerns were increasing regulatory workload
13 and decreasing support. This may not be in toto. It
14 may mean sometimes in specific areas where the
15 resources decrease and yet the workload is increasing.
16 Best mechanism, trying to understand how
17 to manage research to make sure that we get the end
18 result without it being a process of micro-management.
19 To allowing sort of the creative juices to flow, if
20 you will, but just trying to direct those juices in
21 the right direction.
22 Covering research bases versus focus on
23 quality in fewer areas. As you know, our portfolio is
24 tremendous and yet we can't cover every base. So how
25 to approach that successfully.

1 And then developing an explicit and
2 strategic plan for research with regulatory and
3 stakeholder input and as you can see that we're on the
4 road to doing.
5 The issue of mentoring came up in some of
6 the site visits. One of the research regulatory staff
7 actually initiated through one of our internal
8 research committees, coordinating committees,
9 mentoring efforts that they sort of started. They got
10 a manual together and started to promote this and
11 thanks to our Office of Communications and Training
12 they have picked this up and there's now a formal
13 mentoring program at CBER that's been piloted this
14 last year and next year, there's a plan for expansion.
15 Recruitment and retention. Sometimes we
16 do well and sometimes we haven't done so well and we
17 need to continue to attend to that. They suggested we
18 needed increased research program visibility,
19 continuing education support, making sure the
20 scientists are given the opportunity to stay up-to-
21 date, increased collaboration within and outside the
22 FDA, increased FDA base funding, continuing leveraging
23 support, public relations campaign, and a system for
24 reward for successful research.
25 And I want to thank you very much for your

1 attention and overview and rush through it at the
2 50,000 foot level, and I would be happy to take any
3 questions if there are any.
4 DR. FINNEGAN: You talked about your
5 website. Do you know how many hits you have, and how
6 many of those are unique visitors, and how many of
7 those are people outside of the government?
8 DR. CARBONE: You know, that's an
9 excellent question, and I haven't tracked that. I
10 will ask.
11 DR. FINNEGAN: Because you can very
12 definitely -- there's auditing. So you can very
13 definitely --
14 DR. CARBONE: Yes.
15 DR. FINNEGAN: My reason for asking this
16 is because my bigger question and I don't know how to
17 help you answer it is do you know where you fall into
18 Google. In other words, if I were to Google Chagas
19 disease in transfusion medicine, would you show up in
20 the first 50 or 75 because I'm pretty such most people
21 don't go much past those numbers, and I do know that
22 there's an art to how you put your titles in order to
23 come up first in Google.
24 DR. CARBONE: That's an excellent
25 suggestion. We have a staff member in my office, Tom

1 Madrew, who has done a marvelous job with the web with
2 the support of the Communications group and we will
3 look into that. Jesse would like to say something.
4 DR. GOODMAN: Just to recognize the
5 importance of what you're saying in how we
6 communicate, the FDA as a whole is taking a very -- is
7 devoting some resources now to taking a systematic
8 look at how we make our web-based communications have
9 the maximum impact and we're very -- the Center is
10 very gauged in those efforts.
11 But I think you highlight that we tend to
12 focus in those efforts on our direct public health and
13 product related communication and there's also a lot
14 of other layers including the scientific
15 communication, and we need to be attentive to that.
16 It's one of these areas that when you're resource
17 constrained you tend to have less time and expertise
18 to devote. But it's very, very important, and we're
19 also trying to bring into the center an expert on
20 strategic scientific communication and again, that's
21 mostly focused around our complex risk messages and
22 our interactions with the public sector and the media
23 sector. But I think the point you raise is an
24 opportunity there also. Thank you.
25 DR. FINNEGAN: The two groups I'm sort of

1 interested in are college and senior high school level
2 and also public health people because I think that
3 this is information that would be useful for them, and
4 they actually can be your allies if they can figure
5 out how to get to you.
6 DR. CARBONE: Thank you very much. In
7 fact, I was very appreciative of the Office of
8 Communication that moved the scientific research
9 expertise information from a little nine point
10 sentence in the middle of a paragraph and we moved it
11 to the side in a big bar of the same size there. But
12 I think it's important to see how we're doing and
13 thank you for that suggestion. We will look into
14 that.
15 DR. ELGIN: I had a question regarding the
16 four year cycle for individual, I think, this is
17 individual reviews. I'm just a little old city doc
18 with internal medicine in a small nonprofit
19 organization where we do our reviews biyearly or twice
20 a year and I just want to understand better if you're
21 saying that you only review individuals every four
22 years for promotion.
23 DR. CARBONE: This is external scientific
24 experts. Internal reviews are yearly. So you'll see
25 --

1 DR. ELGIN: Okay.

2 DR. CARBONE: -- under this, the annual
3 internal review occurs yearly by supervisors and by my
4 office. That's the -- the four year cycle is with
5 external scientists. For example, it would be really
6 tough to review Dr. Nakhasi's Chagas program because
7 we don't have any other Chagas Disease experts or
8 Leishmania experts. So we actually go out every four
9 years and bring people in, and a research program as
10 you know may take three or four years to become
11 productive when new directions are taken. So that --
12 In fact, the rest of the Agency went to five years,
13 and I got on my knees and begged and said "I don't
14 want -- any more than four years because our staff
15 trainees, the staff fellows, senior staff fellows,
16 they are on a seven year cycle and this four years
17 gives us right around the middle of their tenure.
18 They get an assessment from the outside world and that
19 gives them time to fix it.

20 So, yes, we do internal evaluations every
21 single year and four years --

22 DR. ELGIN: The next slide I think says
23 four years.

24 DR. CARBONE: This is the promotions and
25 conversion. That's a third level review. So there's

1 the internal yearly, the external every four years and
2 then once the external is done, that goes back to a
3 separate committee which is across the Center. So
4 every year the internal supervisory chain reviews it
5 as well as my office, and then every four years a
6 committee that's composed of regulatory and research
7 scientists from across the Center does a formal
8 assessment. This, if you will, is sort of a
9 counterbalance as the internal supervisory with an
10 external/internal review. So that's really three
11 levels of review.
12 CHAIRMAN SIEGAL: All right. Next we're
13 going to hear from Dr. CD Atreya from FDA.
14 DR. ATREYA: Good morning, everybody. I
15 have a little cough. So bear with me if I have
16 coughing in between.
17 I will briefly comment on the OBRR which
18 is Office of Blood Research and Review response to the
19 BPAC and the recommendations that the Office has
20 received for the research program and the Office site
21 visit actually happened on July 22, 2005 and then the
22 BPAC recommendations came back to us on February 10,
23 2006, and now we are reporting back to you as of a
24 response as August 16th.
25 The OBRR response, what we would like to

1 say is that the CBER and OBRR office management
2 actually thank the Blood Products Advisory Committee
3 for its in-depth review and general support for the
4 OBRR research programs, and the recommendations of the
5 committee have received very closely attention at the
6 FDA resulting in some programmatic changes to
7 establish a structured and a transplant management
8 system for OBRR research and also to improve research
9 focus and prioritization as Kathy was mentioning
10 before.
11 So I'll come to the actual issues raised
12 by the committee right away, and there are like four
13 items, issues. One is the sufficient time and
14 qualified personnel available to perform mission
15 related research with respect to enrollment and the
16 retention aspects of it and then to the support for
17 mission critical research.
18 The concerns are that since the funding is
19 really low are you able to find any alternate funding
20 paths and how are you doing the outside funding and
21 leveraging the resources. Those items came up in that
22 review and also the adequate laboratory space which is
23 a problem for everybody on NIH campus and research
24 prioritization process. What it is is that there
25 seems to be a need for a transplant process because

1 there was a process but it was not transmitted to the
2 public. So I think that was a concern. So we are
3 going to address that. And then there is a need for
4 broad expertise or to have a tightly controlled
5 focused research programs so that the funding will be
6 sufficient for those programs and then, at the end,
7 also as Kathy mentioned, the visibility of the OBRR
8 research programs.
9 Let me take up the first one which is the
10 sufficient time and qualified personnel to perform
11 mission-related research. I assure you that the OBRR
12 is committed to resolving regulatory scientific
13 challenges by providing adequate time for its research
14 and review staff to engage in relevant laboratory work
15 and also to ensure that research and review staff are
16 up to date with current scientific and technological
17 advances by encouraging attendance at scientific
18 meetings and supporting other training opportunities,
19 also conducting periodic workload assessment within
20 the Office to address any imbalances in a timely
21 fashion.
22 And then comes the support for mission
23 critical research, how we are addressing this issue.
24 Within CBER, OBRR provides actually seed moneys
25 wherever possible. There is no guarantees, but always

1 we try hard to get these funds as seed moneys and also
2 the non-FTE that is the -- not -- the soft money post-
3 doctoral positions to support research for the young
4 investigators embarking on new priority research
5 projects.

6 We also try to participate in cross office
7 partnerships for co-research support specialties as
8 Kathy was mentioning like for major equipment
9 purchases, service contracts for flow cytometry,
10 TaqMan or sequencing facilities, etc. and we also
11 evaluate laboratory space needs as a part of an
12 interoffice effort rather than just an office effort.
13 This is a new improvement over the years and also
14 CBER expected to relocate to a White Oak facility
15 somewhere around 2012, and we expect that this move
16 will probably facilitate and provide additional
17 laboratory space for not only just to the OBRR
18 research staff but in general to the CBER research
19 staff. That's one expectation we have.

20 And then how we are doing the support for
21 the mission critical research in the other part is
22 that the Office, OBRR, actively seeks external support
23 like many other offices within the CBER. It's not
24 unique to OBRR, but we have our own set list of how we
25 do that. When appropriate, OBRR leverages out set

1 collaborations and partnerships. The Office
2 participates in developing CBER SOPs and memorandum of
3 understandings, the templates to facilitate management
4 of the application process for external grants, and we
5 took recently a leadership role in bringing George
6 Washington University under Center Scientific Training
7 Program to allow student participation in CBER labs,
8 and this is very successful and so far we have like
9 around six or seven students came up from their MPH
10 programs to do their practicum in CBER labs especially
11 right now in OBRR labs, and that's a trend that
12 actually has some implications. In the future,
13 probably these students can engage in having jobs in
14 FDA because they may be interested. They know that
15 CBER does research, that helps as a PR, and also the
16 successful OBRR collaborations have been established
17 with many other government agencies like NIAID, NHLBI,
18 NCI, DOD and others. So these are the efforts we are
19 doing.
20 And also at the office level, a senior
21 leadership team has been established in OBRR, and this
22 SLT team what it does is it identifies and monitors
23 progress in critical areas of regulation and Critical
24 Path research within the Office. And the SLT also
25 collects input from both research reviewers and full-

1 time regulatory scientists on regulatory science needs
2 and then develops a comprehensive prioritized office's
3 portfolio consistent with CBER's overall plan as Kathy
4 was mentioning about, and then we also do review the
5 applications for external grants both at the division
6 and office levels to ensure that they are within the
7 context of mission relevance.
8 So how are we doing about the visibility
9 of OBRR research programs? We use research to address
10 scientific issues that are critical to regulation. So
11 that means the visibility of OBRR research is
12 important to us to ensure that all the information is
13 publicly available, the science that we do, and
14 external measures of quality and significance are
15 there and to promote these objects what we do is, of
16 course, we do publish in scientific work and peer
17 review journals, present these, our data, at local and
18 national and international meetings, organize
19 scientific workshops as appropriate of regulatory
20 interest, present scientific information to advisory
21 committees as we do now and provide information at
22 major scientific conferences and regulatory meetings
23 and also provide opportunities for our scientific
24 staff to interact with external scientists at seminars
25 within CBER and FDA.

1 Now I'll come to the point of how OBRR is
2 managing the research. What is its research plan?
3 How we identify key scientific needs? The way we do
4 that is that we anticipate actually the regulatory
5 scientific needs that are identified by analyzing
6 recent, like one to two year product application
7 submissions and public health needs and policy
8 portfolio.
9 What we do is that we regularly review
10 workload by product class. We analyze that. We look
11 into all the guidance documents, recent ones that we
12 develop and then we analyze the product failures and
13 safety reports. We also do observations at the
14 inspections. We get information from the inspectors,
15 field inspectors, and then input from scientific
16 workshops and interactions with the regulatory
17 industry, other HHS agencies and international
18 partners like WHO. And then what we do also is that
19 research is targeted to identify the scientific needs
20 where the output could lower regulatory barriers,
21 product development or improve product safety,
22 efficacy and consistency as well as availability.
23 So with that, we have some scientific
24 needs identified over the years, in the last year or
25 so. Those are the list of things here, practical and

1 effective control of an expanding number of known and
2 emerging transfusion/transmission of infectious
3 diseases that request new technology for donor testing
4 and product processing. That means actually these
5 technologies include adaptable platforms for rapid
6 response to EID and bioterrorism agents; novel methods
7 to detect malaria and other parasites as well as TSEs;
8 nanotechnology based donor screens; new pathogen
9 reduction methods for blood components and
10 derivatives.
11 Then we come to the point of efficacy and
12 safety of immune globulin products enhanced by
13 improved characterization for effectiveness that is
14 useful for the treatment of primary immune deficiency
15 disorders as well as for passive immunization against
16 pandemic influenza, anthrax, etc.
17 The second tier of scientific needs that
18 we identified are all improvements in the storage
19 enhancing blood component safety, quality and
20 availability; tests for sterility to improve safety
21 and permit extended shelf life; biomarkers of quality
22 and efficacy to reduce needs for clinical trials;
23 advancements in the development of better predictive
24 preclinical tests of safety and efficacy for blood
25 substitutes such as hemoglobulin-based oxygen

1 carriers; and biochemical characterization of HBOCs
2 linking its structure to the clinical risk outcome as
3 well as better preclinical models to predict HBOC
4 safety and efficacy.
5 And the third slide that shows these, the
6 pharmacogenomic and proteomic studies to improve safe
7 use of blood products. Under that, genetic
8 determinants to predict risk for development of
9 clotting factor inhibitors comes under that category
10 and genomic based blood grouping and typing to improve
11 blood compatibility determinations. And then lastly,
12 the radio-frequency ID technology for blood product
13 labeling and tracking which is a promising approach to
14 reduce errors in blood transfusion management. So
15 these are the key issues we found out.
16 So out of that, how do we deal with that
17 and as a plan we cannot do everything on that as Kathy
18 was mentioning. So what we do is based on the
19 identified scientific needs and available resources
20 and expertise within the office and the feasibility of
21 success and public health significance of the expected
22 outcomes as well as the expertise of the Office that
23 we have.
24 What we have done so far is we've
25 identified using all these criteria around six high

1 priority areas for the current research program. They
2 are -- number one, a priority. They are not
3 prioritized as they are listed, but all the six
4 programs are all important.
5 Number one is the novel methods of
6 pathogen reduction and inactivation in blood and blood
7 products. What we expect out of this research is that
8 as a development impact probably more rapid assessment
9 of candidate commercial methods can be happening with
10 this knowledge and then open new avenues to achieve
11 safe and effective pathogen reduction for cellular
12 blood components and we also probably expect that this
13 research area will provide insight into the mechanism
14 of cellular damage by pathogen reduction methods.
15 The second one is multiplex platforms and
16 high sensitivity methods for pathogen detection
17 including genetic variant and imaging infectious
18 diseases and bioterrorism agents. What we expect out
19 of this is that as usual the more rapid assessment of
20 the candidate commercial methods, but also it could
21 probably provide insight into the practical
22 limitations associated with the new technologies.
23 Then the third priority area is to develop
24 infectious agent panels for assay standardization and
25 standards and reagents for product lot release testing

1 which you already heard a couple of talks on that
2 before and what we expect out of that is that probably
3 strategy preparations through development of lot
4 release panels for new infectious agents will be
5 available and replenishment or replacement of existing
6 control panels is a possibility and also international
7 standards for hematological products to ensure product
8 potency.

9 And the fourth one is the development and
10 evaluation of proteomics and genomics based biomarkers
11 for efficacy, quality, toxicity and consistency of
12 blood components, blood-derived products and their
13 analogs including blood substitutes. Out of this what
14 we expect as a regulatory impact is provide probably
15 surrogate biomarkers for product efficacy and safety
16 for more efficient clinical trials.

17 Priority area five, development of
18 predictive models for preclinical evaluation of blood
19 components, blood derivatives and their analogs
20 including blood substitutes and to study pathogenesis
21 of blood-borne EID agents. The regulatory impact that
22 is expected out of this is an appropriate animal model
23 to improve HBOC safety and the in vitro infectivity
24 studies of blood components that could support changes
25 to current policies on donor deferral and reentry.

1 So the area, the last one, is development
2 of methods to evaluate efficacy of immune globulins of
3 pandemic and BT importance. The expected outcomes for
4 the regulatory impact are to provide a scientific
5 basis for dose labeling of immune globulin products to
6 prevent known and emerging infectious diseases and
7 establish protective levels of specific antibodies in
8 immune globulins to treat immune deficient patients.
9 So in conclusion, what I can say is that
10 OBRR and CBER have carefully considered all of the
11 recommendations of the BPAC review of OBRR research.
12 In particular, program changes have been made in
13 response to the major recommendation of the BPAC for
14 more structured and transparent management of
15 research. OBRR and CBER have developed and are
16 implementing a managed research program as you heard
17 from Kathy based on prospective evaluation of
18 regulatory science needs, our available resources and
19 the expected impact of the research.
20 So therefore, we look forward to ongoing
21 and frequent discussions with the managed research
22 program to assist OBRR and prioritize, focus and
23 streamline our research to best address the scientific
24 needs of the day. Thank you.
25 CHAIRMAN SIEGAL: Thank you very much.

1 Are there any questions?

2 DR. DI BISCEGLIE: I had a couple

3 questions at this time. The one was I was pleased to

4 hear about the commitment of the Office to provide

5 protected time for research for staff. I wanted to

6 ask a little bit about how that is done. How much

7 research, how much time is protected for a particular

8 person? How is that measured? How is that assessed?

9 How is that enforced? In other words, how real is

10 it?

11 DR. ATREYA: I mean, there is some reality

12 to it, but do you want to comment on that or you don't

13 want to comment on that?

14 DR. NAKHASI: That's a very excellent

15 question because I think what we do is at least in the

16 divisions we look at the portfolio of a particular

17 researcher, PI, and based on the workload of

18 regulatory workload. Because in the past, if it was

19 not looked at, one person would be overwhelmed with so

20 many regulatory applications and time goes down for

21 research. So now we have definite parameters where we

22 protect, at least let's say, if it is a first time, an

23 initial person. When the new investigator comes into

24 the division, we protect at least 70 percent of his

25 time or her time to research. As the time goes on, as

1 the experience goes on, it can increase to 50 or 60
2 percent of the regulatory work and 40 to 50 percent
3 research work. It again depends. It varies.
4 Sometimes in the month, in a year, a
5 person is busy with -- for example, last year there
6 was a Chagas application for -- we approved the Chagas
7 test. A person who was involved in it had a 70
8 percent of time in the regulatory. But the demand of
9 the application, now his time has been brought into
10 the research area where he can focus on the research.
11 So it has to be an adjustment but made by the
12 managers, but at the same time, looking that you have
13 a protected time.
14 And Jay reminded me that we have an RRS
15 system that is the time reporting system, how much we
16 spend on the regulatory as well as on the research and
17 so that gives an idea.
18 DR. DI BISCEGLIE: But is this coordinated
19 across the laboratory level, the division level or the
20 office level? At what levels is this sort of
21 scrutinized and coordinated?
22 DR. NAKHASI: The RRS is at the Center
23 level and so it looked at the Center level because
24 every three months it is done.
25 DR. GOODMAN: You know, I just want to add

1 one comment. We do have -- we do think, and this is
2 from the commissioner to me and everybody, we want to
3 have a strong scientific infrastructure. We feel that
4 in our area of products that's particularly important.
5 We think our decisions should be both science based
6 and science led.
7 That said though, we're an agency that has
8 a pretty vast portfolio work under constrained
9 resources and I just want to say that whenever a
10 public health problem or a review issue that pertains
11 to a product's quality or safety or availability comes
12 along we all, whether we're the Center director or a
13 junior researcher, we have to have the right people
14 flexible enough to move to be able to do that. So an
15 important long-term challenge for the FDA is to
16 attract scientists who can work in that kind of way
17 and many of us who are in academic medicine are -- I
18 know there are people who can work in that kind of
19 way, but that's exceptional. And also people who are
20 interested in these unique opportunities who look on
21 the importance of developing a new assay, let's say,
22 to replace antiquated assays for influenza vaccines as
23 a major public health contribution but sort of can
24 approach these things flexibly and move to new
25 problems.

1 But I did want to emphasize that often
2 every day we make tough calls about what we're going
3 to devote our time and energy to and it's very
4 important I think as we recruit and develop people,
5 both laboratory people and other people, that they
6 understand the environment that they're working in and
7 that to the extent we can though we pay attention to
8 their personal development as well. So it's a tricky
9 balance and it's made especially challenging in a
10 resource constrained environment.
11 The other way we try to build and develop
12 people is through these collaborations with colleagues
13 at NIH, academia, etc., and one of the things we've
14 done, for example, in starting to evaluate research
15 projects and I think I heard Kathy say this is to
16 explicitly say do we have the right collaborators, do
17 we have the right communication plan and that's not
18 just communicating results but getting input about
19 what we do and that's part of being here. So I think
20 for an extraordinary small amount of resources and for
21 people who are often busy with a number of other
22 things we can be proud of some of the impacts that
23 people have had on public health and I think when you
24 hear, you know, just hearing the list of active
25 standards development and these are things that

1 somebody else just, they're not going to get done if
2 we don't participate and they improve patient safety
3 and they improve industry's ability to get these
4 products which often don't have huge financial
5 incentives out there. Thanks.
6 DR. CARBONE: There's one more level I'd
7 like to mention and that is proactive rather than
8 reactive, you know, having a staff member and trying
9 to protect their time and that is that the analysis of
10 the regulatory workload actually gives us a prediction
11 of where the workload is going and using that
12 mechanism you can then balance staffing models.
13 For example, in another office, they
14 identified a hugely increased workload in two areas
15 that they don't have anybody working in. So to avoid
16 having to sort of task everybody or overtask, they
17 then look at those areas and say, "Well, when
18 resources become available, those are the areas we're
19 going to staff up." So this sort of proactive way of
20 the analysis of the workload gives us the opportunity
21 on a big picture to staff areas that need more, the
22 time for research or staff areas that are bigger
23 regulatory demands so that the staff members aren't so
24 overwhelmed individually. So there is also that
25 planning level too.

1 DR. SCHREIBER: We did the site visit a
2 little over two years ago now and I was just wondering
3 if there's been any change in the ability to recruit
4 and the retention of staff because that was a major
5 consideration or discussion and even Dr. Goodman
6 mentioned it again in his point. So I just wondered
7 if in the two years you've had any differences or seen
8 any changes.
9 DR. EPSTEIN: Well, there are always
10 changes because we live in a dynamic environment.
11 We're always in the process of recruiting and hiring
12 people and also we always lose people to attrition. I
13 would have to tell you that the last year was a
14 difficult year because we had a difficult situation
15 with funding and we did have a temporary freeze on
16 hiring and we did continue to attrit staff during that
17 period and that for the last several months we've been
18 rebuilding.
19 So I think the honest answer is that we
20 have some critical unfilled positions and that we're
21 working very aggressively to fill them. I think that
22 the positive side of the equation is that we do get
23 applicants and our programs are seen as a good place
24 to come work. So I would say right now the situation
25 is that we're in transition. Some of the groups did

1 suffer significant losses of persons who had been at
2 the FDA a long time, were holding major
3 responsibilities, were very active at the bench and so
4 forth and we have had to do a little bit of
5 restructuring and some aggressive recruitment.
6 DR. GOODMAN: I could just comment again a
7 little from the Center and the Agency point of view.
8 I think I agree with what Jay said. The Federal
9 budget process is complex, but I think the good news
10 is I think some of the potential opportunities to
11 strengthen the Agency, etc., are being recognized and
12 we're hopefully entering into a period of more budget
13 stability.
14 I would say that there have been some very
15 fine recruitments within CBER of scientists, of new
16 people. So I think it can be done and I think making
17 the process for how we will manage the research
18 transparent to people who come in can help in that and
19 also showing as we have what are some of the unique
20 opportunities.
21 But it's a continuing challenge. I mean
22 it's very -- as everybody who has worked closely with
23 us knows it's a very challenging situation. I was in
24 academia for a long time and I can say that the five
25 or six major issues I deal with every day at FDA are

1 more complex and more challenging and that's another
2 reason why we really want the best people and to make
3 it a good place for those people to be.
4 So one thing I would mention, for example,
5 we're about to be doing very high level recruitment
6 and this is relevant to your question for a new office
7 director for the Office of Biostatistics and
8 Epidemiology and we see that as a very important
9 scientific not just service that does our safety
10 activities and our statistical activities, but a
11 research and scientific area of incredible importance
12 to the Center. I'm saying that publicly and to you
13 because we welcome and we really try to go outside,
14 both develop our people inside, but also bring outside
15 people in and we welcome the committee supporting us
16 to do that. Thank you.
17 DR. EPSTEIN: I just want to add another
18 dimension to this discussion from your question and
19 Dr. Di Bisceglie's question. We have had a change
20 which was noted both by Drs. Carbone and Atreya which
21 is the ability to seek outside funding support through
22 grants. We can't compete for R01s. It was noted that
23 there's been an assessment that we're at the same
24 standard of people compete for R01s. We can
25 collaborate with holders of R01s. We can compete for

1 interagency grants and we can apply for foundation
2 grants. We can also collaborate under cooperative
3 research and development agreements with industry,
4 although the persons who are in those collaborations
5 cannot also be the reviewers of products from that
6 industry. Obviously, we have to be careful of that
7 issue.
8 But the fact that we're able to bring in
9 outside grants does mean that we have another
10 mechanism to support the laboratory program and I can
11 tell you that where we're most short even though we're
12 constrained in terms of number of people, full-time
13 equivalents, that we can support with tax dollars, we
14 have a worst situation with operating dollars because
15 the operating dollars per capita for a principal
16 investigator are nowhere near the standards that major
17 research institutions whether they be government, NIH
18 or academic. But the ability to bring in ability to
19 bring in grant funding we have somewhat improved the
20 situation and that does have an effect both in terms
21 of protecting the research because you can fund
22 support persons. In other words, you can fund
23 contract hires and of course, you can leverage effort
24 through collaborations and at the same time it has an
25 effect in improving retention because our scientists

1 are able to remain more productive. So they're
2 happier staying within the organization rather than
3 feeling, "I can't do the work I'm interested in unless
4 I move on." So I think that that becomes a very
5 important matter.
6 There's a flip side to it, of course,
7 which is when people apply for and obtain grants.
8 They are also making commitments to the work under the
9 grant. So within this program of management of
10 research, we have to pay a lot of attention to what
11 people are allowed to apply for because we have to
12 ensure that looking over a multi-year time horizon
13 which is, of course, typical for grant funding that
14 the work is highly mission relevant and it does meet
15 our sense of on-going priorities, future-looking for
16 product development. So I think that again grant
17 funding is another mechanism by which we are both
18 protecting the program and also keeping people in the
19 organization.
20 DR. KATZ: I'm going to change focus a
21 little bit with this question, but certainly in our
22 community, in the voluntary blood community,
23 biovigilance is the latest jargon and while FDA may
24 find it difficult to actually do research in
25 biovigilance, there's going to be a body of data

1 developed over the next three to five or eight years
2 that's going to have regulatory implications and I
3 don't see in the research program anything that
4 explicitly begins to prepare the Agency for dealing
5 with the kind of data that we're going to see.
6 DR. EPSTEIN: Okay. Well, let me just
7 give a brief answer and then if Dr. Goodman wants to
8 comment. But we're actually very heavily invested in
9 the whole issue of safety. We're very mindful of the
10 Institute of Medicine report on safety in medicine.
11 We're very mindful of Congressional initiatives and in
12 fact, there is legislation pending which will put a
13 great emphasis on safety reporting.
14 Within CBER, the lead entity is Office of
15 Biostatistics and Epidemiology which is very involved
16 with the whole issue of databases, use of data mining
17 tools and strategies for monitoring safety. We also
18 have increased the focus on Phase IV monitoring of
19 products post approval. We have safety teams that Dr.
20 Goodman has requested be created across CBER and we do
21 have a safety team for blood. We do have a safety
22 team for tissues and we do participate very
23 principally in the interagency activities. The PHS
24 has established a task force on biovigilance. I know
25 you're aware of that and FDA and in particular, the

1 staff in my office are leading participants in that
2 cross-agency initiative and within the blood safety
3 team, the leads are cooperatively with Biostatistics
4 and Epidemiology and with my Office of Blood Research
5 and Review.

6 So there's a lot of activity in that
7 domain and I would say in terms of the research focus
8 at our level it's principally about the databases.
9 It's about how to orchestrate data so that we can
10 extract useful information, report it back out
11 publicly. We've built bridges, for example, with CMS
12 where there's a tremendous amount of hospital data
13 which was not historically available to the FDA and
14 we're also, of course, interested in building bridges
15 with the initiative of AABB and other components of
16 the private sector.

17 So we are very active in that area, but
18 within the research program, I would say the lead is
19 in the Office of Biostatistics and Epidemiology. But
20 we're certainly big time players. Did you want to
21 add? Do you think I covered the base? Yes. Okay.

22 CHAIRMAN SIEGAL: Okay. Any other
23 comments? Mark, I'm sorry.

24 DR. BALLOW: I was on a site visit not too
25 long ago. Maybe it was in the spring if I remember

1 right and one of the issues came up about the White
2 Oak site or location and whether that's going to have
3 all the core laboratory facilities, particularly
4 animal.
5 Whether the White Oak facility is going to
6 have all the core facilities including animal
7 facilities and of course, it takes them away from the
8 NIH campus where a lot of collaborations take place
9 and the travel distance between the new facility and
10 NIH is a potential barrier particularly with the
11 traffic in Washington. Of course, that may translate
12 into recruitment because one of the nice things about
13 your location now is such a huge research campus. I
14 mean it's like it's the most desirable thing that I
15 could think of anyone engaged in basic research would
16 like to see is to be surrounded by other top notch
17 researchers and be able to interact and collaborate
18 with them.
19 So I don't know. How are you going to
20 address some of the barriers or some of the concerns
21 of moving your facility outside the NIH campus?
22 DR. CARBONE: I'll take that on because
23 I'm part of the, well, lead for the White Oak
24 Subcommittee for Laboratories within CBER and also
25 part of the OC's effort. Just sort of as background,

1 White Oak is located sort of northeast of the D.C.
2 area just outside the Beltway and currently CDRH and
3 much of CDER is located there and the plans are to
4 move everybody but Foods to that campus and there are
5 a couple of issues.
6 I mean the one issue about leaving the NIH
7 community is what it is. But the bottom line is we
8 actually will be joining up for the first time with
9 our FDA colleagues which is a wonderful scientific
10 base that we have not had previously. For example,
11 the CDRH group developed a wonderful new engineering
12 building that's just state-of-the-art and has
13 facilities there that don't exist elsewhere. We are
14 given the opportunity for building our research
15 buildings and the animal facilities will be ditto. We
16 currently do not have primate facilities. Right now,
17 for example, we don't have BSL-3 small animal
18 facilities. We've had to work them into our BSL-3
19 laboratories which is less than ideal conditions. So
20 the new animal facilities actually have been designed
21 with CBER input, with CBER numbers and we'll be
22 addressing things like putting in BSL-3 small animal
23 facilities which we currently don't have.
24 The campus is actually quite nice and the
25 opportunities to design buildings, the Building 29

1 currently is an ancient building and is actually very
2 difficult to do research in. We had a pipe burst and
3 it flooded our 200 freezers and put them all at risk
4 in 29A and in 29B we had to decommission a BSL-3
5 laboratory because the ventilation was not up to the
6 new standards. We had to build new laboratories on
7 the top floor because of ventilation issues. So the
8 opportunity to actually construct novel facilities is
9 really tremendous, the ones we can design for
10 ourselves.
11 The issues such as adjoining with NIH have
12 been discussed. We've been talking with the Agency,
13 for example, on our access to NIH library system and
14 they are currently in discussions with NIH to try and
15 see to actually maintain that.
16 The other options we've discussed are
17 shuttle buses to the NIH campus to give staff an
18 opportunity to come down for seminars, etc., and for
19 example, I for most of my academic career collaborated
20 extensively at Hopkins with staff at the University of
21 Maryland that we weren't physically co-localized with.
22 So we will do everything we can. In fact,
23 we've already surveyed the staff to say tell us
24 exactly what you will be losing when you leave the NIH
25 campus and about two-thirds of their concerns are

1 actually covered, things like who will take care of
2 radiation, who will do safety and other things that we
3 can address directly with White Oak.
4 And the remainder, such as travel. We're
5 looking at innovative ways to address it. We actually
6 established tours with the help of the Office of
7 Management to get our CBER staff over to tour the
8 facilities because a lot of people were expressing
9 concerns without ever having visited the site and
10 about an 80 percent response rate of people who
11 visited was actually tremendously positive when they
12 saw the opportunities at that site.
13 The rest in terms of distancing from our
14 NIH colleagues, we will be doing our best to address
15 and resolve those. But the opportunities for joining
16 at White Oak are actually many.
17 DR. GOODMAN: We actually just had a
18 meeting of our leadership within the Center yesterday
19 to discuss this and learn from some of the experience
20 of some of the people who are already there. These
21 are real concerns that you've identified, I think.
22 One thing I would say is I think that what
23 we're trying to do since this is a planning decision
24 that's been made is say what is our vision of how we
25 want our science to be and how do we maximally enable

1 that. For example, we have the opportunity to think
2 about how does the architecture of our offices and
3 laboratories, how can that instead of be an impediment
4 to how we work, fit with how we work and fit with the
5 mission. So there are various models we're going to
6 consider internally and with the architect of bringing
7 laboratory, sort of like many people have gone through
8 in academia with translational research. You know,
9 how do you bring the Ph.D. scientists together with
10 the M.D. scientists and in our case, how do you bring
11 the people who are full-time reviewers together with
12 the scientists. So actually, there are a lot of
13 opportunities.
14 I think a critical, critical thing is
15 going to be we do have many life science relationships
16 and projects that are leveraged with NIH and many
17 personal relationships and also as you said that is an
18 attractive thing in recruiting, etc. And I think we
19 want to look at those and try to be sure we can
20 continue to support those or build other
21 opportunities. I think it's going to make on-going,
22 explicit support for science at FDA very, very
23 important and we're starting to see recognition by the
24 outside and Congress and industry that there should be
25 support for science at FDA because of its value and I

1 think there's going to be this need for our scientists
2 and again, I don't view this as just the laboratory
3 science. I think this is everyone to feel that there
4 is support for building knowledge, improving
5 knowledge, etc. What we're trying to do overall with
6 the research program should strengthen that.
7 I'm not sure exactly how it will play out,
8 but in legislation that Congress is considering, for
9 example, there's a provision for some kind of
10 potential foundation that can support certain
11 scientific activities and things like that again may
12 enhance our abilities. But I know many, many people
13 are concerned about this.
14 The other thing I wanted to mention, I
15 think you guys may have heard this before, but there's
16 a review of science at FDA in toto, the whole Agency,
17 that's being done by a group called The Science Board.
18 It's -- I can't remember the whole board, but it has
19 been chaired this visit at least, the board I think is
20 chaired by Ken Shine who is the former president of
21 the Institute of Medicine and many of us know Ken and
22 then this Review of Research which is on-going is
23 being chaired by, I think, him and Gail Cassell who is
24 the Vice President of Eli Lilly and a former president
25 of the American Society for Microbiology. So they're

1 looking at for FDA to be a 21st century effective
2 science-led organization, what is needed, and I think
3 that report hopefully will help articulate the future
4 going forward. So we've been an active participant in
5 that.
6 And as much as this is a challenge for
7 CBER, there's much of the scientific tradition at CBER
8 and the interactions with NIH that has really helped
9 support us and keep us going and some of the other
10 centers have had even more challenges than we've had.
11 Thanks a lot.
12 MR. ALLEN: Mr. Chairman, I beg your
13 indulgence. We seem to have sort of gotten in the
14 open committee discussion here. So let me just make a
15 couple of comments as the chair of the Review
16 Committee.
17 Dr. Goodman, Dr. Carbone, Dr. Epstein, Dr.
18 Nakshi and Dr. Golding, I would very much like to
19 thank you and your staff for your response to the
20 report. I think it goes far beyond what I had hoped
21 might come out of this and I feel very gratified that
22 we've been able to be part of a process. I'm
23 extremely impressed that this has been responded to
24 not only by OBRR but by the entire CBER structure.
25 I like the Research Management Initiative

1 concept that has been put forward. I like the
2 Research Leadership Council, the Senior Leadership
3 Team and the development of priority research areas as
4 well as the rest of the responses. I think this
5 clearly -- the report that the Committee put forward
6 was looked at very, very carefully and appropriate
7 responses have been developed. They are in the
8 process of being implemented. I don't at all get the
9 sense that this was a one time, it's done, we don't
10 have to respond to it anymore. This is an on-going
11 process and I'm very encouraged between the 1998 CBER
12 report and our 2005-2006 OBRR report clearly there was
13 an improvement in the quality and the focus of the
14 research. I'm encouraged that this is going to
15 continue despite one of our major concerns which was
16 the paucity of resources and I hope that this issue
17 will continue to be addressed. I think it is from
18 what Dr. Goodman has said, because clearly it's
19 important to have the appropriate resources, both
20 financial, personnel and the facilities and the
21 equipment issues are being addressed also.
22 So I want to thank the Office for their
23 response and to the entire CBER staff for the way in
24 which they've responded to this report instead of just
25 putting it up on a shelf somewhere to gather dust. I

1 think it's been useful.

2 CHAIRMAN SIEGAL: Thank you for your

3 comments, Dr. Allen. We now ostensibly have an open

4 public hearing, but I understand that no one has

5 signed up to speak. Is there anyone from the audience

6 or anyone who wishes to contribute at this time?

7 (No response.)

8 CHAIRMAN SIEGAL: And that point we can

9 dispense with the conflict of interest statements.

10 Then we might as well open our committee discussion at

11 this point unless people want to take a break. Let's

12 proceed. Is there any further open committee

13 discussion?

14 DR. FINNEGAN: Mr. Chairman, you're

15 allowing me one rude question per topic. Right?

16 (Laughter.)

17 DR. FINNEGAN: My question has to do with

18 considering managing your regulatory loads the same

19 way you are managing your research protocols. As we

20 were sitting here this morning and I will tell you in

21 advance I have no expertise in potency and standards

22 and after this morning's presentation, that's just

23 fine.

24 But it struck me that a whole bunch of

25 things came due at the same time and perhaps if this

1 was managed and there was a rolling sunset or a
2 rolling review of these things that perhaps this would
3 help with getting more resources to your research.
4 DR. EPSTEIN: Well, I can perhaps shed a
5 little bit of light on that which is that there's an
6 annual review that goes on with standards. In other
7 words, CBER is a WHO collaborating center for
8 biologics and one of the standing components of the
9 WHO is an expert panel on biological standardization
10 and annually there is a meeting convened, generally in
11 October, of what's called an expert committee for
12 biological standardization.
13 And so what goes on is that at that
14 meeting proposals for these reagent standards are
15 reviewed, work plans are established, collaborating
16 centers volunteer their agreement to help develop the
17 standard and then over the course of the year the work
18 goes on generally with additional collaboration from
19 multiple expert laboratories.
20 So when you say that there seems to be
21 convergence of deadlines, what it reflects is the fact
22 that there is an annual cycle for establishing the
23 work. Every year, there's a deadline of one sort or
24 another. Either the deadline is for submitting the
25 proposal or the deadline is for review of the data or

1 the deadline is for determination of the potency of
2 the standard, etc., etc. It's an ongoing effort.
3 With respect to renewal of the reagents
4 themselves, there's a certain level of happenstance
5 here because for example, as you saw with the blood
6 grouping reagents, many of them were established in
7 the 1970s. They're only now running out. But it's
8 not that that hasn't been recognized. In other words,
9 there's been a planning process for several years how
10 one would go about renewing those particular reagents.
11 The bottom line here is that the same
12 could be said every year. Every year something needs
13 renewal. Every year there's some deadline for a new
14 initiative. It's an annual process.
15 DR. FINNEGAN: What struck me this morning
16 is that blood transfusions from 1950 to 2000 has gone
17 from being a rapidly changing learning to sort of a
18 maturing process and it would seem to me that a
19 standard that was set in 1958 or a standard that was
20 set in 1970 probably -- I mean, I would assume that
21 every group has the same resource problem and the same
22 we would rather be doing other things type of process
23 and so it's inertia of the entire group that's letting
24 it go this long rather than someone saying "Look.
25 This is now 15 years old. Maybe as a group we need to

1 say for this particular problem it needs to be moved
2 up the scale." Does that make sense to you?
3 DR. EPSTEIN: Well, I'm not sure I follow
4 the argument fully. What goes on is a constant
5 reexamination whether the available reagent still
6 works. So for example, we participate with a
7 collaborative study that's organized by the Council of
8 Europe. Every year, there is a review of serological
9 reagents for blood grouping and typing.
10 The question is whether the current
11 international reference material or international
12 standard is still operating the way we want it to and
13 as long as it is, it's fine. And it's only as new
14 needs get recognized do we generate new types of
15 reagent and I think what you heard today is that right
16 now there's quite a lot of activity in new types of
17 reagents.
18 For example, we have moved from an era
19 solely of serological reagents to an era of antigenic
20 reagents and now to an era of genomic reagents and now
21 we're looking at genomic subtypes and of course, we
22 also have to keep up with the evolving evolution of
23 agents, for example, HIV and all of the substrate of
24 subtypes, yes, HCV, etc. and you heard it also for
25 Papovirus B19.

1 But when you say if you have the same
2 reagents in place for, say, Anti-A or Anti-B, why
3 aren't we modernizing? The answer is we are. The
4 answer is that standards for monoclonal reagents are
5 being developed. But it hasn't made the polyclonal
6 reagents obsolete and as long as they're not obsolete,
7 they're doing what they say they're supposed to do and
8 they haven't lost their potency and they're still
9 available. Well, you don't need to do anything about
10 it except ask every year if they're still good.
11 I just think that the situation is dynamic
12 even though some reagents stay on the scene for a long
13 time, especially polyclonal reagents. I mean they do
14 tend to be valuable for a very long time precisely
15 because of that nature and for many things, you know,
16 the changing in biology isn't so quick anyway. Look
17 at human blood groups. They're not evolving the way
18 the viruses are evolving but we do have new reagents
19 to deal with new technologies to be sure.
20 Is that helpful because again I'm not sure
21 I precisely understood your question?
22 DR. FINNEGAN: I think my question was
23 less about the blood typing. I agree with you
24 completely on that. I think I was more perplexed as
25 to why there was depletion of so many standards at the

1 same time and some of those standards have been around
2 for a long time.
3 DR. EPSTEIN: Again, some of it has to do
4 with when they were made and some of it also has to do
5 with the fact that as more manufacturers may enter a
6 field there is an acceleration in just the utilization
7 of reagents. But I'm not sure that I have any greater
8 insight than that. You know, we tend to target
9 something like a seven to ten year life span for one
10 of these international standards and so there's a
11 certain amount of guesstimate that goes on about the
12 rate of use and sometimes the guess was right and
13 sometimes the guess was wrong.
14 But to the extent that when a field kind
15 of emerges -- let's look at it this way. Right now,
16 we're generating a whole class of RNA and DNA reagents
17 and it's happening over a relatively short span of
18 years. You know, over a two to three year span of
19 years you're going to have HIV, HCV, HBV, B19 genomic
20 reagents. Well, one could say that won't they all get
21 exhausted, for argument sake, five years from now and
22 it will be because there is a cohort effect. In other
23 words, the science has matured to the point where we
24 recognize the need for the reagents and we're making
25 them, but that's all kind of happening in a cluster.

1 Now I can't tell you that a B19 reagent
2 will be exhausted more quickly or more slowly than an
3 HIV reagent. But to the extent that they all mature
4 at the same time, that the fields do, we may see
5 another cohort effect a few years hence.
6 DR. FINNEGAN: Why could you not monitor
7 the use of the reagents and figure out what's going to
8 be depleted?
9 DR. EPSTEIN: We do. Again, that's part
10 of the annual review at the WHO is how quickly are
11 they being exhausted, how much is left, are they still
12 stable, are they still the reagent that you want, are
13 they fit for purpose. So we do that.
14 DR. GOODMAN: One -- I was at the
15 committee meeting last year at WHO about this and
16 there was a similar portfolio of things that each year
17 people are taking on or identifying. But what I would
18 say is this is another area. It's not sexy. It's not
19 finding the gene for disease X and it's not
20 necessarily -- there's not necessarily funding
21 dedicated to it. So at the WHO level, at our level,
22 there are only a few places in the world that do this
23 stuff. The Paul-Ehrlich-Institut is another one which
24 is a counterpart of ours in Germany, the National
25 Institute of Biologic Standards in Great Britain. But

1 among that group, that said, there is not the
2 possibility of taking on every standard preparation or
3 assay improvement effort that could be done. So by
4 necessity, people are looking at what are the
5 priorities, what are the most critical needs.
6 One of the things we've tried to do with
7 this research management and with the whole FDA
8 critical path initiative is identify that this is an
9 area of science that needs attention and everybody
10 benefits from that. Patients benefit on the quality
11 and safety end. Industry benefits on the quality and
12 availability end.
13 So I think in a way it's good we're having
14 this discussion. It's good that we do this work. But
15 it's not something the world has paid the same
16 attention to as, let's say, standards for
17 semiconductors or something where there's a huge
18 economic drive for it.
19 DR. EPSTEIN: I just wanted to --
20 DR. DI BISCEGLIE: Can I ask a related
21 question? Sorry.
22 DR. EPSTEIN: That's fine.
23 DR. DI BISCEGLIE: For either of you.
24 Just the idea of the distinction between mission-
25 related research and mission-related laboratory work.

1 This development of standards I would think of more
2 as very important, very necessary laboratory work but
3 not necessarily innovative, and therefore, not
4 necessarily research. Or maybe I'm wrong and I'm just
5 thinking about how you measure in terms of time and
6 effort and so on, those two types of laboratory work.
7 DR. CARBONE: Actually, in some ways I'll
8 reiterate what Dr. Goodman just said which is the lack
9 of recognition of the development of standards and
10 assays as a science is one of the things we hope to
11 change.
12 Developing a standard requires that you
13 have an adequate way of measuring it. It requires
14 that you have an adequate way of measuring the
15 disease. It requires that you have an adequate model
16 sometimes of starting out. So there are quite a few
17 scientific creative elements and the end product is
18 "just a standard."
19 So we define our research not -- we don't
20 use other people's definitions of what is quality
21 research. We define our research as what we need to
22 do the job well and in many cases, there's a great
23 deal of science and if you will, the lack of knowledge
24 or the science makes it difficult sometimes to
25 generate these standards. So the element -- the end

1 product I agree with you. It's a standard. It's
2 fairly -- by definition, it's standard. But the act
3 of getting there in the right manner often requires
4 some innovative science. So from our perspective, it
5 is counted as a laboratory research endeavor and it
6 gets the scientist credit.
7 We do obviously the peer review
8 publications which is kind of the standard academic
9 extramural NIH type measurement because we feel it's
10 important to have our science peer reviewed, have our
11 science out there in public. But in fact, we measure
12 that as important and it's important science for CBER
13 as well.
14 DR. EPSTEIN: I would say that there tends
15 to be an underestimation of the scientific element of
16 this endeavor because the end product looks simple and
17 everybody understands that certain aspects of it are
18 rote. After all, if you want it lyophilized, how much
19 science does it take? That's straightforward.
20 On the other hand, what goes into it as
21 Dr. Carbone was explaining is really multi-factorial.
22 I mean it starts with epidemiology. What's out
23 there? What are we trying to measure? Why are we
24 trying to measure it? What are the characteristics of
25 the assays? For what assays and what types of assays

1 are we trying to make a standard? So that requires a
2 certain kind of exploration.
3 Then you can get into many, many
4 subtleties about the assays. For example, we didn't
5 go into the details, but let's say you want a standard
6 for von Willebrand disease. Well, what are you
7 looking for? So there's a lot of effort that goes
8 into figuring out the standard assay as well as the
9 standard reagent and it's full of betwixt and
10 betweens.
11 And then you come to the reagent itself
12 and should it be liquid? Should it be lyophilized?
13 Should it be purified? Should it have a single
14 specificity? Should it be multiple specificities?
15 Should it be naturally derived? Should it be
16 recombinant? Should it be the natural sequence?
17 Should it be a consensus sequence? So there's a lot
18 of judgment that goes into relating its
19 characteristics to its utility and of course, that
20 requires a scientific dialogue and often some
21 experimental work.
22 Then you come into the whole issue of now
23 your goal is to have a physical material that has a
24 meaningful unitage. But when you then characterize it
25 with an array of assays through a scientific

1 collaboration what you end up with is a range of
2 answers and then you're trying to figure out what's
3 meaningful in that range of answers and that gets you
4 into a whole set of questions about the methodology.
5 It raises statistical questions. If you have an assay
6 and it gives you an outlier result or you have an
7 assay and it has high variance, just exactly how do
8 you deal with that result when you assign unitage and
9 what's going to be the significance of giving a
10 unitage that may not work in that assay and is the
11 problem with the standard or is the problem with the
12 assay? And we mustn't forget that that has a lot of
13 implication for product potency. I mean, if that's a
14 standard for Factor 8 and you want to reliably dose
15 the patient with Factor 8 or Factor 9, you want to be
16 very, very sure that you've measured the right thing.
17 So you have that whole aspect to it.
18 So what I'm trying to explain is that
19 although some aspects of it may be mundane science
20 because it's well established. I mean, we know we
21 should refrigerate liquids. Right? But on the other
22 hand, you get into all these subtle questions. Should
23 it be inactivated or not inactivated? If we
24 inactivate it, does it change its character in an
25 adverse way because it's no longer a natural material

1 and we don't know what assay is going to come next.
2 So all I can say is that a seemingly
3 simple activity is actually laden with myriad
4 scientific questions that require extensive
5 collaboration and for which the answers are not
6 straightforward. Just to give you one more example,
7 there's this whole debate about what's called
8 metrological traceability. If you give an unitage
9 which is always an arbitrary unit, should you be able
10 always to relate it to some actual physical measure?
11 For example, is an antigenic potency unit sufficient
12 or must it be referable to physical mass or if it's
13 only referable to antigenic mass, is that with a
14 standard antibody and how do you know that the
15 standards stayed the same?
16 And a lot of the effort goes in -- Dr.
17 Finnegan was talking about refreshing these reagents.
18 The immediate question is how do you determine
19 sameness and sameness is very difficult to assess.
20 You're going to have a new reagent. It's going to
21 come from a different human donor or a different human
22 pool and you want to figure out whether the unit is
23 actually traceable to the prior unit because if the
24 unitage turns out not to be equivalent, when for
25 example, Mei-Ying was explaining the unitage for the

1 Factor 8 standard, you don't want to have a shift in
2 product potency because you misidentify the equivalent
3 unitage of the new reagent compared to the old
4 reagent. But then the question is how is it traceable
5 to the original potency and does it require merely a
6 functional determination or does it actually require a
7 biochemical determination and how exactly can that
8 consistency be demonstrated?
9 So all of these issues converge into a
10 scientific effort and I think what you heard Dr.
11 Carbone say and what I've tried to illuminate is that
12 it's actually a science onto itself and I think that
13 that's the point that's been underappreciated that you
14 do need people who understand all of the details of
15 that at the very, very simplest level. You know,
16 should it be delipidated and lyophilized to the most
17 sophisticated level which is is it or isn't it
18 representative of the genomic variation of the thing
19 you're targeting and that's just the science. That's
20 the science piece. Does that help?
21 (Laughter.)
22 CHAIRMAN SIEGAL: That was very good.
23 Thank you. Okay. Are there any more comments?
24 DR. KATZ: That was neat, Jay. Good job.
25 That was not mine. This may be for Jim because lo

1 these many years ago I was doing site visits as well
2 and writing reports and actually the evolution of
3 management of the research program is pretty
4 spectacular over the last ten years. So that's one
5 side of the field of endeavor.
6 But we keep talking about the resources
7 and I'm just wondering what the Committee says about
8 what anybody who's interested can do about the
9 resource issue and I didn't know then and I don't
10 think I know now.
11 DR. ALLEN: It's hard to say. Certainly,
12 those of us who are not now in any way connected
13 except through this committee with the Federal
14 Government, we are certainly free to contact Congress
15 and to advocate on behalf of the Agency and the need
16 for those resources. I think that's an extremely
17 important function that we all should be doing. We
18 should be talking with our own Representatives and
19 Senators about the importance of this and trying to
20 get our colleagues at academic environments to do
21 likewise.
22 There isn't a good lobbying group out
23 there for the FDA. The NIH certainly has a very
24 broad-based research community that is out there and
25 has organized to assure that their message is heard by

1 Congress and by others. The CDC was slow to do so,
2 but has subsequently developed a reasonably active
3 public health support group.
4 The FDA has a lot of industries that it
5 regulates or is regulated by the FDA and these groups
6 have their own special interests. They aren't out
7 there in the same way as a strong support group for
8 the Agency and resources for the Agency. But I think
9 it's really incumbent on all of us to do what we can
10 to try to get that message out.
11 I'm delighted to hear that there is an FDA
12 review group that's out there and certainly I assume
13 that they have been given copies of the report. Dr.
14 Goodman certainly indicated that he's been talking
15 with them.
16 This whole issue of perhaps a foundation
17 to support research efforts hasn't come to fruition
18 yet, but at least it's being discussed and I think
19 that's helpful. Again, support from those of us who
20 believe that that might be useful certainly might be
21 helpful. And I think we just need to look at ways
22 that we can do that to always in everything that we do
23 be supportive of the Agency and in particular, of the
24 programs that are important to us.
25 DR. CARBONE: I just briefly want to

1 mention that as part of the total FDA review we
2 supplied the office site visit reports for all the
3 offices to the Office of Commissioner. So that
4 message certainly has been delivered.
5 CHAIRMAN SIEGAL: Okay. Anybody else
6 prepared to lobby?
7 (Laughter.)
8 CHAIRMAN SIEGAL: Dr. Szymanski.
9 DR. SZYMANSKI: I was quite impressed
10 about the response I think in all areas as Dr. Allen
11 said. But I was wishing that there would be one other
12 area included, but I guess it doesn't belong to FDA
13 and that is the standards of transfusion of various
14 products. I think this is such a very important area
15 clinically and it would be lovely if some overall
16 agency would look at this because now it seems to
17 remain in each hospital their own affair and I would
18 love to see an overall scientific review of the
19 standards of transfusion.
20 DR. KATZ: Clinical Transfusion Medicine
21 Committee at AABB is embarking as we speak over the
22 next several months on a very formal guidelines
23 development process. It doesn't carry force of law or
24 regulation, but I think most physicians would prefer
25 that clinical guidelines come from clinical

1 organizations as opposed to regulators.
2 CHAIRMAN SIEGAL: If there are no other
3 comments, then perhaps we should adjourn for lunch.
4 But it's actually about 15 minutes early. So that
5 means we should come back 15 minutes early. So let's
6 reconvene at 1:00 p.m. You're allowed to check out in
7 your lunch hour.
8 (Whereupon, at 12:01 p.m., the above-
9 entitled matter recessed to reconvene at 1:03 p.m. the
10 same day.)
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1:03 p.m.

CHAIRMAN SIEGAL: Let's resume please. We're going to have to revise the schedule slightly. But the topic this afternoon is Measles Antibody Levels in U.S. Immune Globulin Products which we already began to discuss a little bit earlier. We're going to have an introduction by Dr. Basil Golding from FDA. Dr. Golding.

DR. GOLDING: Thank you and good afternoon. Before I start, I would just like to give credit to people who provided very important input. Some of the presentation is going to involve information that was generated at the FDA, worked on across offices, between people in the Office of Vaccines and the Office of Blood. Judy Beeler is the virologist that does the measles titer assays together with Susan Audet who is the first author of the paper that was generated and a lot of that information relates to the position that we're in where we're able to deal with this project.

And keeping in mind what was discussed during this morning's topics, I think it's very apt to remind people that the research that was done here was very mission related and was very proactive because we realized that the titers were dropping and people in

1 the research group, in our group, Dot Scott and Mei-
2 Ying Yu, collaborated with the Office of Virology and
3 started looking at the lots and trying to figure out
4 what was going on and that led to an information base
5 which we can use to formulate some kind of approach
6 which we're going to discuss this morning.
7 I also want to thank the other speakers
8 who are coming and some of them haven't yet arrived
9 but who are going to present certain aspects which
10 will help inform us and hopefully inform the Committee
11 to make a decision regarding the questions.
12 I'm going to be talking about measles
13 antibody levels in the United States related to immune
14 globulin products and the main issue that we've come
15 to address is FDA seeks the advice of the Committee on
16 a proposal to lower the minimum recommended lot
17 release titer for measles antibodies in immune
18 globulin intravenous IGIV and immune globulin
19 subcutaneous IGSC.
20 The background for this is that measles
21 antibody titers serve as a potency test for lot
22 release of all immune globulins licensed in the United
23 States. Measles antibody levels in products have been
24 declining in recent years and a failure in potency
25 testing which is a release test would result in

1 rejection of lots with a negative impact on product
2 availability for primary humoral immune deficiency
3 diseases. CBER proposes to lower the minimum measles
4 antibody titer of IGIV and IGSC to levels expected to
5 be effective in pre-exposure protection in patients
6 with PIDD. Immune globulin intramuscular or IGIM is
7 indicated for post exposure protection mainly in
8 normal individuals and will not be considered at this
9 juncture, but we will have to deal with this
10 separately.
11 In general, a lot release test, what are
12 the regulatory requirements? Well, this comes from
13 the CFR. "Laboratory controls shall include the
14 establishment of scientifically sound and appropriate
15 specification standards, sampling plans and test
16 procedures designed to assure that drug products
17 conform to appropriate standards of identity,
18 strength, quality and purity."
19 Potency testing for immune globulins, the
20 rationale is based on the assurance of strength and
21 quality and what do the specifications really provide?
22 They allow for a measure of lot-to-lot consistency
23 for assurance of product integrity, especially tests
24 that measure a function of antibody rather than just
25 binding and they measure activity that is relevant to

1 the indication, in this case, for patients with
2 primary immune deficiency disorders.
3 So in general, what are the current U.S.
4 immune globulin product potency tests? The current
5 requirements are that you measure antibodies to
6 measles, diphtheria, polytype 1203 and hepatitis B
7 surface antigen and it came up in a question before by
8 Dr. Siegal, you know, what about testing for more
9 appropriate antigens. Well, we are working on that
10 and this was discussed at the workshop and we will be
11 developing hopefully in the near future a testing that
12 will be more relevant to the antigen such as
13 haemophiles and influenza and strep pneumococcus. So
14 all the above tests except the antibody to Hepatitis B
15 surface antigen are neutralization assays, functional
16 assays. But the anti Hepatitis B surface antigen
17 titer does provide additional assurance of viral
18 safety both for manufacturing and for pre-exposure
19 prophylaxis in the patient group.
20 IGIV and IGSC in measles antibodies, the
21 measles antibody levels are a standard measure of
22 potency for these immune globulins. Historically,
23 when measles was a much more serious problem as a
24 public health issue, having this protection was
25 important. Potency tests are available and correlate

1 with protection in normal subjects. They are measured
2 by bioassay and the two types of functional assay are
3 the hemagglutination inhibition assay and a
4 neutralization assay which is really a plaque
5 reduction assay.

6 The important issue that we have to face
7 now is that declining antibody levels have been
8 observed in these products over the past several
9 years. The first question is why are these antibodies
10 declining in donors. Well, natural infection does
11 result in higher antibody levels and the proportion of
12 vaccinated as opposed to naturally infected donors is
13 likely to be increasing. The vaccine was licensed in
14 1963 and implemented over ensuing years and naturally
15 infected populations of donors are aging and these
16 people are more likely to be deferred and there are
17 pure donors now available who were naturally infected.

18 This is from a paper by Markovitz which
19 just compares the titers from natural measles
20 infection with those from the vaccine. On the X axis,
21 you can see time after natural infection or
22 immunization. On the Y axis you see the actual titers
23 and the upper graph shows the titers with natural
24 measles infection remaining higher for a longer period
25 of time compared to the titers from attenuated measles

1 vaccine immunization.

2 So the measles potency test for immune
3 globulins has a history. In 1944, a paper by Stokes
4 demonstrated that measles prophylaxis by IGM is
5 effective. Around about 1953, the NIH came out with a
6 statement that there should be a minimum requirement
7 for immune serum globulin. This is the intramuscular.
8 Several lots should be effective in prophylaxis of
9 measles. And as measles potency tests became
10 available, CBER developed standards to facilitate the
11 potency testing of these products.

12 This is the history of the actual antibody
13 potency standard. In 1961, the Lot 1 was the first
14 standard. It was serum from immunized nonhuman
15 primates and ISG or intramuscular the standard was
16 required that it should be at least 0.25 times the
17 standard Lot 1. The cutoff was established based on a
18 study of 60 IM preparations, IM lots, considered
19 potent for measles prophylaxis and the cutoff
20 permitted future lots to pass specification with a
21 probability of 95 percent.

22 Many years later, 1971, Lot 1 was replaced
23 with Lot 175. Then again in 1992, Lot 175 was
24 replaced by 176 which is the current standard. The
25 current lot release criteria lot should have at least

1 0.6 times the potency compared to Lot 176 when
2 compared at the same IGG concentration and we now have
3 a plan that was mentioned, alluded to, by Dr. Yu
4 earlier today to replace Lot 176 with Lot 177.
5 Incidentally, we're not going to have time
6 to do it, but each replacement lot was carefully
7 titered against the previous lot to make sure that
8 there was a continuity and that we weren't changing
9 the standard and that the standards are all connected
10 one to the other based on actual functional assays.
11 So the clinical issues. Measles
12 prophylaxis in PIDD patients. Measles incidence is
13 now rare in the United States, only 66 confirmed cases
14 in 2005 according to the CDC. Reports of measles
15 infection in PIDD patients are rare. A lack of
16 exposure to measles could be due to lack of exposure
17 to measles or due to protection with immune globulin.
18 So these patients are on treatment.
19 The last major outbreak in the United
20 States was `89 to `90 and it was one with more than
21 55,000 cases reported and this was prior to widespread
22 use of two dose vaccination. Since 2001, measles
23 outbreaks in the United States are rare and usually
24 attributable to exposure outside of the United States.
25 Nevertheless, measles remains an important

1 pathogen worldwide. Twenty-one percent of disease
2 related deaths in children less than five years of age
3 worldwide are due to measles. Antibodies are needed
4 to prevent infection while measles virus clearance is
5 dependent on CD8 positive T cells. So this is
6 important because antibodies are not the entire story.
7 Primary immune deficiency disorder patients
8 especially those with combined humoral and T cell
9 deficiencies are susceptible in severe measles
10 disease.
11 Protective titer against measles infection
12 and this obviously comes from vaccine studies. This
13 is based on a study by Chen, but we actually, the
14 people in the Office of Vaccines, Susan Audet and Judy
15 Beeler, took the titers from the paper and using our
16 standard were able to make calculations to refer back
17 to our own standard. So we can use this in looking at
18 this problem. A serum titer of 120 mIU per mL was
19 found to be protective against clinical disease in
20 healthy vaccinated individuals. But you need a higher
21 titer, greater than 1,052 mIU per mL to protect
22 against infection, in other words, to achieve
23 sterilizing immunity.
24 There's a lack of published
25 pharmacokinetic data analyzing measles titer in IGIV

1 products administered and the consequent trough level
2 measles neutralizing antibody in PIDD patients, but
3 you will hear from subsequent speakers from industry
4 that they are going to present some data today which
5 is relatively new data and which we should take into
6 consideration. The protected level in PIDD is unknown.
7 More than 100 distinct PIDD syndromes exist.
8 Therefore protective measles antibody levels may vary
9 as well because these people may have varying degrees
10 of T cell deficiency.
11 The rationale for new measles antibody
12 specification. The package inserts, if you look at
13 package inserts for all the immune globulins, the IGIV
14 and IGSC preparations, you will find that they range
15 between 200 to 800 mg of IGG per kg given every three
16 to four weeks. Now even though that is correct for
17 the package insert, from a practical point of view,
18 most if not all physicians that are treating these
19 patients will use 400 mg/kg or even higher doses.
20 So in considering trough measles antibody
21 titers for patients receiving 400 mg/kg every four
22 weeks, the estimated range of the measles titer would
23 be 250 to 718 mIU/mL based on CBER testing of lots and
24 calculated trough levels. In the paper that I alluded
25 to earlier, they looked at 166 lots from seven

1 manufacturers, calculated, not calculated, assayed
2 them and then based on their value, calculated what
3 the trough levels would be if you gave a dose of 400
4 mg/kg to PIDD patients and that's the range they
5 calculated which is more than twice what is needed for
6 a protective level.
7 On the other hand, if you look at the last
8 bullet which would be a worst case scenario, if a
9 physician decided to use the lowest dose on the label
10 and used 200 mg/kg, that would achieve a trough level
11 of 120 mIU/mL which would be 1,200 IU/mL or 0.48 times
12 the CBER standard Lot 176.
13 Just to remind you, the current lot
14 release standard in order for the lot to pass it has
15 to be 0.6 times the CBER standard. So what we're
16 saying is even the worst case scenario if you gave a
17 lower dose, you would achieve a protective level at
18 the time of trough level prior to the next dose of
19 product.
20 What could be the possible strategies to
21 address declining measles antibody titers in immune
22 globulin products? What we're going to propose is to
23 lower the recommended measles lot release
24 specification titer for IGIV and IGSC if there is
25 assurance that the minimally protective titers are

1 present. Another approach could be to revaccinate
2 plasma donors in an attempt to increase antibody
3 levels, but unfortunately the likelihood of achieving
4 substantially higher and durable levels is estimated
5 to be low in adults and you may see in a subsequent
6 presentation actual data to show you that the second
7 immunization is not associated with a very big
8 increase in titer.

9 What are the questions to the Committee?
10 First, we're not going to ask you obviously to answer
11 but to frame the questions so that you'll have these
12 in mind during the coming presentations. Do committee
13 members concur with the FDA proposal to lower the
14 minimum measles antibody specification for IGIV and
15 IGSC from 0.6 times the CBER standard to 0.48 times
16 the CBER standard?

17 CBER is considering requesting additional
18 studies to confirm that PIDD patients will achieve
19 trough levels of measles antibodies above the
20 protective level, in other words, 120 mIU/mL, if
21 treated with IGIV and IGSC products that meet the
22 proposed revised potency standard of 0.48 times the
23 CBER standard. Do the committee members agree that
24 this information is needed?

25 Thirdly, please comment on the need for

1 feasibility of any alternative strategies that CBER
2 should consider to reduce the likelihood of failed
3 lots of IGIV and IGSC based on potency testing for
4 measles antibody in order to ensure availability of
5 product for PIDD patients.

6 Thank you. That is my talk.

7 CHAIRMAN SIEGAL: Okay. Thank you very
8 much, Dr. Golding. Are there any questions for Dr.
9 Golding at this point?

10 DR. FINNEGAN: Do you have any idea about
11 the CDC patients? Were they never vaccinated? Were
12 they older and far out from their vaccination? Were
13 they wild type that had never been vaccinated?

14 DR. GOLDING: I'm not sure which cases
15 you're referring to, but most of the cases that have
16 occurred in recent years they've been imported, so, in
17 other words, somebody traveling to an area where
18 measles is endemic coming back to the country. Now
19 you're asking were those people who got the infection
20 locally, were they vaccinated or not. I don't have
21 that information. My guess is that -- I know the
22 vaccination is effective. So my guess is either they
23 weren't vaccinated or they were long time off the
24 vaccination. Because what happened is that it was
25 shown an epidemic of `89 -`91 with 55,000 or more

1 cases who were infected was at a stage where people
2 were not getting two doses. So it could be that
3 people between the first and second dose had their
4 titers dropped sufficiently that they are now getting
5 infected. But I'm not sure. But Jane Seward is going
6 to be here from the CDC hopefully in about an hour.
7 So she can answer that more correctly.
8 CHAIRMAN SIEGAL: Mark.
9 DR. BALLOW: I was just curious. Going
10 over the historical data about the IM gamma globulin,
11 the first slide was 0.25 or something like that and
12 then all of a sudden it jumped to 0.6. What's that
13 all about?
14 DR. GOLDING: Yes. For the first lot was
15 more -- Let me think. Was it more potent or less
16 potent? It was more potent. So you could have a --
17 Now why did it drop over 20 years? Again, I think
18 it's related to there were many more natural
19 infections at that time and the titers in the donors -
20 - This lot didn't just drop out of the air. It was an
21 regular industrial manufactured lot that we were able
22 to acquire to use as a standard or part of it was
23 acquired to use as a standard. So what you're
24 pointing out is that it's not that it's just dropped
25 over the last few years. Since 1961, the titers have

1 dropped considerably.

2 CHAIRMAN SIEGAL: One more from Mark.

3 DR. BALLOW: Nell and I were just talking
4 and we were asking what's happening with the Hepatitis
5 B titers. In other words, you have all these -- You
6 use polio, measles, Hep B titers and I can't remember
7 the fourth one.

8 DR. GOLDING: Diphtheria.

9 DR. BALLOW: Diphtheria. I mean obviously
10 with diphtheria and polio it may not be an issue, but
11 what's happening with the Hepatitis B surface antibody
12 titer?

13 DR. GOLDING: As far as I know the Hep B
14 titers have not been a problem, but Dr. Yu looks at
15 this more carefully than I do.

16 DR. YU: Well, there is a minimum
17 requirement by CBER for the Anti-HBs present in immune
18 globulin product and that 1 IU/g of IGG, per gram of
19 IGG. So you have a five percent albumin. No, five
20 percent of immune globulin. Then you need to divide
21 it, 1 IU divided 20 mL because that is 50 mg/mL. So
22 that's a minimum requirement for us. It's very low.
23 But in actual reality, the titer is much higher, but
24 it's the minimum requirement is 1 IU/g of IGG. That's
25 what we set.

1 DR. BALLOW: But has it changed? Has it
2 changed over the last --
3 DR. YU: -- Usually --
4 DR. BERGER: I think the question about
5 Hepatitis B titers in IGIV products is whether the
6 titers are moving in the opposite direction of the
7 measles titers because now the population is getting
8 immunized. So perhaps the titers are actually going
9 up.
10 DR. YU: I think the titer certainly is
11 not decreasing. It's not. That's what we understand.
12 It's anti-measles is decreasing, but not anti-HBs or
13 other markers that I know of. But many manufacturers
14 are here and they may be able to provide the answers.
15 DR. GLYNN: Yes. I had a question on the
16 level of 120 that you've been using for your
17 calculations. After looking at the paper, I'm not
18 really -- Can you go over why you chose 120 because
19 from what I see there was a patient who got full-blown
20 measles at that level. So I'm not sure why you're
21 saying that that level is protective.
22 DR. GOLDING: That level is from the
23 vaccine studies where they showed that that level was
24 a protective level for pre-exposure prophylaxis. Now
25 it's 120 was the lowest level that was protective. So

1 I don't think that it's surprising that now and again
2 you'll get a breakthrough infection. But on
3 aggregate, the 120 was a protective level in the
4 vaccine trials.
5 Now I'm not saying that we should aim --
6 What we're proposing is to aim for achieving a titer
7 that's at least double that even if we reduce the
8 titer. So if the intent of your question is say are
9 you happy with the 120, I would say no. We need to
10 have a margin of safety and what we're proposing is at
11 least having immune globulin products out there that
12 are delivering a dose which would give you at least
13 twice that level, somewhere in the range of 240 or 250
14 which would occur if you're using 400 mg/kg.
15 DR. KATZ: Are you actually failing lots
16 at this point?
17 DR. GOLDING: That's a very good question.
18 So I can't give you details of that because it's
19 proprietary information. But there have been and even
20 in the paper that was appended to your package, there
21 was one set of lots that were failing based on our
22 testing. So there are lots that are failing. It's a
23 small number at this point. But if you're looking at
24 declining titers, I think we can't wait for more lots
25 to fail because this is a very important product for a

1 life threatening disease.
2 At the moment, I would say that there are
3 failing lots or lots that are very close to the cutoff
4 and that if we waited much longer or even longer, we
5 would start to see more lots failing and there would
6 be a problem of availability of this product.
7 DR. DI BISCEGLIE: Basil, you sort of used
8 IGSC and IGIV sort of interchangeably. Are there any
9 differences with regard to levels of antibody and is
10 this something the Committee needs to consider?
11 DR. GOLDING: Okay. Well, what happens is
12 this is really that the answer is based on
13 pharmacokinetics and what happens when you're giving
14 IGIV every three to four weeks is you get a sawtooth
15 patent. When you're giving it every week as a sub
16 cut, you're getting a much flatter curve which means
17 that your peak levels are lower and also means your
18 trough levels are higher with the IGSC. So if
19 anything, the IGSC trough levels are higher. I think
20 it's less worrisome to some extent with the IGSC
21 concerning the actual trough.
22 But on the other hand, you still want to
23 have sufficient titers in those products that are also
24 going to have a high assurance that through the period
25 they're going to be above, considerably above, the 120

1 mIU/mL.

2 DR. SCHREIBER: Do you have any
3 information on whether there have been any patients
4 with immune deficiency disease that have experienced
5 measles while on IGG?

6 DR. GOLDING: That's also a very good
7 question. At the workshop, we discussed this and
8 they're putting a registry in place. I don't think,
9 if somebody who was at the workshop recalls, but I
10 don't think anybody, we've seen cases to my knowledge
11 in this country of PIDD patients developing measles
12 while they were on treatments. An assumption from
13 that is that the current treatment is very effective
14 in pre-exposure, but the truth is that it hasn't been
15 tested very well in the last few years because as you
16 see there have been very few cases for the last 20
17 years.

18 DR. GLYNN: And so do you have an
19 estimation of the current levels right now with the
20 current IGG?

21 DR. GOLDING: Yes. We can calculate it
22 based on pharmacokinetic principles. But better than
23 that, you're going to get these two presentations
24 today where the manufacturers are going to talk about
25 the actual measured trough levels. We don't have, as

1 I mentioned in my slide, a lot of data especially
2 published data on that. So the speakers will provide
3 us with some information about actual levels. What we
4 have is mainly based on what the titer is, either
5 product, and then based on PK principles what we
6 expect the trough levels to be.
7 DR. SZYMANSKI: Can you tell me what
8 percentage of IGIV products are given to
9 immunodeficiency patients and which ones to other
10 patients for other diseases?
11 DR. GOLDING: I'm not sure I have an
12 accurate answer. I think there may be somebody in the
13 audience who can help. But we know when we looked,
14 when there were problems with the availability of the
15 product and we started asking treaters and major
16 centers what is going on in terms of IGIV usage, we
17 found out that 60 or 70 percentage of the usage was
18 off-label and there are some other indications besides
19 PIDD like ITP, Kawasaki and a few others. So I'm
20 guessing, but I would think that only about 20
21 percent, 20 to 30 percent, is used for PIDD and the
22 rest is used off-label or for other indications.
23 CHAIRMAN SIEGAL: Do we know what
24 proportion of IG product is used subcutaneously these
25 days as compared to IV? Do we have any idea about

1 that?

2 DR. GOLDING: We have one newly licensed
3 product for IGIV sub cut and we have six or seven --
4 other manufacturers. I don't know what the market
5 share is. I don't have that with me.

6 CHAIRMAN SIEGAL: But we don't know in
7 practice how it's being used?

8 DR. GOLDING: But do you mean to what
9 extent compared to the IV?

10 CHAIRMAN SIEGAL: Yes. I mean you can use
11 the same product sub cut.

12 DR. GOLDING: Right.

13 CHAIRMAN SIEGAL: And so the question is
14 how much is actually being used sub cut as compared to
15 IV?

16 DR. GOLDING: Well, I don't know offhand.

17 CHAIRMAN SIEGAL: Anybody have any sense
18 of that? Okay. All right. Basil, thank you very
19 much. I think we should go on.

20 DR. KATZ: I don't see anywhere on the
21 agenda where I think this could be answered but I'm
22 kind of interested in the implications of FDA changing
23 its criteria and maybe the manufacturers can address
24 this if I bring it up ahead of time. If they are
25 manufacturing in some way with an eye on what gets

1 approved in the U.S., would lowering the threshold
2 make a difference in the rest of the world where
3 measles might be more common and I think probably you
4 can give an FDA perspective and they can talk about
5 what they think.
6 DR. GOLDING: I think that on balance we
7 have to make a decision which I think we can make and
8 have the best of both worlds in the sense that we can
9 lower the titer and still be reasonably assured that
10 the product is going to be safe and effective in
11 preventing measles. But we may reach a point sometime
12 in the future where the titer had declined to an
13 extent where that won't be the case. As far as public
14 health in the United States, it seems that this is
15 such a rare disease that it may be a much more
16 compelling reason to have that titer outside the
17 United States and we may not need it. So I think the
18 manufacturers surely have to deal with that.
19 CHAIRMAN SIEGAL: Mark.
20 DR. BALLOW: Just a comment. You know,
21 even though the package insert says 200 mg/kg, I and
22 my colleagues are actually tending to use higher doses
23 because of the recognition that even at 400 mg/kg some
24 of these patients are still developing chronic lung
25 disease and bronchiectasis. So, for example, in

1 patients with Bruton's disease or X-lined
2 agammaglobinemia the suggestion is to use 600 to 800
3 mg/kg. So that means that they would be getting more
4 measles antibody.
5 CHAIRMAN SIEGAL: All right. I understand
6 that Dr. Seward has in fact arrived. So I would like
7 to introduce Dr. Jane Seward from CDC who is going to
8 talk about the epidemiology of measles in the United
9 States.
10 DR. SEWARD: Good afternoon and sorry I
11 was late. It wasn't the weather. It was a GameBoy
12 that got dropped down the toilet in the plane I was
13 on.
14 (Laughter.)
15 DR. SEWARD: So that two hours delay for
16 that reason.
17 CHAIRMAN SIEGAL: Terrorist attack.
18 DR. SEWARD: And then we had to get off
19 the plane. They cancelled the plane altogether.
20 So I'm here to talk about measles
21 epidemiology in the United States and I think that
22 will give you a good understanding of what the risks
23 are for exposure to measles now and where we are with
24 measles control and elimination.
25 As everybody knows, I'm sure, measles is a

1 highly contagious viral disease. In the pre-vaccine
2 era, there was nearly universal infection during
3 childhood because of its contagiousness. Morbidity
4 and mortality in the United States by the 1950s was
5 described as 450 deaths annually, 48,000
6 hospitalizations and 4,000 cases of encephalitis among
7 other complications. The morbidity and mortality was
8 much higher than this earlier in the century. So this
9 was after a lot of improvements in health care and in
10 hygiene, etc.
11 Measles vaccine was licensed in 1963.
12 Almost all the vaccine now is administered as the
13 combination MMR vaccine and when it's available I
14 guess the MMRV vaccine which is not currently
15 available, although it's licensed. Measles vaccine is
16 highly effective. It's one of the most effective
17 vaccines that we have. One dose administered at 12
18 months or older is 95 percent effective. Two doses at
19 least four weeks apart administered at the same age on
20 or after the first birthday is 99 percent effective.
21 These effectiveness estimates are lower if measles
22 vaccine is given at a younger age, but this is the age
23 of recommendation for the United States.
24 In the U.S. we give two doses of measles
25 vaccine to children, the first at 12 to 15 months, the

1 second dose at four to six years and two doses is
2 recommended for all school students, for college
3 students or other students in post high school
4 educational facilities, health care workers and
5 because of their risk of exposure overseas for
6 international travelers.
7 The strategies to control and eliminate
8 measles in the United States are to maximize the
9 population immunity to measles by delivering the first
10 dose on time as close as possible to the 12 months, to
11 increase the second dose coverage in school children,
12 although that is already extraordinarily high as
13 you'll see in a minute and to vaccinate high risk
14 adults, to assure adequate surveillance so that we
15 understand the risks of measles and what's happening
16 in the country with measles disease, to respond
17 rapidly to outbreaks and to work to improve global
18 control because that will reduce the risk of
19 importations into the United States.
20 This shows reported measles cases. Is
21 there a pointer? Reported measles cases in the United
22 States from 1950 through 2006 and it's on log scale as
23 you can see there. I can't get this to work, but it
24 doesn't matter. You'll see the vaccine was licensed
25 in 1963 and measles disease in terms of reported cases

1 declined rapidly after that. There was a big push for
2 school immunization laws in the 1970s and 1980s in
3 response to measles still occurring in schools.
4 There was an increase in measles in the
5 late 1980s, around 1989 and 1990 there was a
6 resurgence of measles in this country and you'll see
7 why in a few slides and then in 1989, there was a
8 second dose measles recommendation made and improved
9 first dose coverage in preschool children. Since
10 1998, we've had measles incidence in the United States
11 has been less than one case per million population and
12 measles elimination was declared in 2000.
13 I'm sorry for that red color for total. I
14 have two slides here, one showing the total number of
15 cases and then some breakdown by age. You can see
16 that in the late 1970s there were still 50,000 to
17 60,000 cases reported a year. However, that dropped
18 rapidly as there was better implementation of school
19 requirements. The resurgence that you see in 1990, up
20 to 30,000 cases reported in one year, was mainly due
21 to low vaccine coverage in urban communities in
22 preschool children and that led to an influx of money
23 into vaccine programs and the Vaccine for Children
24 Program being established and then monitoring of
25 vaccine coverage in children 19 to 35 months. That is

1 the current ongoing coverage that is monitored and
2 there's been a dramatic improvement in vaccine
3 coverage among preschool children since that time.
4 This shows the breakdown by age without
5 the totals showing that in the late 1970s the highest
6 number of cases were in the school age children. But
7 the resurgence in 1990 occurred mainly in children
8 under five.
9 If you look at age specific measles
10 incidence by less than 15 and greater than 15, again
11 we're at extraordinarily low levels. So this doesn't
12 mean a whole lot. Most people 50 and above aren't
13 susceptible to measles. So you can see there that
14 incidences are very low in both. For less than 15,
15 it's a little bit higher.
16 These are the largest outbreaks that we've
17 had in the United States from 1999 to 2006. As you
18 can see, they're pretty small. The largest was in
19 Indiana just two years ago. All the outbreaks have
20 originated from imported cases as you can see there
21 except for one unknown source case that were likely to
22 be, two unknown outbreak sources that were likely to
23 be imported. Almost all of these outbreaks have
24 occurred in unvaccinated populations and as an
25 example, the top two, the Indiana one was an import

1 from Romania and a remaining U.S. resident who had
2 been working with a church group in Romania. She came
3 back, went to church, her church. This was a day
4 after she returned which was her day of rash onset and
5 this was a church group that didn't believe in, a lot
6 of the people that attended this church didn't believe
7 in vaccination and so there was an outbreak of about
8 34 cases, of exactly 34 cases. Measles can still be
9 serious. One of these cases in an adult health care
10 worker was hospitalized with severe complications for
11 a week with AIDS.

12 The Boston outbreak that occurred last
13 year was an import from India into inner city Boston
14 in a computer group. The person, the import, was from
15 India. He was a computer contractor who then went to
16 work and 17 other people mainly at the worksite,
17 mainly adults, got infected.

18 The Indiana outbreak was published last
19 year in *New England Journal* and one of the things that
20 we really highlighted in that article was there was
21 absolutely no spread into the community and that's the
22 case for most of these outbreaks. We had
23 extraordinarily successfully high population immunity
24 because of our high coverage of measles vaccine in the
25 United States and these outbreaks just do not

1 penetrate into the communities.

2 This shows the age distribution of measles
3 cases showing by age just the number of cases and this
4 shows the vaccination status, again, to show you that
5 most of the outbreaks have been because of
6 introductions into small vaccine objector groups or
7 into groups that are not as highly vaccinated such as
8 the adults in Boston. Adults sort of 30s to 40s were
9 little children when the vaccine program started in
10 the `60s and that's the age group that most
11 susceptible that may have missed out on exposure to
12 disease and vaccination and that's why they were
13 affected in the Boston outbreak. Nevertheless, it was
14 a pretty small outbreak.

15 This slide is to show that as our
16 surveillance has improved the number of cases has gone
17 down. We've been able to do virologic confirmation
18 and molecular epidemiology on all these cases and we
19 can show that almost 100 percent of cases now are
20 definitely imported. We can look at the genotype and
21 then look globally where that genotype is circulating,
22 know where that person came from and say it's an
23 importation or an import associated case if it leads
24 to a small outbreak in the United States. In 2007,
25 100 percent of our cases are import associated.

1 This shows one of the evidences that was
2 used to document elimination of measles. By
3 elimination of measles, I mean absence of endemic
4 transmission of measles. You know as I've highlighted
5 I think we stay at risk for importations in this
6 country until those global measles are eradicated or
7 eliminated.
8 And there will always be some spread. I
9 mean, you can vaccinate children under one. One of
10 the small outbreaks that I didn't point out a few
11 slides ago was in a daycare center where a little
12 child came back after visiting with his family in the
13 Philippines and nine out of ten children in his baby
14 room in the childcare center got infected. That's how
15 infectious measles is. But it didn't spread it to the
16 older children who were vaccinated. So there's no way
17 to have no cases at all, but we have very few cases in
18 the United States.
19 During the resurgence in `89 to `92, all
20 the viral isolates were D3 genotype. There weren't
21 many specimens taken for genotyping before that time.
22 Since that time, since 1993 onwards, there have been
23 probably now more than 150 isolates and they're all
24 just different genotypes from different parts of the
25 world.

1 Just to show you the countries that these
2 importations come from which reflects measles in that
3 country and also the probability of travel from those
4 countries. There are a lot more measles in some other
5 countries like in Africa, but not so much travel from
6 there. Japan does not have a good vaccination program
7 and they have a lot of measles. In fact, they had a
8 huge outbreak this year and we've had six importations
9 just this year from Japan.
10 In the United States last year and these
11 are provisional data, but the final data, we had 55
12 cases reported from 16 states. Eighteen of those were
13 the outbreak in Boston, Massachusetts, 10 in New York,
14 California, Florida. Ninety-five percent of the cases
15 were import associated which either means they were
16 direct importations or epi-linked to imported cases
17 such in the Boston outbreak or they were a virus
18 genotype that we don't think circulates here.
19 We can't always find the original source.
20 We've had instances in the past where we've had a call
21 from a European country that some person from their
22 country developed measles rash and they flew through
23 Utah the day before and then there's a case in Utah
24 two weeks later which we pick up. I mean that's sort
25 of low probability of finding the original source if

1 there's an exposure in an airport. But we sometimes
2 do find those.
3 This just shows last year's source
4 countries: India at the top; Ukraine because there
5 was a large outbreak there; China, we have a number of
6 children come in from China as adoptees and China
7 doesn't have a great program for their children and
8 orphanages anyway and quite regularly we do see
9 measles coming in among their adoptees with some
10 spread.
11 The largest outbreak last year, I
12 mentioned the Boston one and the others are just very,
13 very small. You know, three cases in Florida among
14 cruise ship employees. Three cases in Yemen, one who
15 came back from Yemen and then two spread cases in the
16 Yemen community and then three mothers exposed in
17 China during their adoption. So a little cluster of
18 cases related to adoptions in China.
19 And this shows you the cases in 2006 with
20 the genotypes and we can just say where every one of
21 them comes from. We've even been able to document
22 exposure at Disney World and mixing there with a case
23 from another country and just to highlight that it's
24 exactly the same pattern in the year before, in 2005,
25 and in years before that. This was the year that we

1 had that fairly large outbreak from Romania.

2 So the evidence for elimination of endemic
3 measles or elimination of endemic measles transmission
4 in the United States, the following, we have
5 extraordinarily low incidence. The majority,
6 essentially 100 percent of cases, are internationally
7 imported or import associated. Our surveillance
8 system is adequate and that was scrutinized very
9 closely during an external review meeting we had to
10 examine evidence as to whether measles had been
11 eliminated in the United States.

12 Population immunity is very high. There
13 is no endemic strain of measles virus circulating.

14 The evidence for adequate surveillance to
15 detect endemic measles are these. We have consistent
16 detection of imported measles cases. We have
17 detection of isolated cases and small outbreaks. High
18 level of investigative effort for measles to which we
19 thank the state and local health departments who work
20 incredibly hard. In that Boston outbreak, the City of
21 Boston administered 10,000 to 15,000 doses of MMR
22 vaccine in response to that small outbreak.

23 Molecular typing is consistent with
24 elimination of indigenous genotype of measles virus.
25 We have very high population immunity with high first

1 dose coverage of greater than 90 percent since 1996
2 for preschool age children. First dose coverage being
3 greater than 97 percent of school age children.
4 Second dose required for 82 percent of school children
5 as of 2001 and that's higher now, but we haven't
6 calculated it again recently. And then the most
7 recent seroprevalence data from 1999 to 2004 shows 96
8 percent immunity, well I should say, antibody measured
9 by Eliza in ages six to 49 that may or may not
10 indicate immunity but it's the best measure that we
11 have.
12 These are slightly older data from Ann
13 Haines from the National Health and Nutrition
14 Examination Survey that were published that were
15 presented of evidence of immunity for the measles
16 elimination meeting to show the dip in seroprevalence
17 in the age group of people born between 1967 and 1976.
18 That was the age group most affected during the
19 Boston outbreak. So we do have populations at risk in
20 the United States, but their risk of exposure now is
21 incredibly small.
22 Now we worry a little bit about duration
23 of vaccine-induced immunity. It's not because we see
24 any evidence waning to susceptibility from our
25 epidemiological data, but just because we're now 40

1 years into a program. The younger cohort are not
2 being exposed at all to wild measles virus, so aren't
3 having any external boosting and we think it's very
4 important to monitor population immunity including
5 whether immunity remains above the so-called
6 protective level.
7 This paper was published earlier this year
8 by Charlie LeBaron and Judith Beeler who is probably
9 here today showing measles antibody response measured
10 by neutralizing, plaque reduction neutralization
11 testing, I think, in children vaccinated, I'm sorry
12 about the quality here, but hopefully it's better in
13 your slides, children vaccinated in the left-hand
14 graph at kindergarten, getting the second dose at four
15 to six years versus getting it at 10 to 12 years,
16 showing that there's quite a boost in immunity with
17 the second dose at whatever age you get, but then
18 immunity declines again and you tend to stay in the
19 quartile that you were before you got your second
20 dose. Most of these levels are above the protective
21 level still though.
22 Dr. LeBaron then tried to model these data
23 to project out 30 years in the future what might
24 happen. He acknowledges in the paper that this is
25 just a model and that you may not get decline at the

1 slope as shown there on the left, but if you did, we
2 will have a more susceptible population in the future
3 and so we need to monitor this very closely.
4 Another small study that's been done
5 following up people from a vaccine trial in 1971 and
6 they were about 30 years after their last measles dose
7 with no known exposures to measles, nine percent of
8 that small group had PRN titers of less than 120, not
9 considered protective but, of course, they may have
10 good cellular immune memory still and may be able to
11 mount that in response to exposure to measles.
12 In conclusion, measles is no longer
13 endemically transmitted in the United States. Almost
14 100 percent of cases, I mean, 100 percent are import
15 associated. We just can't show that all the time.
16 This time 100 percent of our cases are import
17 associated. Importations continue to challenge our
18 population immunity, but we see extremely limited
19 spread from importations due to high population
20 immunity. There's no indication of immunity waning to
21 susceptibility from our epidemiological data. With
22 these small outbreaks, there is no spread into
23 schools, in daycare centers age groups, etc., but we
24 should continue long-term monitoring of vaccine
25 induced immunity. Thank you very much.

1 CHAIRMAN SIEGAL: Thank you very much, Dr.
2 Seward. Are there any questions?
3 DR. SEWARD: I would like to thank a lot
4 of people at CDC that provided the data for the slide.
5 I didn't make an acknowledgment slide but Charlie
6 LeBaron, Susan Redd, Susan Reef and a number of people
7 in the MMR team.
8 DR. DI BISCEGLIE: You pointed out that
9 measles can still be a very severe disease. What's
10 the evidence? Is there evidence of its increasing
11 severity in patients with immune compromised
12 situations of one kind or another?
13 DR. SEWARD: Well, we don't see it in
14 those people anymore. But, yes, my understanding is
15 it is more severe.
16 DR. DI BISCEGLIE: People on
17 corticosteroids or post transplant. Is it just
18 because we don't know because they don't get it
19 anymore?
20 DR. SEWARD: They don't get it anymore.
21 My understanding from the literature is that it is
22 more severe in those people.
23 CHAIRMAN SIEGAL: Is there any boosting
24 effect to bystanders from MMR?
25 DR. SEWARD: To bystanders --

1 CHAIRMAN SIEGAL: In other words, do
2 parents of children just immunized have a vaccine
3 effect?
4 DR. SEWARD: Yes, that's a good question.
5 Not that we know of. We did a study looking at wild
6 virus to see if there was any evidence of subclinical
7 transmission and boosting and there was not with wild
8 virus. So it would be much less likely with vaccine
9 virus. I don't know that that's been looked at
10 specifically though. It has been for wild virus.
11 DR. BALLOW: And a related question.
12 Transmission of two siblings from other siblings that
13 have been immunized, I mean, that hasn't been
14 reported, has it?
15 DR. SEWARD: No.
16 DR. BALLOW: No. Okay.
17 DR. SEWARD: I don't know the detailed
18 literature on that as well as I do Varicella for
19 example. That's sort of my specific area of
20 expertise. But if there is, you could count them on
21 one hand and there have been hundred of millions of
22 doses administered. So it's not considered a problem
23 at all.
24 DR. QUIROLO: Can you say something about
25 the PRN value of 120 and where that came from? In the

1 paper that we were given, the people in this outbreak
2 that didn't get measles all had much, much higher PRNs
3 than 120.
4 DR. SEWARD: Right. That value comes
5 mainly from a study by Bob Chen at CDC who was
6 fortunate enough to find blood from a blood drive that
7 had been done before an outbreak, I think, in a
8 college and examined the data and noted that the
9 attack rate was much higher in people below that
10 level. That was clinical disease as I remember. I
11 haven't read the paper for awhile and between eight
12 and 120 seemed to be the range for protection from
13 infection.
14 I mean, it's a small study. There hasn't
15 been -- I think there's another study from Europe that
16 indicates approximately the same level. It's a small
17 study with limitations that go along with that, but
18 it's the best that we have and we don't have that for
19 almost any other of that same for preventable
20 diseases.
21 I think the immunity that we're seeing,
22 measuring, in the community using similar testing and
23 the absence of measles and spread, I think, in
24 vaccinated people 10, 15, 20 years out from
25 vaccination would lead me to believe that's probably

1 it's a reasonable level.

2 DR. QUIROLO: That does sound right except
3 that only thing that I'm just thinking about is that
4 that may be the case in college students who have a
5 normal healthy immune system. But in people who are
6 getting IVIG who have PIDD or something, they may not
7 have T cell response after it. So I wonder if these
8 college students were getting infected but not getting
9 clinical disease and I don't know that paper. So it's
10 hard to know the answer to that.

11 DR. SEWARD: I think some got infected but
12 they had levels between eight and 120 is my --

13 DR. QUIROLO: Right. But would you not
14 recognize people who maybe had a level of 200 who got
15 infected but never progressed to clinical disease.
16 You would never pick up those people in this study.
17 Right?

18 DR. SEWARD: Yes, they had bloods before
19 and after -- Oh. I think they did. I'm sorry. I
20 haven't read the paper for awhile.

21 DR. QUIROLO: They didn't take everybody's
22 blood after the fact to see who got infected. Every
23 single person.

24 DR. SEWARD: I think they took some who
25 developed measles and some who didn't to try to answer

1 that question.

2 DR. QUIROLO: Okay.

3 DR. COLVIN: Yes, in that paper actually I
4 think they have evidence of viral replication with
5 boosting reaction between levels of 120 and 1052 if
6 you have a copy of that paper. So it looked actually
7 only levels above 1052 were protective. That's how I
8 read the paper. So that I had asked also my question
9 before where the 120 came from.

10 DR. SEWARD: So it protected from
11 infection not disease.

12 DR. COLVIN: That's right.

13 DR. SEWARD: Right.

14 DR. COLVIN: But these were healthy
15 vaccinated college students. We're not talking about
16 immunocompromised patients.

17 DR. SEWARD: Right. Maybe some clinicians
18 would like to comment. Many of you are. I mean
19 measles, my understanding is that it's more severe,
20 but not dramatically so compared to something like
21 Varicella. That is just extraordinarily more severe
22 in immunocompromised people.

23 DR. BERGER: We can only imagine. We
24 don't have data as several people have pointed out.
25 But certainly we must imagine there there are one year

1 olds in homes, immune deficient one year olds, in
2 homes where the four year old is being immunized when
3 they go to kindergarten.
4 DR. SEWARD: I think there are children
5 with Skid who are immunized at 12 months who were late
6 with their diagnosis.
7 DR. BERGER: Right. But I mean but with
8 Bruton's and antibody deficiency and a lot of the
9 other immunodeficiencies there must be kids in homes
10 where an -- You pointed out --
11 DR. SEWARD: I think some children who are
12 severely immune deficient are being immunized.
13 DR. BERGER: Right. This is also
14 unquestionably true.
15 DR. SEWARD: Yes.
16 DR. BERGER: And we don't hear cases of --
17 I don't know -- Again, we don't have any sort of
18 accumulated data, but I certainly have never a case of
19 severe measles in an undiagnosed Skid patient.
20 DR. SEWARD: Right.
21 DR. BERGER: Whereas, for example, we hear
22 about Varicella in undiagnosed Skid patients.
23 DR. SEWARD: Right.
24 DR. BERGER: But there must be -- but you
25 pointed out this outbreak in a daycare in the baby

1 room. So your implication is that there might be one
2 year olds whose protection by maternal antibody has
3 waned and they have not yet reached the age of
4 immunization.
5 DR. SEWARD: Yes. A lot of these children
6 are --
7 DR. BERGER: So there must be a lot of
8 babies like that in homes where a four year old is
9 getting immunized for the second time when they go to
10 school and you don't hear a lot of cases like that,
11 although there is no systematic data of which I'm
12 aware of.
13 DR. SEWARD: About transmission?
14 DR. BERGER: Yes.
15 DR. SEWARD: It's not a problem. It is
16 not a problem. We've stopped looking for it it's so
17 rare.
18 CHAIRMAN SIEGAL: Any other questions?
19 DR. FINNEGAN: This may be a really simple
20 way to look at things, but we're here today because
21 the protective level in the donor blood is dropping
22 from people who have been vaccinated. Do you not see
23 this as a potential public health problem down the
24 road?
25 DR. SEWARD: I was at the previous meeting

1 where some of these issues were discussed and my own
2 feeling is that, right now, the population is very
3 adequately protected and to the levels in IVIG from
4 vaccinated individuals will be adequate. I know
5 there's another issue with the testing and pass/fail
6 on the EIA test that's used for the lots which is a
7 separate issue. But right now, I wouldn't be worried
8 about the levels in IVIG.
9 Now 10 or 15 or 20 years from now, it
10 might be a different story depending on what happens
11 with that graph in Dr. LeBaron's paper. But right
12 now, vaccinated people are absolutely adequately
13 protected. There's no spread in this country. So I'm
14 not worried from a public health perspective for
15 today. Twenty years from now, perhaps, but we can
16 continue to monitor immunity levels in vaccinated
17 people.
18 Measles vaccine is just a phenomenal
19 vaccine. It was very, very effective and immunogenic.
20 We had a large mumps outbreak in this country last
21 year with 6,000 cases and I won't say the same for
22 mumps vaccine. But measles and rubella are just very,
23 very good vaccines.
24 But it doesn't mean, as I said. I
25 concluded by saying we need to continue to monitor.

1 But we see absolutely no evidence, epidemiologically,
2 that there is waning to susceptibility in any of the
3 vaccinated populations.
4 DR. SZYMANSKI: Would you in any phase
5 consider a third vaccination at some age, later age,
6 when levels are very low?
7 DR. SEWARD: Not unless we see waning to
8 susceptibility. I mean, we'll continue to watch very
9 closely. I think that's the big challenge with the
10 U.S. vaccination program now is the duration of
11 vaccine-induced immunity. We have the most mature
12 vaccine program in the world and absence of disease
13 doesn't mean absence of risk. We know the 30-year
14 olds out there, 10 to 15 percent of them, or 40-year
15 olds are susceptible. So we'll monitor very closely
16 vaccine-induced immunity and it would only be if it
17 wanes and we see the epidemiology changing with
18 outbreaks in vaccinated people like we saw with mumps
19 last year. Then we would consider changing vaccine
20 policy. There is no indication right now that we need
21 to.
22 CHAIRMAN SIEGAL: All right. If there are
23 no more questions, thank you very much and let's
24 proceed to Dr. William Moss who is going to talk about
25 measles infections and estimated protective titers in

1 primary immune deficiency diseases and potential
2 reemergence of epidemic measles in vaccinated
3 individuals, from Hopkins.
4 DR. MOSS: Thank you very much. I'm here
5 in part representing Dr. Dianne Griffin, who gave a
6 talk at the immunoglobulin workshop in April of this
7 year and will be giving a similar presentation. The
8 title on the agenda was not my title. So I hadn't
9 seen that title, to be honest, before.
10 But the questions regarding measles in the
11 immunocompromised hosts are a nice segue into what
12 I'll be talking about and because most of what we know
13 about measles in immunocompromised hosts is not in
14 children with primary immunodeficiency disorders, as a
15 number of people have already mentioned. I'm going to
16 use some other examples, particularly malnourished
17 children, HIV-infected children and studies in
18 immunosuppressed monkeys to provide some insight into
19 measles and immunocompromised hosts.
20 I'll also come back to some of the issues
21 that have been already touched upon, particularly this
22 magic number of 120, that we talked about a number of
23 times. I also want to just reiterate the point that
24 was made, but there have been no documented cases of
25 transmission of measles vaccine virus.

1 So let me just briefly run through measles
2 in the immunocompetent host and talk a little bit
3 about the normal immune responses and that will set us
4 up for talking about measles and the immunosuppressed
5 host. Measles has very characteristic clinical
6 features. It starts off with what I'll refer to as
7 the three Cs, cough, Coryza and conjunctivitis, then
8 early papoules that occur on the buckle mucosa called
9 Koplik spots. During this time, there is fever and
10 then the characteristic morbilliform rash that
11 typically starts on the head and neck and extends over
12 the entire body and that's typically when clinicians
13 will diagnose measles, though a very astute clinician
14 can diagnose it based on the presence of Koplik spots
15 and these are just some photographs, a little
16 difficult to see, but the characteristic morbilliform
17 rash on the left and this will be important because
18 we'll talk about different rashes that can occur in
19 the immunosuppressed host and then the child on the
20 right a little bit of conjunctivitis and crusty nasal
21 discharge.
22 And then on this picture again, it
23 projects a little. It doesn't project very well, but
24 there are small white papoules that are seen on the
25 buckle mucosa. Those are the Koplik spots that

1 proceed the rash. But what I want to point out on the
2 right side is that on that middle panel just
3 summarizes briefly the clinical manifestations we
4 talked about. But I wanted to just mention that the
5 virus is very active during the asymptomatic
6 incubation period before the onset of fever with
7 replicating, initially, in the upper respiratory tract
8 and spreading to the lymph nodes. Then there's a
9 generalized viremia and replication of measles virus
10 in many organs, including the skin.

11 In addition, there's also an intense
12 immune response and I'll come back to this, but
13 initial CD-4, primarily TH-1 type response, with
14 production of interferon gamma and a cytotoxic T cell
15 response that starts about the time of the rash and
16 you can also see that when the rash is beginning, the
17 level of virus replication decreases. So really the
18 rash is a manifestation of the host cellular immune
19 response and I'll come back to this. But there have
20 been a number of cases of confirmed measles
21 particularly in persons with AIDS without a rash, and
22 that makes sense understanding that the rash is a
23 manifestation of the immune response.

24 There's initial IGM antibody response
25 that's transient that lasts several weeks and then an

1 IGG response follows. It's initially an IGG Type 1
2 and then switches to an IGG Type 3 predominantly and
3 that's the titer, the protective antibody class that
4 we've been talking about.
5 The immune response of measles virus is
6 more complex than that. I just want to touch on it
7 briefly. There's as with all infections an early
8 innate immune response with Type 1 interferon. It
9 appears that wild type measles virus has evolved
10 mechanisms to inhibit the host interferon response
11 that are not seen in the attenuated vaccine response
12 and I should mention, although you all probably know
13 this, that the vaccine is a live attenuated vaccine
14 that requires replication in the host in order to
15 induce protective immune response.
16 Then there are the antibody responses we
17 talked about, the IGM and various subclasses of IGG
18 that are protective. There are also IGA responses and
19 it's not clear what role they play in protection from
20 disease at the mucosal surfaces. The cellular immune
21 responses are very complex. I talked about CD-4
22 responses, early Type 1 response and then that's
23 followed by a Type 2 response with characteristic
24 production of IL-4 and IL-5 and IL-13. There is also
25 prolonged increase in IL-10 production that may be

1 related to the immune suppression that follows
2 measles.
3 Measles is a strong inducer of immunologic
4 memory, particularly wild type measles. Some of the
5 classic epidemiologic studies of measles were done by
6 a Danish physician named Peter Panum in the mid 19th
7 century on the Faroe Islands where he observed where
8 there was an outbreak of measles that he was called on
9 to investigate. The prior outbreak was 65 years
10 earlier and no one who was live during that prior
11 outbreak got measles again, suggesting really life-
12 long immunity following wild type measles virus
13 infection. Dr. Seward talked a little about whether
14 that occurs after vaccine-induced immunity.
15 Measles is an immunosuppressive virus and
16 much of the mortality and morbidity from measles
17 results from secondary infection. So it's actually a
18 immunosuppressive virus in itself and these are just
19 some, I won't go through this in detail, potential
20 mechanisms by which measles virus has been suspected
21 or studies have suggested how measles virus may
22 suppress the immune system. It's unclear whether or
23 how much measles vaccine virus suppresses the immune
24 system. Some of these differences have been
25 documented following measles vaccination.

1 So measles and the immunocompromised host,
2 Bob Good several decades ago with others published a
3 paper that suggested that children with deficient
4 antibody production, with B cell deficiencies, would
5 have normal recovery from measles and would clear
6 measles virus, but would have limited protection from
7 reinfection because of the absence of antibody. But
8 it was really children with T cell deficiencies, with
9 deficient cellular immunity, who had delayed viral
10 clearance and progressive disease.
11 So one way, a common way of thinking about
12 immunity to measles, is what immune responses are
13 required to actually clear the virus once infection
14 has taken place and in children with impaired
15 clearance, there are kind of two broad clinical
16 pictures. One is a desquamating rash and I'll show
17 you a picture of that. That's been best characterized
18 in severely malnourished children who have deficits in
19 cellular immune function and then in people and
20 children and adults who are most severely immune
21 suppressed as a progression disease that can often
22 occur without a rash as I mentioned and with measles
23 virus replication particularly in the brain and in the
24 lungs.
25 And then in terms of protection, and I'll

1 come back and talk about the difference between
2 protection from clinical disease and we've already
3 touched on this and protection from actual infection,
4 the best correlative protection is the neutralizing
5 antibody titers that we've talked about.
6 I'm going to be presenting a little bit of
7 data using a rhesus macaque model. Obviously, monkeys
8 are the best animal model for studying measles and
9 there have been several studies I'll show you in which
10 the monkeys were immunosuppressed and then challenged
11 with wild type measles virus. But this is just to
12 show that rhesus macaques developed a characteristic
13 measles rash, a type of viremia that's very consistent
14 with what humans develop and measles also induced a
15 peripheral lymphopenia that develops that's shown here
16 that was also observed in macaques.
17 Sallie Permar, who was at Hopkins, but
18 then went onto Harvard and worked Norm Lepton's lab
19 did some studies where, first, they depleted monkey of
20 CD8 T cells and then challenged them with bilthoven
21 which is a wild type measles virus strain. On the
22 left side, you see log infected cells per 10^6
23 peripheral blood mononuclear cells in control animals
24 and then in CD8 depleted animals and I just want to
25 make a few points. So these animals were depleted CD8

1 T cells with monoclonal antibodies. They had higher
2 levels of measles virus and for a prolonged period of
3 time, but they all eventually cleared measles virus
4 and none of them developed a progressive fatal measles
5 virus infection.
6 They followed that up with an analogous
7 type of study, but instead of solely depleting CD8 T
8 cells, they depleted B cells as well using a
9 monoclonal antibody to CD-20 and let's just focus on
10 the right-hand side. This is using a real time PCR
11 assay. So you have a log scale quantitating measles
12 virus on the right side. The top is a control group.
13 The middle panel is our monkeys depleted of B cells.
14 So they won't have an antibody response and then the
15 bottom panel are monkeys depleted of both CD8 and B
16 cells and, consistent with the early observations in
17 humans, monkeys depleted of B cells had a normal
18 clinical course of measles. They didn't have
19 prolonged viremia or higher levels of viremia and they
20 had the disease progression similar to that of the
21 control group, whereas again the CD8-depleted monkeys
22 had a more prolonged viremia. So there was a delay in
23 clearance of measles virus.
24 Interestingly, some of the monkeys that
25 were CD8-depleted also developed a desquamating rash

1 and that's another type of rash that can develop in
2 immunosuppressed hosts, as I already mentioned and, I
3 won't go through this in detail, but on the right side
4 is a picture of the rash and you can see in that small
5 insert on C the desquamating characteristic of the
6 rash in the monkeys and then the histopathology in F
7 of that rash with inclusion bodies of measles virus
8 shown in the insert.
9 So in humans, what we know about in
10 children and adults who have immunodeficiencies and
11 fail to clear measles virus, there are two broad
12 category of disease that are frequently described, a
13 giant cell pneumonitis, measles caused syncytia
14 formation and a measles inclusion body encephalitis
15 and I'll come back to that. Often, as I've already
16 mentioned, there is no rash at the time of measles
17 virus infection and again, this has been best
18 described in HIV-infected children and adults. But
19 there is this progressive pulmonary or CNS disease and
20 in the absence of rash, this is a very difficult
21 diagnosis to make and really has to be suspected and
22 looked for.
23 The desquamating rash was first described
24 by David Morley who was working in Nigeria in the
25 1960s, and this is a little cartoon showing the

1 complications of measles particularly in severely
2 malnourished children and most children with measles
3 in sub-Saharan Africa die of secondary bacterial
4 pneumonia and diarrheal disease and then on the
5 bottom, he describes this characteristic desquamating
6 rash that occurred in severely malnourished children.
7 I primarily work in Zambia with measles, studying
8 measles in HIV-infected children and this is an HIV-
9 infected child with that desquamating rash that you
10 can see is peeling off this child's face.
11 There have been, and we've already alluded
12 to this, case reports, but no real extensive case
13 series of progressive measles virus infection
14 associated with various immune deficiencies both in
15 primary immune deficiencies, usually combined
16 deficiencies of T and B cells. There have been a few
17 small case reports, particularly one of a measles
18 inclusion body encephalitis, of a child in whom the
19 underlying immunodeficiency was not well
20 characterized. And then in addition, there have been
21 case reports, but again not a lot of experience in
22 part because the exposure has been low in the United
23 States of children with secondary immune deficiencies
24 related to malignancies or immunosuppressive therapy
25 in transplants of progressive measles disease. So we

1 don't have a lot of information on these groups of
2 children.
3 We have a little bit more in HIV-infected
4 children and I'll talk a little bit about that.
5 Measles in HIV-infected children was first, best
6 described by a report from the Centers for Disease
7 Control back in 1988, during that last big measles
8 outbreak that we've already talked about, where severe
9 and unusual measles was described in five HIV-infected
10 children. There were a number of case reports out of
11 that outbreak and about half of the children, half of
12 19 co-infected children in the United States, had
13 either an absent or some unusual type of rash with
14 measles. About three-fourths had pneumonitis and
15 about one-third of these children died of progressive
16 measles virus infection which is much higher case
17 fatality ratio than is otherwise seen.
18 There have been a few small reports of HIV
19 amongst children in Africa. This is just showing what
20 the measles giant cell pneumonitis looks like. It
21 forms some syncitia and you can see the staining for
22 measles virus nuclear protein in these cells.
23 We've conducted studies of measles in HIV-
24 infected children in Zambia and I just want to say
25 that during hospitalization, so this would be a

1 country with high prevalence of HIV and endemic
2 measles virus transmission, there was increased
3 mortality during hospitalization among HIV-infected
4 children. There was also increased mortality in
5 children who had a desquamating rash, suggesting again
6 that this is a marker of severe disease and perhaps
7 underlying immune defects.
8 We've also looked at the ability of HIV-
9 infected children to clear measles virus and this is
10 using an RT-PCR assay approximately one to two months
11 after rash onset and a higher proportion of HIV-
12 infected children failed to clear measles virus RNA
13 during this time period after measles. It's not clear
14 whether these children are still contagious, but this
15 indicates that they have failure to clear measles
16 virus.
17 I did want to mention that there's been
18 one report of fatal infection with measles vaccine
19 virus in a person with AIDS. This was a young man who
20 received a second dose of MMR. As part of the
21 regulations for a second dose that Dr. Seward talked
22 about, this young man had no rash after MMR
23 vaccination, presented 11 months later. Really at the
24 time of immunization, he had no clinical evidence of
25 severe immunosuppression although his CD-4 count was

1 very low. He had been previously vaccinated against
2 measles and he had a number of invasive procedures
3 that eventually identified measles vaccine virus in
4 his lung tissue and he died 15 months after MMR
5 vaccination and this one case actually helped shift
6 measles vaccination policy by excluding people with
7 severe immune suppression.

8 I mentioned briefly the neurologic disease
9 that can be due to measles virus in immunosuppressed
10 hosts. There are a number of different neurologic
11 diseases associated with measles. There is an
12 autoimmune demylinating condition that can occur
13 several weeks after. That's not an immunocompromised
14 host. But then there's this measles inclusion body
15 encephalitis where the actual measles virus
16 replication within the brain that occurs in
17 immunocompromised hosts and that has been described in
18 children with primary immune deficiencies as well as
19 persons with HIV/AIDS. And just briefly again, one
20 sees within brain tissue inclusion bodies and staining
21 for viral antigen.

22 As I've mentioned the best evidence is
23 that cellular immune responses are critical for
24 clearance of measles virus. There is some evidence,
25 though it's not strong evidence, that antibodies may

1 play, at least, assist the cellular immune arm in
2 clearing measles virus. There are some studies by Don
3 Forthal suggesting that antibody-dependent cellular
4 cytotoxicity is associated or correlates with
5 clearance of viremia. There is certainly evidence,
6 older evidence, that low antibody responses predict
7 poor outcome and some in vitro studies suggesting that
8 antibodies can down regulate intercellular virus
9 replication. So some evidence that antibodies play a
10 role in clearance.

11 But where antibodies are really critical
12 is in protection from disease and I think probably one
13 of the most important questions facing the committee,
14 for which I, unfortunately, don't have evidence for
15 is, what role the cellular immune arm is playing in
16 protection that might assist in a way the antibody
17 responses and either require higher or lower titers of
18 antibodies for protection.

19 The evidence that antibodies alone are
20 protective against measles come from numerous studies
21 showing that young infants with passively acquired
22 maternal antibodies are protected against disease.
23 Obviously, the passive administration of immune
24 globulin which this committee is considering and
25 really as we've talked about the best correlate is

1 this neutralizing antibody titer and I'll come back to
2 the 120.
3 Just to remind you, neutralizing
4 antibodies are primarily to the two surface
5 glycoprotein of measles virus and particularly
6 hemagglutinin which is the larger structure shown
7 there which is what binds to measles virus receptors
8 on host cells, human cells. There is also a fusion
9 protein on the surface and there's probably some
10 contribution of neutralizing antibodies to these.
11 So when one is measuring neutralizing
12 antibody titers using a plaque reduction
13 neutralization assay, one is primarily measuring
14 antibodies to the H protein. Just to show that, show
15 how those antibodies to different proteins vary in
16 relative amount, we'll just focus on the right-hand.
17 You can see antibodies to H there in the middle. Most
18 of the antibodies to measles virus are made to
19 internal protein, the nucleocapsid protein. So one
20 uses an ELISA assay to measure antibody titers, one is
21 primarily measuring antibodies to N rather than the
22 functional neutralizing antibody to H.
23 This is just evidence in a graphic form
24 from Neal Halsey showing declining levels of maternal
25 antibodies and an increasing incidence of measles and

1 showing just to reiterate the fact that passively
2 acquired antibodies from the mother can protect the
3 young infant and this might be one of the best ways to
4 try to get a handle on what are protective titers in
5 children who lack cellular immune responses to
6 measles, though these would be in otherwise normal
7 infants.
8 It's known too that these levels of
9 maternal antibody can inhibit response to vaccine and
10 this is one study from, again, Laurie Markowitz,
11 showing that seroconversion rates to the vaccine were
12 much higher in infants who had very low or no
13 neutralizing antibodies to measles virus and as I
14 mentioned before, in order to get a protective
15 response to the vaccine, the vaccine has to replicate
16 within the host and basically cause mild measles and
17 these maternal antibodies will neutralize that vaccine
18 virus and prevent the immune response.
19 So this is the data that each of the prior
20 speakers has alluded to, that magical 120 number, and
21 it was really a serendipitous discovery and I think
22 that explains partly why we have so few data about
23 what the protective titers are. There was a blood
24 donation program at Boston University and concurrently
25 a measles outbreak. So at the time of exposure to

1 measles virus there were blood products, serum,
2 available to test for neutralizing antibodies at the
3 time of exposure. So it was really kind of a unique
4 epidemiologic situation and the investigators were
5 clever enough to take advantage of it.
6 But as I think as a number of people have
7 suggested, this is not written in stone and it's the
8 best data we have on levels that protect and this is
9 protection from disease, protection from clinical
10 disease, this 120. But you can see the numbers of
11 individuals were small in the group with levels less
12 than 120. It was really the highest titer in the
13 college-aged students who developed measles was
14 exactly 120.
15 They did look at, as was already
16 mentioned, boosting antibody responses. So young
17 adults who boosted their antibody response, but didn't
18 have clinical disease presumably had a subclinical
19 infection but were protected against disease and this
20 is where that 152 comes from and again the number are
21 very small. But this is what we have, because that
22 kind of epidemiological circumstance has not been
23 repeated.
24 In Dianne Griffin's lab, they've done
25 studies with a number of -- these are DNA vaccines, so

1 very different vaccine construct that what's used in
2 people, but I just want to bring up again this issue
3 of protection from disease compared to protection from
4 infection and these are monkeys that got different
5 kind of constructs of DNA vaccines. But you can see
6 the neutralizing titers there and some monkeys,
7 particularly those with a titer of 135 or greater, had
8 evidence of viremia without rash. So they didn't have
9 sterilizing immunity and then those between three and
10 105 had a rash as well as viremia.

11 But I want to mention that titers below
12 120 although they may not protect against clinical
13 disease, they probably protect almost certainly
14 against severe disease. So there's an entity vaccine-
15 modified measles where children will get a milder form
16 of measles if they have some level of immune
17 protection but not enough to protect clinical disease.

18 And the vaccine itself, particularly the
19 first vaccine used in the United States, the Edmondson
20 B vaccine, actually induced fever and rash in 15
21 percent or so of children and immune globulin was
22 given concurrently with that often to modify that. So
23 this 120 may in the normal host certainly would
24 prevent severe disease.

25 But I think the critical question is what

1 the impact is of cellular immunity on these protective
2 titers and part of the problem is the inability to
3 really quantitate cellular immune responses in a good
4 way or at least in a way analogous to antibody titers
5 in children and certainly there are assays to measure
6 cellular immune responses, but there is not the same
7 threshold that's been identified.

8 In summary, clearance of measles virus is
9 dependent primarily on cellular immunity. Defects in
10 clearance are associated with unusual manifestations
11 of measles and those with the most severe
12 immunosuppression, they can have a progressive disease
13 without rash. Those with moderate immune suppression
14 may have a desquamating or unusual type of rash and
15 we've talked about this neutralizing antibody titer
16 being the best protection but the data is rather
17 limited on what those thresholds are.

18 And I'll just thank my colleagues, but
19 particularly Dianne Griffin for her help.

20 DR. BALLOW: If I may, I have several
21 questions for you. Thank you for that presentation.
22 It was really an excellent overview.

23 DR. MOSS: Thank you.

24 DR. BALLOW: You mentioned that in order
25 for the measles vaccine to be productive there has to

1 be replication of the virus.

2 DR. MOSS: Right.

3 DR. BALLOW: So we give a booster

4 immunization at preschool age. Correct?

5 DR. MOSS: Right. Well --

6 DR. BALLOW: And presumably they have

7 antibodies. So is the virus still able to replicate

8 and what's happening? Is it boosting up the cellular

9 immunity as well as the ambient response of the IGG?

10 DR. MOSS: The -- I may let Dr. Seward

11 respond. But I'll just say that the real reason for

12 the second dose is not a booster dose. It's not to

13 booster antibody titers. The reason for the second

14 dose is twofold and it's part of a measles -- the

15 second dose is critical to measles elimination, to

16 really interrupt measles virus transmission, so to

17 obtain a very high level of population immunity.

18 So the second dose is really to do two

19 things and I think more globally it's often referred

20 to as a second opportunity by WHO and it's to immunize

21 those children who never received the first dose to

22 provide an opportunity for those children and to

23 immunize those who don't respond to the first dose.

24 So at 12 months of age, it's 95 percent is kind of the

25 dogma, the percentage of children that respond. But

1 that leaves five percent of children aren't responding
2 to the first dose. So that second dose is to immunize
3 those five percent.
4 I don't think of the second dose as -- the
5 purpose behind it as boosting the antibody response.
6 DR. BALLOW: But there must be data
7 though.
8 DR. MOSS: There is some. So there is
9 some boosting and the amount of boosting will depend
10 upon, is a function of the pre-existing antibody
11 titer. So those who have had some waning of immunity,
12 you'll observe more boosting of the antibody response.
13 Those who have very high titers, you may not see an
14 increase in the antibody response with the second
15 dose.
16 DR. BALLOW: That makes sense. The second
17 question; with HIV children, do they take away the
18 recommendation to give MMR vaccine?
19 DR. MOSS: For HIV-infected children, it's
20 an interesting history because prior to the 1989 --
21 I'll talk about for the United States, because the WHO
22 recommendations have not always been consistent with
23 the or not consistent with the U.S. recommendations.
24 But prior to the 1989 outbreak of measles, people were
25 very concerned about giving a live, attenuated virus

1 to HIV-infected children. So a lot of those children
2 didn't get the vaccine.
3 Then when these severe cases were
4 described during late `80s and early `90s, there was
5 kind of this shift toward providing MMR. It was
6 recognized that it was very important to protect HIV-
7 infected children against measles. That case report
8 that I showed you actually changed the policy back.
9 So the current recommendations are not to give the MMR
10 vaccine to persons and particularly children with HIV
11 who are severely immunosuppressed, defined as a CD-4
12 percentage less than 15.
13 DR. BALLOW: Less than 15?
14 DR. MOSS: Less than 15.
15 DR. BALLOW: Wow. Okay and then the last
16 question to get back to patients with primary immune
17 deficiency, as we enjoy the day and engender some
18 conversation about now and what's going to happen over
19 the next 10 or 15 years, one wonders whether it would
20 be beneficial to give patients with antibody
21 deficiency, not T cell deficiency, but antibody
22 deficiency, even recognizing that some of those
23 patients like CVID may have some subtle T cell
24 abnormalities but nevertheless to give them MMR
25 vaccine to try to elicit or enhance their T cell

1 responses so that if there is an outbreak at least
2 they'll be able to clear the virus more readily.
3 DR. MOSS: Right.
4 DR. BALLOW: But at the same time, since
5 all these patients are IVIG, one wonders whether they
6 will be able to actually develop a T cell immune
7 response, given the fact that they have measles
8 antibody.
9 DR. MOSS: Right.
10 DR. BALLOW: I guess we don't know unless
11 we try it.
12 DR. MOSS: Right. That's a very
13 interesting question and the tools for measuring
14 measles virus specific T cell responses have just
15 really been developed and perfected over the past
16 couple years. Before people would do lympho-
17 proliferation-type assays but you can really do very
18 precise assays now. So I think we now have the tools
19 to begin to measure some of those responses.
20 There are a number of groups and Dianne
21 Griffin's group is one that are working on new measles
22 vaccines that are nonreplicating vaccines and not all
23 people in the measles world agree that that's a --
24 certainly as has been mentioned, the current measles
25 vaccine is highly effective and it's a great vaccine,

1 a very safe vaccine. And some people question the
2 need for a new measles vaccine, but that might be a
3 population where, if you could immunize with a non-
4 replicating vaccine, a DNA-based vaccine or there are
5 alpha virus-based vaccines, there is a whole array of
6 different types of vaccines that are development, that
7 might be a select population where that might be
8 useful for inducing T cell responses. Yes.
9 DR. DI BISCEGLIE: I have a question if I
10 may. Are there any antiviral agents effective against
11 measles virus that might be given to immune-deficient
12 -- I'm thinking of Ribavirin in particular.
13 DR. MOSS: Yes. Obviously, there have
14 been no large trials or studies, but there are case
15 reports of using a number of agents particularly
16 ribavirin is the most experience with and people feel
17 that -- or certainly that has been used in that
18 situation and some people have used it in combination
19 with alpha interferon.
20 CHAIRMAN SIEGAL: Thank you very much.
21 That was a nice talk. Next we'll hear from Toby Simon
22 from CSL Behring on measles antibody titers in plasma
23 donors.
24 DR. SIMON: Thank you. I'm very grateful
25 for the opportunity to be here on behalf of my

1 colleagues at CSL Behring and also speaking for our
2 industry group, PPTA. It was also a pleasure to work
3 with Dr. Scott and the group from FDA on the workshop
4 and to work on developing this issue for presentation
5 today.
6 I'll just set up the stage quickly. With
7 the information that you've already seen, in the pre-
8 vaccine era, there were approximately 500,000 cases
9 per year in the United States. In 2005, there were 66
10 confirmed cases, 34 from a single outbreak associated
11 with a traveler and that's the largest outbreak in the
12 U.S. since 1966. The current incidence is less than
13 one in a million.
14 The measles vaccine was introduced in
15 1963. By the 1970s, most states started requiring it
16 for school entry and that was pretty complete by the
17 1980s. And in 1989, the two-dose vaccine requirement
18 was phased in. In 2001, 96 percent of states required
19 two doses for school entry and the median coverage was
20 97 percent.
21 Our problem, as you have heard, is that
22 the antibody titers as quoted here from a text on
23 vaccines "elicited by vaccination do decline over time
24 as do those induced by natural infection and may
25 become undetectable." Vaccine-induced antibody titers

1 are typically lower than those induced by natural
2 infection. So as younger donors enter our donor
3 programs, they come in with lower titers than what we
4 had seen in our older donors.
5 And we have been measuring these titers in
6 our donors using the ELISA method for measles IGG.
7 The particular methodology that we'll be using in the
8 report today is from the Eddie Mac system,
9 manufactured by Diasorin with an internal calibrator
10 that we have developed using the WHO 66/202 standard.
11 The reporting range is 0.5 to 10 IU/mL and the
12 coefficient of variation goes from 2.7 to 14.7 percent
13 and that, unfortunately, is higher at lower
14 concentrations which means we lose sensitivity in
15 those donors who have very low values. We have
16 correlated this with in-process testing by our
17 manufacturer's assay aboard using the Dade-Behring
18 ELISA and it's a very high correlation of 0.95.
19 And this is the data that we showed at the
20 workshop, which shows that the donors depending on the
21 birth year as you see on the left side of the slide,
22 the donors who are older and then with the
23 introduction of the vaccine in 1963, which is that
24 inflection point before it goes down, we get to very
25 low levels with universal employment of the vaccine

1 below 0.5. Many of the donors will actually have a
2 0.0 level on this test and so we assign them a low
3 value of 0.1 to get the mean.
4 This is based on a random sample of 4,356
5 source plasma donors conducted in three snapshots,
6 March of 2006, December of 2006 and then March of
7 2007. So the aggregate picture here is of falling
8 levels of titers in the donor population and then as
9 young donors replace the older donors we see a falling
10 or decline in those titers in the product made from
11 their donations. Based on the current age profile of
12 our donors, the group that has greater than 1.5 as the
13 titer shown on the left of the slide constitutes about
14 20 percent of our source plasma donors at the present
15 time. By 2010, if the age profile remains the same,
16 they will constitute less than 15 percent of our
17 donors. So we're rapidly moving to plasma that will
18 reflect our current younger vaccinated donors with the
19 lower titer.
20 And that gives us the problem that we face
21 in terms of making product with a higher titer that's
22 currently required. Now about 20 percent of the
23 plasma product in the United States comes from normal
24 recovered plasma obtained from whole blood donations
25 at community blood centers and that does have a higher

1 level because of more older donors. However, that
2 percentage is declining as more and more blood centers
3 go to collecting red cells by apheresis. That is
4 they'll collect two units of red cells and no plasma.
5 So the amount of recovered plasma available is
6 declining.
7 Now you might ask why aren't we recruiting
8 more older donors and we would like to do that.
9 However, source plasma donation is relatively
10 physically demanding. It's about an hour and a half
11 process and our donors can donate twice a week. The
12 typical donor donates four or five times a month in
13 contrast to the normal whole blood donor who donates
14 once or twice a year or up to about six times a year.
15 So it's a more physically demanding process and what
16 we find is as people age they tend to leave the donor
17 pool and then younger donors come in and, of course,
18 one of our most successful recruiting areas is among
19 students. I think it will be with great difficulty
20 that we will make very significant change in that age
21 profile over time.
22 When we presented this data in the
23 workshop, Dr. Scott and Dr. Epstein asked that we go
24 back and measure titers using the neutralization assay
25 and the reason for this is twofold. First, that is

1 the assay that we use for the product release. So we
2 do have a disconnect here, this assay that we're using
3 to screen donors versus the viral neutralization or
4 functional assay that we use for product release. In
5 addition, we do have the problem of the very low
6 levels in donors and the doctors pointed out at the
7 workshop that they do get measurable levels in
8 individuals who have been vaccinated of about 1 IU/mL
9 using the neutralization assay.
10 So for this reason, we conducted an
11 additional fourth snapshot of our donors on June 20,
12 2007 in order to compare the enzyme immune assay with
13 the viral neutralization assay and we set this up
14 using our statistician's advice on how to conduct
15 mini-pools. The neutralization assay is much more
16 technically demanding than is the EIA which is the
17 reason we don't use it to screen donors. It's more
18 difficult to perform. It's performed on tissue
19 culture systems. It's more expensive to perform and
20 therefore, in order to practically do this, we needed
21 to create mini-pools.
22 So this is a snapshot actually of 520
23 donors based on the statistician's advice of how many
24 donors to have in each age group, based on the data
25 that we had previously obtained. And then on each

1 group, we sampled a certain amount for the mini-pool.
2 So in the older age groups we were sampling one in
3 three or one in five for the mini-pool and the younger
4 age groups one in ten to one in eleven. We
5 constituted a mini-pool for each of the age groups and
6 then we took five aliquots from each of the minipools
7 and sent them to the laboratory in Bern, Switzerland
8 that did the viral neutralization functional assay.
9 That assay is calibrated against the third WHO
10 standard 21 IU/mL of anti-measles activity. So it
11 gives a different measurement than the EIA.
12 I'll proceed now to show you that data and
13 this graph shows the five datapoints, one from each of
14 the aliquots for each of the age groups based on birth
15 year and for those individuals born before 1962, the
16 first two groups on the left, you can see a relatively
17 high level of approximately 4 IU/mL. Then the next
18 group, during the years when the vaccine was first
19 introduced, individuals born in 1963 to `67, a reduced
20 level, but still higher than the younger individuals
21 born after the vaccine had been completely introduced
22 in the United States from 1968 on. Pretty tight `68
23 to `72 and then the aliquots tend to vary a little bit
24 more, but still fairly consistent levels of between 1
25 and 2 IU/mL for the younger donors compared to 2.5 in

1 the individuals from that period when the vaccine was
2 introduced and then the higher levels of around 4
3 IU/mL in the older donors.
4 And then this slide we've put the data
5 from that one snapshot in June of 2007 for both the
6 EIA assay and the viral neutralization. The viral
7 neutralization are the higher numbers shown in red and
8 with the one standard deviation above and below the
9 mean shown on the graph they are consistently higher
10 and the statisticians tell us that that is consistent
11 and that the difference is, of course, greater in
12 measurable units at the higher levels than it is at
13 the lower levels. So this data does give us more
14 confidence in the younger individuals who have the
15 lower levels of antibody.
16 And for the ELISA test, we have shown both
17 the minipools that we measured by ELISA, comparable to
18 the minipools that were measured by viral
19 neutralization, plus all the individual units,
20 individual samples, that were measured on the ELISA
21 assay as well, and those values are quite close, and a
22 very consistent picture emerges. So individuals born
23 before 1963, before the introduction of the vaccine on
24 the ELISA still have a measurement of around two IU,
25 on the functional assay about four IU. That falls on

1 individuals born between 1963 and 1967 to about two to
2 three IU on the viral neutralization assay, about one
3 on the ELISA, and then below one on the ELISA for the
4 younger individuals, and slightly above one, about one
5 and a half, for the younger individuals on the
6 functional assay. So what you see on the right will
7 be the donor pool that will emerge as time goes on.
8 And to show you the impact on this, we've
9 created this histogram from the May 2006 measles
10 snapshot using the EIA. If you look to the right,
11 that would be the percentage of individuals that are
12 below 10 IU/mL. And then as you move to the left, we
13 go to lower levels. So if you focus at about two, two
14 and a half IU/mL, you can see among what we call the
15 senior donors, the individuals born before the
16 introduction of the vaccine, that about 60 percent of
17 them, or about half, will be below this level, and
18 about half will be above the level.
19 If you look at our junior or younger
20 donors, you can see that 90 percent of them will be
21 below that level, so would not be able to constitute a
22 pool of around two to two and a half IU/mL, which is
23 what we calculate we would need to reach the current
24 CBER standard. And as you can see, the total donors
25 are beginning to approximate the curve that we have

1 shown for the younger donors.
2 So the message that we're trying to give
3 you is that the donor pool is moving over time to
4 represent the vaccinated population with the lower
5 level of antibodies that will, in turn, be reflected
6 in the product, making it more and more difficult for
7 us to produce product to meet the current CBER
8 requirement for release.
9 Now the next obvious question is, why
10 don't we go ahead and immunize donors, because many of
11 you may know that plasma centers are capable of doing
12 this, and we do this for several products. This was
13 analyzed by one of my medical colleagues, who was with
14 the organization before I was, who looked at 2005 as
15 the problem started to become acute, whether an
16 immunization program was practical, and concluded that
17 it was not.
18 First, I think we have what I have termed
19 here the "ethical issue." If there's no clear patient
20 benefit to offset the donor risks, then we have a
21 problem putting donors through the discomfort and
22 risks of the immunization. And I contrast this to our
23 rabies program. In other words, what we heard at the
24 workshop from the clinicians who treat patients who
25 are immunodeficient is that measles is not a

1 significant clinical problem, and that we could not
2 tell donors that participating in one of these
3 immunization programs was making a difference in
4 either quality or quantity of life for the patients.
5 By contrast, if one of you were to be
6 bitten by rapid animal, the injection of a rabies
7 immunoglobulin would likely be lifesaving for you. So
8 we can certainly tell our donors to whom we give the
9 rabies vaccine that we are producing a product that is
10 likely to save human lives. So I think that is one
11 thing to keep in mind.
12 Another very practical point is that the
13 measles vaccine is constituted with live attenuated
14 virus, and we do not conduct, at the present time,
15 vaccination programs in our centers with live
16 attenuated vaccine, and have some issues doing so.
17 The virus replicates in the body for six weeks, so
18 there would be issues in drawing those donors while
19 they have a replicating virus, particularly for an
20 immunoglobulin product for that virus.
21 The side effects are slightly higher with
22 the measles vaccine than with some of the other
23 vaccines that we use, and the handling and management
24 of the vaccine is more complex than is the case with
25 our other programs. The vaccine has to be protected

1 from light, it has to be shipped and maintained at
2 refrigerated temperatures, and while these may seem
3 minimal for clinics and hospitals, for a busy donor
4 center, it creates more complexity from the program
5 than our other vaccination programs do.
6 And importantly, in our discussions at
7 that time with the experts from Merck who manufacture
8 the vaccine, there was significant uncertainty about
9 the levels that we would achieve in order to make a
10 product that would have adequate antibody. Their
11 estimate was that 25 to 50 percent of the individuals
12 would boost to the high levels that we were looking
13 at, and there was a question about how long that would
14 be maintained, and as has already come up in the
15 discussion, there was question about the effectiveness
16 of the second dose in helping with that. So we have
17 concluded that an immunization program is not the way
18 to go here in order to create a more effective
19 product.
20 It was brought up in the workshop of, why
21 don't we seek out individuals who are vaccinated, and
22 the couple of instances were brought up, for example,
23 military recruits who are frequently vaccinated, and
24 further discussions with the military, and I realize
25 we have an expert that can amplify on it here today,

1 indicates that they generally get the vaccinations at
2 the end of their basic training, shortly before
3 they're shipped out, and as you know, many of them now
4 are being deployed to foreign locations, and it's
5 questionable whether individuals preparing for combat
6 would want to enter a plasma apheresis program at that
7 time.

8 Health care workers were also suggested.
9 One of the speakers from Johns Hopkins said that
10 hospital immunizes health care workers if they have
11 low immunization levels, but that is not the common
12 practice in the United States. In general,
13 individuals who go to work for hospitals and say that
14 they have been vaccinated are not further tested.
15 Individuals planning international travel would
16 obviously be going off overseas in the near future.
17 So we don't believe that there are, on a practical
18 level, populations available who are being vaccinated
19 whom we could bring into our plasma apheresis
20 programs.

21 Therefore in summary, falling measles
22 titers are anticipated over time in normal donors.
23 It's about a nine percent drop per year in recovered
24 plasma, perhaps a little bit higher in source plasma.
25 It's increased when we have times of significant

1 growth, when we're bringing in more younger donors,
2 and we have verified that by snapshot data,
3 particularly in our source plasma donors on four
4 different occasions in the last year and a half.
5 Reductions in the plasma titers currently
6 being seen will make it very difficult for us to
7 achieve product specifications in the future, and it's
8 already creating some difficulty currently.
9 Immunization programs pose significant issues, and are
10 not seen by us as a solution to the problem.
11 And therefore, we believe that measles
12 antibody specifications for the immunoglobulin
13 products need to be reconsidered, as has been done by
14 the Agency, and we certainly would support movement to
15 the lower standard that's been recommended, and I
16 think based on the data from the donors, and I think
17 some of the data that you're going to hear from my
18 colleague who has data on the patient side, it might
19 be possible to even move to a slightly lower level for
20 the specifications, as well.
21 This presentation does represent the
22 efforts of a global group at CSL Behring. The
23 serology work was done in our lab in Knoxville,
24 Tennessee. I thank Robin Jenness, Connie Farrar for
25 that work. Nancy Danvers organized that, and the June

snapshot, the viral neutralization assays were done in our laboratory in Bern, Switzerland. Peter Bailloid and Marian Kuehne were responsible for those measurements. The statistical analysis was referred to our chief economist at our headquarters in Melbourne, Australia, Sam Lovick, who brought in a statistician, John Small, who helped us, who works in New Zealand. I also thank Jonathan Knowles and Gordon Naylor from our executive group for helping with the presentation.

CHAIRMAN SIEGAL: Thank you, Dr. Simon. Are there any questions for Dr. Simon?

DR. SZYMANSKI: I just wonder what effect the multiple donations have at the titer level. Do they go down in the young donors, and what about the older donors who are naturally immunized by natural virus? Do they go down, or is there any difference? Do you understand?

DR. SIMON: Yes. Of course, with the snapshots we have newer and older donors all included at a given point in time. All the protein levels are subject to decline over time, and donors, depending on their frequency of donation, we do monitor this every four months. I don't actually monitor the total protein at each donation using a refractometer. We

1 use the serum protein electrophoresis every four
2 months, and individuals are rested when their protein
3 levels fall below a certain level. But there is an
4 element of decline involved in frequent serial
5 donations.
6 DR. SZYMANSKI: But also the measles
7 titers. Right?
8 DR. SIMON: Well, all proteins.
9 DR. SZYMANSKI: Yes. All proteins.
10 DR. SIMON: All the immunoglobulins are
11 subjected.
12 DR. SZYMANSKI: Do you think they go the
13 same way?
14 DR. SIMON: Yes. I think they -- our data
15 indicates they all decline pretty much the same.
16 DR. SZYMANSKI: Thank you.
17 DR. GLYNN: Could you please quantify a
18 little bit more? You're saying, if we do not do
19 anything, if nothing is changed, what is going to be
20 the impact on the amount, the supply, of the IGG
21 products, I guess? I have a hard time understanding.
22 It's going to be difficult, but is it going to be
23 possible, or is it going to be impossible, and it's
24 going to be going down by 10 percent, 20 percent? I
25 mean, can you quantify?

1 DR. SIMON: I think maybe one of the
2 industry speakers on the product side after me,
3 perhaps, could do a better job of quantifying that.
4 Perhaps Don Baker could do that. But what will happen
5 over time is that more and more lots will fail the
6 specification, and if they can't be released, then
7 they will be unavailable for product for patients who
8 need the product. So the exact quantification is
9 difficult. Obviously, our product people do
10 everything they possibly can to mix the product to
11 meet the specifications, but we've been seeing
12 increasing difficulties in the last couple of years,
13 which was what caused this whole subject to come up
14 for discussion, why the FDA organized and included it
15 in the workshop, and have brought the question today.
16 So more and more lots will fail over time, and that
17 will be progressive problem.
18 DR. GLYNN: And I guess you asked the same
19 question before, but how many right now are -- what's
20 the failure rate right now, I guess?
21 DR. SIMON: I think the product side would
22 have to answer that. I don't have a specific number
23 on that right now.
24 DR. KATZ: Toby, it looks to me like
25 you're kind of approaching the asymptote now that I'm

1 actually surprised that 20 percent of the donors were
2 from that higher titer age cohort. I couldn't
3 tolerate plasma apheresis, and I'm just a kid. So it
4 looks like most of the impacts been seen in the
5 titers, if I'm looking at the histogram that you
6 showed correctly.

7 DR. SIMON: Yes. We try to do what we can
8 to make up the product and to enrich it with the older
9 donors to the extent possible. But it's simply a
10 progressive problem. They constitute, as I said,
11 about 20 percent right now. In 2010, approximately 15
12 percent, by 2025, zero percent. We have a 65 age
13 limit. So you can see it simply becoming progressive,
14 and I think it became a big problem as this group
15 entered their 40s in the last few years, and that's
16 when we began to see it.

17 CHAIRMAN SIEGAL: Thank you very much.
18 The next speaker will be Don Baker from Baxter
19 Healthcare, measles antibody levels over time in
20 licensed product, and patients with primary
21 immunodeficiency diseases.

22 DR. BAKER: Okay. We've had a lot of
23 discussion so far today, and I bet if I turn this --
24 is this mike on? I can't tell.

25 We've had a lot of discussion today about

1 the potential for decreasing measles antibody titer in
2 final products, and now I'm actually going to show you
3 some data on decrease over time. Longitudinal studies
4 are conceptionally one of the most simply studies you
5 can do. You just study a variable over time.
6 However, everyone knows that, despite their simplicity
7 in concept, they are tremendously difficult in
8 actually carrying out.

9 And what this study today is going to do
10 is, we're going to examine the change in the measles
11 antibody titer and Gammagard S/D IGIV for the period
12 January 1997 through June 2007. This is a product
13 that has been in continuous production at Baxter since
14 1994. The reason I didn't go back to 1994 is because
15 I didn't have the data in electronic format that
16 allowed me to easily recover it for the time since
17 1994.

18 Now, Gammagard is produced from two plasma
19 flavors, our source plasma donors, these are apheresis
20 donors, and this is the demographics of our source
21 plasma donors. And as you can see, the cohort that are
22 currently naturally immunized to measles is somewhere
23 probably south of 20 percent of our total donors.

24 I didn't have the same demographic data
25 for our recovered plasma donors. These are the donors

1 where the plasma is collected and recovered from a
2 whole plasma donation. This data I got from the Red
3 Cross. However, you can see obviously the same
4 general decline in the older donors with time. I
5 would estimate that the recovered plasma donors,
6 there's probably about -- the prevalence of this, as
7 Toby put it, the senior donors, is probably about
8 twice what it is in our source plasma donors. So if
9 we have somewhat less than 20 percent in our source
10 plasma donors, who are naturally infected with
11 measles, there's something little less than 40 percent
12 in the recovered plasma donors. But again, time will
13 gradually result in a total reduction of these
14 naturally infected individuals.
15 Okay. What do we assume in a longitudinal
16 study? We are assuming that the only thing that is
17 changing is the percentage of donors that were
18 naturally infected with measles. In terms of the
19 other potentially confounding variables, the assay, we
20 have used the hemagglutinin inhibition assay
21 continuously to test the measles antibody titer in our
22 final product. There has been no change in the assay.
23 In the assay site, all of these were performed at our
24 plant in LeSiens, Belgium, and I would dare say, given
25 the stability of the European work force, probably no

1 change in the people actually conducting the assay.
2 The standard has been the same, the CBER
3 reference, there's no change there. The process, we
4 have obviously tweaked the process over the last ten
5 years. However, I did go back and take a look at the
6 significant process changes. Obviously, all of these
7 were evaluated at the time to not impact the product,
8 and in going back over them, I would conclude with
9 that original evaluation. I don't see that there's
10 any reasonable likelihood that any of the process
11 changes would have impacted the measles antibody
12 titer.
13 And the donors. There has been no change
14 there. The majority of donors over time on the source
15 side were from our Baxter Source Centers, and we used
16 ARC recovered plasma. So by in large, the donor
17 screening questions, the donor testing, the donor
18 selection criteria, there have been minor changes over
19 this ten year period, but again, nothing that I think
20 would impact the demographics or the measles titer.
21 This is just some selected characteristics
22 of Gammagard S/D, just for those of you that may not
23 be familiar with the product.
24 Okay. So what do we see? This is the
25 source plasma product. As you can see, the

1 specification is 0.2 relative to the NIH 176 reference
2 standard, and for those of you that are baffled by
3 numbers, why do you see 0.2 as opposed to 0.6? The
4 0.2 is the adjustment for protein concentration. This
5 is a five percent protein concentration, IGIV
6 concentration. The reference standard is 16.5
7 percent, I think. So the 0.2 is an adjustment for the
8 protein concentration.
9 As you can see visually, there appears to
10 be a decline in titer. If you look at the trend, you
11 do see a more or less consistent trend, or the rolling
12 average, again, a consistent trend downward over time.
13 The situation with recovered plasma,
14 again, is somewhat similar, and exactly what you would
15 expect given that the percentage of donors is older.
16 The older donors are more represented in the recovered
17 plasma. So there the titers are somewhat higher. But
18 again, the same trend decline over time, and the same
19 trend in decline in the rolling average.
20 So, the data from the longitudinal study
21 does support the hypothesis. The decline of donors
22 with a history of natural measles infection is leading
23 to a decrease in the titer of antibody measles virus,
24 and absent a change in specification for measles
25 antibody or any mitigating step, we will have IGIV

1 lots that will begin to fail the measles titer
2 requirement.
3 Now there was a question from one of the
4 committee members about how many lots are we losing.
5 The fact is that right now we don't lose any lots,
6 because the measles antibody titer is not required in
7 Europe. So lots that don't meet the measles antibody
8 titer we redirect to European or other distributions.
9 So right now, we're not losing any.
10 However, the issue is, for our company,
11 for example, the vast majority of this product is
12 distributed in the United States. So were we to
13 continue to divert product to Europe, obviously the
14 American consumer would, a patient would lose product.
15 Given the, I would say, fine balance between IGIV
16 supply and IGIV demand in this country, then we would
17 begin to lose product for distribution in the United
18 States.
19 Okay. That was it.
20 CHAIRMAN SIEGAL: Thank you. So we have
21 time for a couple of questions.
22 DR. COLVIN: I'm curious as to what is the
23 measles incidence in Europe?
24 DR. BAKER: I don't know.
25 DR. COLVIN: Because I'm assuming, based

1 on what we've heard before, it's a bit higher than it
2 is in the U.S.
3 DR. BAKER: It is higher than in the U.S.
4 DR. COLVIN: So in other words, I'm just
5 throwing something ethical out at you for a second.
6 So you're saying that when the measles titer is lower,
7 perhaps not reaching the level that people who have an
8 immunodeficiency might need to, in fact, prevent
9 infection with the virus, you're sending now this
10 product to try to protect people from infections in a
11 place where the incidence of this infection is
12 actually higher than it is here.
13 DR. BAKER: You know, there's two
14 responses to that. Number one, the European community
15 and the regulators in the European community have
16 taken a different perspective on measles antibody
17 titer. They feel that the titer that we have in the
18 product is adequately protected. So that's a
19 difference in regulatory view, and I'm certainly not
20 going to get into that right now.
21 Secondarily again, we have not seen, in
22 the primary immunodeficient patient population in
23 Europe, any cases of measles infection, either. So
24 that would suggest that the titer in the product
25 distributed in Europe is adequate for protection.

1 DR. COLVIN: Or it could be that most of
2 the time they're getting European source plasma that
3 actually has a much higher titer because it has more
4 naturally infected patients donating.
5 DR. BAKER: Fair enough.
6 CHAIRMAN SIEGAL: Anybody else? Okay.
7 Very good. Thank you very much. Now Othmar Zenker,
8 M.D., from Behring.
9 DR. ZENKER: Good afternoon. I am
10 representing CSL Behring. I'm head clinical research
11 in Bern Switzerland. So I'm coming from Europe. The
12 measles incidence in Europe is definitely higher, I
13 think, mainly due to less vaccinations. So the
14 vaccination program is not as good as here in the
15 United States. But I would like to talk about measle
16 antibody titers in primary immunodeficiency patients.
17 A short introduction. I think this is all
18 repetition. We have heard this this afternoon.
19 Falling measles titers are anticipated over time in
20 normal donors. The measles antibody titers serve as a
21 potency test for immunoglobulin lot release, with a
22 cutoff level of 0.6 times the CBER standard. We've
23 heard a lot about the history of this cutoff level in
24 the previous talks. This should usually not lead to
25 any issues. But here, one has to think about, is the

1 lower measles titer that will come into the product
2 into the future. Can patients be protected against
3 measles?
4 If there are more and more lots that will
5 not fulfill the current cutoff level, there is an
6 increase of immunoglobulin shortage.
7 Now back to the patients. The titers for
8 immunocompetent persons that are protective are known.
9 This is 0.12 IU/mL. This has been associated with a
10 protection against the clinical measles disease in
11 several outbreak studies. We mentioned a study by Dr.
12 Chen published in 1990.
13 Currently, there seems to be no concern
14 for primary immunodeficiency patients with respect of
15 measles. Even in Europe, where there is currently an
16 outbreak in Switzerland, and also a smaller outbreak
17 in Germany, we have not heard from any case that our
18 patients are affected on that, and this was also, I
19 think, discussed intensively in the workshop in April.
20 Nevertheless, the accepted protective titer for
21 primary immunodeficiency patients is not known.
22 What we did is we used retention samples
23 from two of our clinical studies and tested these
24 samples at the trough levels in functional assay and
25 with ELISA. This obtained us results on anti measles

1 trough levels after subcutaneous and intravenous
2 immunoglobulin treatment in PIDD patients.
3 These are the methods we have used for the
4 ELISA. We used a commercial kit, and calibrated it
5 with in-house plasma standards against the 3rd WHO
6 standard. The neutralization assay is the assay we
7 use normally for a lot release, and we measure the
8 measles antibody in relation to the reference
9 immunoglobulin in Lot 176, and we converted these into
10 units per mL by using a factor of 2.54 for a one
11 percent immunoglobulin, as published by Dr. O'Day last
12 year.
13 So now to the clinical studies. The first
14 one is a subcutaneous study. We have chosen 20
15 subjects with available retention samples, analyzed
16 them by the neutralization assay, and in addition, 60
17 samples by ELISA. The demographic data of these
18 patients are typical for primary immunodeficiency
19 patients, as shown here with respect to IGG trough
20 level, and also the weekly subcutaneous dose. The
21 treatment was given every week, and for this analysis,
22 we have calculated the anti-measles specific dose in
23 units per kilogram per week by using the lot release
24 test.
25 As a lot could have been changed during

1 this study, so a patient could have been treated with
2 several lots. Even just prior to the drawing of the
3 samples, we took the four last infusions into
4 consideration, the four infusions that were given
5 prior to the trough level sampling, and used the mean
6 of these values. This takes into consideration the
7 half-life of three to four weeks of the
8 immunoglobulin, so that we have no carryover, or less
9 carryover effect from different lots.
10 Here you see the results of the dose
11 response in the neutralization assay. On the X axis,
12 we have drawn the anti-measles specific dose, and on
13 the Y axis, the anti-measles titer. At 0.12, we have
14 drawn a line which represents the minimum protective
15 level in healthy patients, not to develop measles
16 disease. It's obvious that, here in this study, all
17 patients are well protected. There was no single
18 patient that had an anti-measles titer below one
19 IU/mL. The mean titer in this patient population is
20 3.17 IU/mL. So I would say at least two to three
21 times higher than the usual donors, as shown
22 previously by my colleague. Just for your
23 information, this is a graph that shows the IGG trough
24 levels, and the anti-measles titer. As expected,
25 there is also a correlation between the dose and the

1 trough levels.

2 Now to our second study, the results after
3 the intravenous infusion. Again, we have chosen
4 retention samples here, 53 subjects, 58 of the samples
5 were analyzed by neutralization assay, and 140 samples
6 by ELISA. As you can see from the numbers, we have
7 some repeated measurements in some of the patients.
8 Again, the demographic data are typical for primary
9 immunodeficiency patients. Here the treatment was
10 given every three to four weeks. In this case, the
11 dose was the dose of the three weekly treated patients
12 were intercollated to monthly dose so that we can
13 compare the three and the four weekly dosing groups.

14 Again, to avoid any carryover effect of
15 different lots, we have chosen here for this study
16 samples only if the same lot was given on three
17 consecutive infusions prior to the sampling. Here you
18 can see the result of the neutralization test assay.
19 Again, all patients are protected. They were well
20 above the 0.12 cutoff level.

21 The mean titer here is 2.98 units per mL.
22 When you compare these results between the intravenous
23 and the subcutaneous administration route, there seems
24 to be a higher anti-measles titer during subcutaneous
25 treatment. This is not unexpected. I think we have

1 just discussed previously that the difference between
2 the intravenous and the subcutaneous administration
3 route is that, by the intravenous route, we have a
4 high trough level and a somewhat lower -- a high peak
5 level, sorry -- and a somewhat lower trough level than
6 compared to subcutaneous administration.
7 In the following, I will present to you a
8 simulation, a trough level simulation. We have the
9 important question "how do the previous shown results
10 translate into trough levels when we are using a lot
11 with a lower anti-measles titer than given in this
12 study?" For that, we had to do some assumptions.
13 The first assumption is that we use a
14 hypothetical lot with a potency of 0.3 times the CBER
15 Standard Lot 176. We calculated the dose of anti-
16 measles antibody given to the patient according to
17 this hypothetical lot under the assumption of a linear
18 dose titer correlation. We did not take into
19 consideration that some of the patients would probably
20 have some endogenous anti-measles antibody titer. So
21 in our view, this is a very conservative approach.
22 We did a simple mathematical model, and I
23 will show you now the results. Or I will show you
24 graphically how we did it. You see the red line. For
25 one of these patients, this is the patient 1010. He

1 had an anti measles titer of a little bit less than
2 one in the retention sample. We drew the line through
3 the zero calculated, the hypothetical dose. With a
4 lot of 0.3 times the CBER standard, here this is
5 approximately 30 units per kg per month, and so now
6 that, with this interpolation, the patient would have
7 at least an anti-measles titer of 0.15.
8 So we did this with all the patients, with
9 all the dots you see here in this graph, except of
10 one. We had to exclude one patient where we saw no
11 dose trough level correlation in the ELISA test. Here
12 you can see that, even with a higher dose, the patient
13 showed no increase in the trough level. Therefore we
14 have excluded this patient from the following chart.
15 So this is the result of this simulation.
16 Again, all the patients would be protected. They
17 would have shown a trough level that is above the
18 0.12. The difference between the cutoff line and the
19 calculated numbers is not so high as in the real
20 samples that should be considered. But once again, we
21 have to mention that this is a conservative approach
22 as the endogenous production of anti-measles
23 immunoglobulin was not taken into consideration.
24 So let's summarize. All the tested
25 samples were well above the protective level of 0.12

1 unit per mL. Treatment with subcutaneous
2 immunoglobulin results in a higher trough level than
3 intravenous immunoglobulin. Three or four weekly IGIV
4 treatments with product under the current
5 specification of trough levels is far above the
6 protective titer of 0.12. Even a hypothetical lot
7 with a potency of 0.3 times the CBER Lot 176 would be
8 sufficient to protect patients in the study, as shown
9 by the linear interpolation.

10 The FDA has proposed to lower the cutoff
11 level to 0.48 times the CBER lot standard. With this
12 data, this cutoff level -- or it could be taken into
13 consideration to lower this level of 0.48 even more.
14 So the data show that patients are protected with a
15 lot of 0.3.

16 These are my acknowledgments. Thank you.

17 CHAIRMAN SIEGAL: Okay. Thank you very
18 much, Dr. Zenker. Are there questions for Dr. Zenker?

19 DR. EPSTEIN: First, thank you very much.
20 These are the first data that we've seen on trough
21 levels in primary immunodeficient patient, so it's
22 very much appreciated.

23 My question is about the methods for
24 estimating administered dose. Did you base the
25 calculation of administered dose in a patient on the

1 actual known content of the product lots administered,
2 or did you simply assume that they were at 0.6 times
3 CBER standard? Because in reality, many of those lots
4 might have been much higher than 0.6 times CBER
5 standard, and then you would have had an incorrect
6 extrapolation for a lower potency.

7 DR. ZENKER: No, we have used the actual
8 dose --

9 DR. EPSTEIN: The actual dose.

10 DR. ZENKER: -- that were given in the
11 analysis.

12 DR. EPSTEIN: Okay.

13 DR. BALLOW: On the patients that were
14 receiving immunoglobulin by the intravenous route, I
15 noticed your trough levels -- I think that was a
16 trough level. It was like 971 mg/deciliter. Was that
17 what I saw?

18 DR. ZENKER: The average trough level, the
19 immunoglobulin trough level?

20 DR. BALLOW: Yes.

21 DR. ZENKER: The average trough level was
22 970, yes.

23 DR. BALLOW: Yes. I mean, that's
24 extraordinary. That's much higher than many of our
25 patients achieve unless we infuse above 700 millirems

1 per kilo. So in the real world, I know that was part
2 of a study, but in the real world, I mean those are
3 trough levels much higher. So I'm a little bit
4 worried about using some of the data, given that high
5 of a trough level, because we just don't see that in
6 our patients.
7 DR. ZENKER: So these were the data from a
8 clinical study which was performed mainly in the
9 United States. So these are --
10 DR. BALLOW: No, I understand that.
11 DR. ZENKER: -- these are reflecting the
12 treatment in this clinical study in the United States.
13 CHAIRMAN SIEGAL: Anybody else? Dr.
14 Szymanski.
15 DR. SZYMANSKI: I have a question for you.
16 Now, when measles is so rare, and so what do you
17 think? Is it necessary to protect these
18 immunocompetent individuals all the time, so that they
19 will all the time have good titers, anti-measles
20 titers, or would you let them go down, and when there
21 is a problem, increase, give them more immunoglobulin?
22 DR. ZENKER: Maybe this is more a question
23 to the clinicians here. From the data we have seen,
24 it should be possible to reduce the measles titer in
25 the product, and when we all assume that the 120 is a

1 sufficient cutoff level, then we can reduce the lot
2 specification. As I stated before, in Europe, there
3 is no lot release specification at all for
4 immunoglobulins.
5 CHAIRMAN SIEGAL: Anyone else? I would
6 certainly agree with Mark that most of our patients
7 don't achieve a trough level of 900 mg. It's more like
8 the lower limit of normal, if we're lucky. So that
9 might make a difference in terms of the titers that
10 are actually achieved.
11 Anyone else? Okay. Well, thank you very
12 much. Now we're already about 20 minute behind. I
13 don't know how the committee feels about it, but I
14 know that some of us have to make planes and trains,
15 and that perhaps we ought to forego the break and move
16 onto the rest of the program. Is there a sense that
17 people need to take a break for a moment?
18 (Off the record comments.)
19 CHAIRMAN SIEGAL: Do you want to do five
20 minutes? But really a five minute break. Okay. Not
21 25. Off the record.
22 (Whereupon, at 3:36 p.m., the above-
23 entitled matter recessed and reconvened at 3:41 p.m.
24 the same day.)
25 CHAIRMAN SIEGAL: On the record. Let's

1 get started. Because we are having an open public
2 hearing, I'm obligated to read an announcement for
3 such meetings concerning conflict of interest.
4 Both the Food and Drug Administration
5 (FDA) and the public believe in a transparent process
6 for information gathering and decision making. To
7 ensure such transparency at the open public hearing
8 session of the advisory committee meeting, FDA
9 believes that it is important to understand the
10 context of an individual's presentation.
11 For this reason, FDA encourages you, the
12 open public hearing speaker, at the beginning of your
13 written or oral statement to advise the committee of
14 any financial relationship that you may have with any
15 company or any group that is likely to be impacted by
16 the topic of this meeting. For example, the financial
17 information may include the company's or group's
18 payment of your travel, lodging or other expenses in
19 connection with your attendance at the meeting.
20 Likewise, FDA encourages you at the beginning of your
21 statement to advise the committee if you do not have
22 any such financial relationships.
23 If you chose not to address this issue of
24 financial relationships at the beginning of your
25 statement, it will not preclude you from speaking.

1 With that in mind, I understand we have two
2 representatives. The first will be Mary Gustafson
3 from the PPTA, the Plasma Protein Therapeutics
4 Association. Dr. Gustafson.
5 DR. GUSTAFSON: Thank you very much. And
6 in terms of conflict of interest, I am a salaried
7 employee of PPTA. PPTA is the international trade
8 association and standard setting organization for the
9 world's major producers of plasma derived and
10 recombinant analog therapies. Our members provide 60
11 percent of the world's needs for source plasma and
12 protein therapies. These include clotting therapies
13 for individuals with bleeding disorders,
14 immunoglobulins to treat a complex of diseases and
15 persons with immune deficiencies, therapies for
16 individuals who have Alpha 1 antitrypsin deficiency
17 which typically manifests as adult onset emphysema
18 and substantially limits life expectancy and albumin
19 which is used in emergency room setting which is used
20 to treat individuals with shock trauma, burns and
21 other conditions. PPTA members are committed to
22 assuring the safety and availability of these
23 medically needed life-sustaining therapies.
24 PPTA agrees with FDA's proposal to lower
25 the minimum titer for measles antibodies and immune

1 globulin intravenous (human) and immune globulin
2 subcutaneous (human) recommended for lot release. The
3 original measles antibody release requirement was
4 related to a standard obtained from a donor population
5 with different immunologic profile.

6 In the 1960s, the immune globulins were
7 licensed by FDA. Today's immune globulin products are
8 used by people with immune deficiencies to protect
9 them on a day-to-day basis from pathogens in their
10 environment. Routes of administration are intravenous
11 or subcutaneous. As in the 1960s, the antibody
12 composition of the immune globulin products reflect
13 the herd immunity of the population from which the
14 source material is collected. Today's donor is more
15 likely to have been immunized against childhood
16 infections including measles rather than having had
17 the illnesses.

18 Both demand for and production of immune
19 globulins are rising. In 2006, the distribution of
20 intravenous immune globulins in the United States was
21 a record high of approximately 32.4 million grams.
22 Manufacturers increased the distribution of
23 intravenous immune globulins over 60 percent between
24 the years 2000 and 2006. This increase has resulted
25 from proactive steps such as incorporating yield

1 improving technologies to obtain more globulin from
2 each leader of plasma, increasing plaque capacity and
3 implementing new product formulations. The increased
4 distribution is dependent on the antibody composition
5 of the final product reflecting the herd immunity of
6 the donor population.
7 Manufacture of immune globulins is
8 complex. It is important to recognize that it can
9 take up to 12 months to manufacture a single batch.
10 Failure of a batch to pass lot release specifications
11 has serious ramifications. It is important that each
12 lot release specification is relevant and realistic.
13 The proposal by FDA to lower the minimum
14 titer for measles antibody is based on both clinical
15 relevance and the realities of manufacturing immune
16 globulins from today's donor populations. And if I
17 could add, based on data in Drs. Simon's and Zenker's
18 presentations, we ask that the committee and FDA
19 consider if an even lower titer is clinically
20 appropriate to help ensure the continued
21 sustainability of the product. Thank you.
22 CHAIRMAN SIEGAL: Thank you, Dr.
23 Gustafson. The next speaker will be Marsha Boyle from
24 the Immunodeficiency Foundation.
25 MS. BOYLE: Thank you, Dr. Siegal and the

1 committee for allowing me to present.

2 The Immunodeficiency Foundation is the
3 national patient organization for the primary
4 immunodeficiency diseases. Many of our patients
5 depend on regular infusions of life saving
6 preparations of IVIG in order to replace the
7 immunoglobulins and antibodies that they themselves
8 are unable to produce because of a genetic defect
9 involving their immune system. The primary rationale
10 for using this treatment is that these products
11 contain sufficient titers of antibodies to be
12 effective in preventing and treating a broad range of
13 infectious diseases to which our patients are likely
14 to become exposed.

15 When the original potency standards for
16 immune serum globulin, IGIM, were established, they
17 were based on the titers of antibodies to measles,
18 diphtheria and polio. These potency standards have
19 subsequently been applied to the preparation of IGIV
20 and IG subcutaneous.

21 IDF has been aware for some time of the
22 concern by the FDA and the industry about the
23 gradually falling titers of anti measles antibody in
24 the general donor population that has been reflected
25 in similar reduced titers and preparations of IGIV.

1 Along with the FDA, we were pleased to
2 cosponsor a workshop held at the NIH campus on April
3 25 and 26 of this year. The workshop brought together
4 experts from the FDA, CBER, industry, academia and the
5 CDC to explore in the detail this problem and
6 potential solutions. BPAC's consideration of this
7 issue today is very timely. From what we understand,
8 it appears that we're nearing a time when newly
9 manufactured lots of IGIV may need to be rejected
10 solely because they did not meet the standard for
11 titer of anti measles antibody.
12 The supply of IGIV has been tight for
13 several years. In addition, the amount used by other
14 disorders has been increasingly substantially, further
15 adding pressure on the supply of this lifesaving
16 treatment for patients with primary immune deficiency.
17 Measles is a serious disease and the protection of
18 our patients from measles via immunoglobulin
19 replacement is highly desirable but it is only one of
20 a myriad of infectious diseases against which our
21 patients need the protection afforded by this
22 treatment.
23 If new loss of IGIV or IGSC products are
24 rejected because this single specificity is below the
25 potency standard originally established for IM that

1 was given in much lower doses than currently possible
2 with IGIV, we fear shortages of these products would
3 inevitably occur. This could then result in
4 infections with many other organisms with predictable
5 consequences for patients with antibody deficiency.
6 In addition to these supply issues, we're
7 encouraged that the levels of measles immunization in
8 the general population has been sufficient to keep
9 herd immunity high enough to prevent epidemic
10 outbreaks of measles during recent years in this
11 country. Certainly the risk that a primary
12 immunodeficient patient would encounter, wild type
13 measles is much lower than their risk from other
14 agents that are not part of the potency standard. And
15 we also encourage CBER to continue efforts to define
16 the specificities of different antibodies in the
17 products.
18 We therefore urge that the BPAC accept the
19 recommendations of the CBER staff to lower the potency
20 standard for anti measles antibody in preparations of
21 IGIV and IGSC. IDF further urges the CDC to continue
22 its surveillance program for outbreaks of wild type
23 measles in this country. Efforts must continue to
24 determine whether patients with primary
25 immunodeficiency are among the cases reported and, if

1 so, determine the immunoglobulin replacement status of
2 those patients.
3 We're pleased that CBER is maintaining the
4 current measles standard for the IM preparations and
5 we feel that it would also be beneficial to our
6 patient population if CBER could consider the
7 feasibility of having available preparations of
8 immunoglobulin that are manufactured, IGIV that are
9 manufactured, to contain higher than standard titers
10 of anti measles antibody and some other specificities
11 as well for short term use by patients who need to
12 travel to areas of the world where these infectious
13 diseases are endemic such as Africa or the Middle
14 East.
15 We would also like to see continued and
16 expanded research to more fully understand the roles
17 of the various components of the immune system in
18 protection against measles to help clarify the
19 relative risk to patients with antibody deficiency,
20 cellular immunodeficiency or combined forms of
21 immunodeficiency.
22 Also I forgot to say at the beginning that
23 I personally have no conflicts. But the
24 Immunodeficiency Foundation does receive unrestricted
25 educational grants from many of the companies that

1 produce immunoglobulin. Thank you.
2 CHAIRMAN SIEGAL: Thank you very much. Is
3 there anyone else who wishes to make a statement
4 during the public part of the meeting? If not, we'll
5 proceed. Thank you very much.
6 Now we need to address our questions. You
7 can all read them. The first question is do committee
8 members concur with the FDA proposal to lower the
9 minimum measles antibody specification as described.
10 Is there discussion on this matter?
11 MS. ELGIN: May I?
12 DR. SZYMANSKI: I would like just to bring
13 up a couple of issues. We discussed here. We learned
14 that about 60 percent of patients who receive
15 immunoglobulin receive it not because they are
16 incompetent and the measles antibody I don't think
17 matters in those cases. So any level of measles
18 antibody would be fine to treat those individuals.
19 Now I think the Swiss presentation sort of
20 was quite convincing that even if you lower the
21 antibody level even more than it is proposed now the
22 patients were not at the risk for measles in even
23 incompetent patients. So I think it seems to me that
24 it does not present a great danger if you lower the
25 level to 0.48 from 0.6. I just wonder what anybody

1 else is thinking.

2 DR. EDWARDS: May I? On this same
3 question, I have actually a burning question. First
4 of all, in answering the question, I felt that from
5 the presentations and the literature that we've had so
6 far that there is no reason why we shouldn't lower it
7 to the 0.48. But my question and I'm hoping that
8 someone in the audience if not my colleagues here
9 around this table might answer this question. As
10 we've seen, we're saying that we get better vaccine
11 from those who have had the disease naturally and the
12 question that keeps coming to my mind is that while we
13 have seen less incidence here in the U.S. and
14 therefore don't have the numbers here that have
15 natural measles and therefore can't develop vaccine
16 from that, why is that we're not talking about
17 developing vaccine from those countries where we still
18 see measles as a major disease there and occurrence in
19 that population? Is there any specific reason why
20 we're not going outside of the U.S. for that herd
21 immunity that we talk about?

22 DR. GOLDING: I think -- Well, the issue
23 there is collecting plasma outside the U.S. and there
24 is a whole host of problems for doing that that we
25 only accept products that are made from U.S. licensed

1 plasma because of the way that donors are deferred and
2 infectious disease risk from those donors. So I'm not
3 saying it's impossible, but it is huge problem to ask
4 for non U.S. plasma to be used. What would have to
5 happen is that in countries where they have high titer
6 measles antibody you would have to have plasma centers
7 that then could get U.S. licenses in order to collect
8 the plasma and then ship it to the U.S. It's not
9 impossible but extremely difficult.
10 CHAIRMAN SIEGAL: Are there any other
11 comments concerning this?
12 DR. DI BISCEGLIE: Just a question. I
13 don't see -- I'm in agreement with the idea of
14 lowering the measles antibody specification. But I'm
15 not sure about the number, 0.48. Is there some basis
16 for that and why that?
17 DR. GOLDING: There's a lot of
18 mathematical calculations based on what a protective
19 titer would be. But starting from a protective titer
20 of 120 IU/mL, what we found and what I presented is
21 based on pharmacokinetic calculations. You would
22 expect that if you dropped the titer to 0.48 you
23 dropped the lot release requirement instead of 0.6 to
24 0.48 of the standard, you would end up in practice of
25 having immunoglobulin preparation that if you gave

1 them at 400 mg/kg which is probably from a point of
2 view of the standard the lowest dose you would end up
3 with a trough level that's, if our calculations are
4 correct, around 240 mIU/mL which is twice what we
5 think is the protective level.
6 Part of our thinking is that in the immune
7 deficient population, we don't have data to know what
8 is protective in that population. We heard from
9 several speakers that T cell immunity may also be
10 important. So we want to have a margin of safety here
11 for that population. So some of this is -- A lot of
12 this is based on estimates because we don't have the
13 data.
14 We saw today from CSL with very high
15 trough levels which we're going to ask, being a
16 continued discussion with them and try to look at that
17 data more carefully. But based on what we knew going
18 into this meeting, the 0.48 level seemed to us a
19 reasonable estimate. It also means that based on all
20 the lots we've been looking at over the last few years
21 that 100 percent of those lots would pass the lot
22 release test. So it ensures from the point of view of
23 the FDA both having continued supply without problems
24 of lots failing and at least double the protective
25 level in the lowest dose that is used clinically.

1 DR. DI BISCEGLIE: A follow-up if I might.
2 Is that okay, Mr. Chairman? Sorry. So by choosing
3 0.48 given that the titers are failing, might we be
4 facing a similar hearing five years from now to say we
5 can't keep up any longer?
6 DR. GOLDING: I think that is possible and
7 I think we can look into those calculations. But I
8 think there is the one way of addressing that which is
9 saying you have to give higher doses. But there's a
10 problem with that because there's cost involved and
11 there's also availability involved with higher doses.
12 So if the titers continue to fall, we could end up
13 five years from now that 0.48 is not sufficient. But
14 we may be --
15 DR. DI BISCEGLIE: So it's incumbent on I
16 think maybe both the agency and the manufacturers to
17 prepare for that now by getting some of the data that
18 might support saying we can go even lower or we cannot
19 go lower.
20 DR. GOLDING: Well, I agree with you, but
21 I think one of the things we have is in the question
22 is to ask -- One of the questions is to actually do
23 pharmacokinetic studies, asking the manufacturers to
24 do studies to get actual data and to then compute that
25 and then look at that in terms of the falling titers

1 and see maybe there is a more realistic number for the
2 next five years.
3 MS. BAKER: I had some questions for Dr.
4 Baker and the other manufacturers. You had mentioned
5 that when some lots seemed to be in danger of failing
6 that you have a policy to ship them overseas and I'm
7 wondering -- I didn't hear you clearly. If you could
8 clarify. Is this something that is currently
9 occurring? At what antibody specification do you make
10 a decision to ship overseas? How often has this
11 occurred? When did it start? In what proportion of
12 the lots has this occurred?
13 DR. BAKER: Sure. I can answer that. In
14 terms of the lots that have failed, we have had one
15 and it was marginal failure. I think I took the
16 question in a more hypothetical sense that if we have
17 a large number of lots failing what could we do and in
18 a hypothetical sense since we don't have a requirement
19 that is similar to the measles antibody and titer we
20 could divert those products to Europe or to use as
21 European production. But the reality is there has
22 been a grand total of one and it was just at the
23 margin.
24 CHAIRMAN SIEGAL: I have a question for
25 the FDA actually. Dr. Epstein perhaps. I just want

1 to know whether there's a absolute requirement that we
2 use measles antibody levels for certification of this
3 product in the long run or could that be changed and
4 therefore sidestep the whole issue in the long run?
5 DR. EPSTEIN: Okay. Well, the answer,
6 first of all, the regulations require a titer for
7 intramuscular immune globulin. It has been a policy
8 and consistent practice to apply the same titer and
9 principle to the intravenous and subcut preparations
10 but that's not actually in the regulations. Whether
11 we need to maintain that policy is up to us and the
12 Director of CBER has discretion where to set the
13 threshold for lot release if we maintain that.
14 But I think your question leads to your
15 suggesting do we need this at all which was your
16 opening remark and I guess that's a question we could
17 ask this committee. Is there the sense that this is
18 playing a protective role or not? And I guess having
19 heard Dr. Moss' presentation the question arose in my
20 mind in the following way. If you believe the monkey
21 data that the natural history is essentially identical
22 from an immune deficient to an immune competent
23 subject as long as there's cellular immunity intact.
24 What does that suggest? It suggests that if you
25 didn't have this titer in the product you wouldn't be

1 putting at risk the immunodeficient patients who have
2 cellular immunity.
3 Conversely, if you do have deficient
4 cellular immunity, the question is whether given a
5 replacement to achieve titers that are less than
6 associated with sterilizing immunity, that is to say,
7 prevention of infection plays any role at all and I
8 think what we saw here is that although a large of
9 proportion of subjects who get these higher
10 replacement levels exceed roughly 1,000 mIU/mL or 1
11 IU/mL that at the projected lower titer, in fact, you
12 don't expect very many to be anywhere near that level.
13 So the point is in actual practice we're
14 not giving patients enough product to get sterilizing
15 immunity which raises the question of whether we're
16 actually benefitting the people who are cellular
17 immune deficient. So I think what's really going on
18 is that the PID population is being protected by the
19 herd immunity of the general population and there's
20 rather an open question whether the low level
21 replacement compared to sterilizing immunity places
22 any role, whatever. In a certain peculiar way, that
23 suggests to us that we can be a little bit less
24 worried about lowering the titer because its punitive
25 benefit may not be an actual one.

1 CHAIRMAN SIEGAL: That's clarifying.
2 Thank you.
3 DR. EPSTEIN: Sorry. I know it was a
4 little circuitous.
5 CHAIRMAN SIEGAL: No, it was very good.
6 DR. EPSTEIN: But I'm trying to assimilate
7 a lot of results here.
8 DR. CRYER: It seems to me that with
9 taking all the data today that we've heard that it's
10 pretty clear that we could support a yes to No. 1 and
11 not really worry about it again unless one of three
12 happened and the three things would be that some of
13 the donated units start falling below the 0.48 level.
14 The second would be that some of the people getting
15 those units started getting measles. And the third
16 would be that the epidemiologic studies start to show
17 penetrants into the population who have been immunized
18 when there are some of these sporadic outbreaks. So
19 it seems to me -- I mean this seems pretty clear cut
20 from a commonsensical point of view.
21 DR. GLYNN: But I think that also brings
22 the question of travel in those patients. So what is
23 usually done when someone with immunodeficiency is
24 going to be traveling. Do you give them a dose just
25 before they travel? What's the usual practice?

1 CHAIRMAN SIEGAL: Well, in practice, you
2 can simply up the dose.
3 DR. BERGER: I think if a patient with an
4 immune deficiency who is maintained on immunoglobulin
5 replacement is going to travel most of us would
6 probably give that patient a dose before they
7 departed. But it also raises questions about how long
8 they're going and can they get a dose while they're
9 overseas and so on?
10 DR. GLYNN: And do you think your practice
11 would change if we decreased the dose of the titer or
12 you would just give --
13 DR. BERGER: Well, if somebody is going to
14 -- It also depends -- It's not totally clear to me
15 that if we vote to advise the FDA to carry out
16 positively on question one whether we're also going to
17 change the specification for IM. Because if we don't
18 change the specification for IM which is not
19 indicated, then you may say if you're going to a
20 measles endemic place, take an IM dose before you go.
21 So that possibility would remain open as would the
22 possibility of giving a higher IV dose before they go
23 or subcu and ask for a subcu dose or something like
24 that.
25 DR. GOLDING: I just wanted to add, the

1 IM, we would think might be used for normals. But the
2 problem with IM is the same. We're going to have to
3 deal with it separately. We are going to have to deal
4 with the titers are falling down in the IM as well.
5 So it's not necessarily going to be a solution.
6 CHAIRMAN SIEGAL: Last comment I hope.
7 DR. FINNEGAN: You're not going to like
8 the comment. I am very concerned that we are being
9 asked to answer a question for which we have been
10 given almost no scientific data for a problem that is
11 still theoretical although it is approaching and for
12 people who are significant risk of dying if, in fact,
13 we guess wrong. And I think we're setting a precedent
14 that really concerns me. I mean I have not heard good
15 scientific data today I don't think.
16 CHAIRMAN SIEGAL: Further comments?
17 Louie.
18 DR. KATZ: My only response to that is
19 that IVIG in particular and "subcu" immunoglobulin are
20 used for important things than measles now and to
21 start losing lots over the risk of measles as somebody
22 who has to ration intravenous immunoglobulin from our
23 distribution hub pretty much constantly for several
24 years I don't measles to be the reason that I have to
25 tell somebody they can't some.

1 DR. FINNEGAN: But are there other ways of
2 handling it besides dropping down to 0.48? In fact,
3 the woman for Immune Deficiency said can we have a
4 higher level if we're going to travel. Can you have a
5 lower level that you just put on that does not work
6 for measles?
7 DR. KATZ: I think that gets to question
8 three which I hope we'll have time to discuss as a
9 separate kind of --
10 CHAIRMAN SIEGAL: Well, I'd like to get a
11 vote on this question first and I'd like to go around
12 the room. So I'm asking people whether they agree or
13 disagree. Let's start with Mel Berger.
14 DR. BERGER: I agree.
15 EXECUTIVE SECRETARY JEHN: So we'll go
16 around the table here. So Dr. Berger, you're a yes.
17 Dr. Ballow.
18 DR. BALLOW: Yes.
19 EXECUTIVE SECRETARY JEHN: Dr. Colvin.
20 DR. COLVIN;: Yes.
21 EXECUTIVE SECRETARY JEHN: Dr. Cryer.
22 DR. CRYER: Yes.
23 EXECUTIVE SECRETARY JEHN: Dr. Di
24 Bisceglie.
25 DR. DI BISCEGLIE: Yes.

1 EXECUTIVE SECRETARY JEHN: Dr. Edwards.
2 DR. EDWARDS: Yes.
3 EXECUTIVE SECRETARY JEHN: Dr. Finnegan.
4 DR. FINNEGAN: No.
5 DR. GLYNN: Yes.
6 EXECUTIVE SECRETARY JEHN: Dr. Glynn, yes.
7 Dr. Quirolo.
8 DR. QUIROLO: Yes.
9 EXECUTIVE SECRETARY JEHN: Dr. Schreiber.
10 DR. SCHREIBER: Yes.
11 EXECUTIVE SECRETARY JEHN: Dr. Szymanski.
12 DR. SZYMANSKI: Yes.
13 EXECUTIVE SECRETARY JEHN: Dr. Whittaker.
14 DR. WHITTAKER: Yes.
15 EXECUTIVE SECRETARY JEHN: Ms. Baker.
16 MS. BAKER: Yes.
17 EXECUTIVE SECRETARY JEHN: Dr. Siegal.
18 CHAIRMAN SIEGAL: Yes.
19 EXECUTIVE SECRETARY JEHN: Opinion from
20 Dr. Katz?
21 DR. KATZ: Yes.
22 CHAIRMAN SIEGAL: Let's proceed to the
23 second question for which we need to vote as well.
24 CBER is considering requesting additional studies to
25 confirm that primary immune deficiency patients will

1 achieve trough levels of measles antibodies above 120
2 mIU/mL if treated with IGIV and IGSC products that
3 meet the proposed revise potency standard of 0.48
4 times the CBER standard. Do the committee members
5 agree that this information is needed?
6 DR. FINNEGAN: I think a preliminary study
7 before that is what exactly is the level that's needed
8 to prevent infection because I don't think anybody
9 knows. It's somewhere between, it looks like, 200 and
10 1,000, but nobody seems to know what the real level
11 is. So I would say that a more basic step would be
12 that.
13 CHAIRMAN SIEGAL: Mel.
14 DR. ALLEN: I think that data like the
15 data presented by Dr. Zenker is achievable and so if
16 we had data comparing the titer and lots that patients
17 were given at least with the trough levels, if not,
18 the formal pharmacokinetics of the whole
19 pharmacokinetic curve, then it would be possible -- We
20 would be on much firmer ground to make a mathematical
21 extrapolation that any given titer in the product this
22 and this trough level would be achieved. So that's
23 something that when we have to revisit this five years
24 from now or if the data that she just talked about
25 were available one could at least make a mathematical

1 projection of what titer in the product would give a
2 trough titer in the patient that would be
3 satisfactory. And that data is certainly available
4 from patients being treated now. You just need a
5 sample of the lot they're given and a sample of their
6 trough level.

7 DR. GLYNN: I think it would be really
8 important to those data because everything we've seen
9 are just simulations. So I think we need to actually
10 check that the numbers pan out the way we thing that
11 they would.

12 CHAIRMAN SIEGAL: From what we've heard
13 Dr. Epstein and from what we've been thinking about
14 it, it strikes me that part of the problem is that the
15 really susceptible population are the kids with
16 combined immune deficiency and others with C-8
17 deficiency and things of that sort for which there are
18 no data at all. And that really probably what we need
19 to do for populations like that is to provide
20 sterilizing protective antibody immunity and it's
21 clear that you need much higher titers than the FDA
22 standard proposes to achieve that so that if we're
23 going to look at that, we might be looking to do this
24 with specialized immunoglobulin preparations that are
25 exceedingly high titered. You can't do that with the

1 IM stuff because you just can't give enough. So IM
2 immunoglobulin was traditionally protective against
3 measles because it modified measles in healthy adults
4 really. Isn't the genesis of the standard? And that
5 wouldn't apply to a kid with severe combined immune
6 deficiency actually confronted with the virus I think
7 anyway.
8 But I personally agree that we should do -
9 - we should find out what actual peak and trough
10 levels are and that would be a useful and relatively
11 simple study to do and it's already been partially
12 provided to us. Other comments? If not, we can go
13 around the table again.
14 DR. QUIROLO: I have just one question for
15 you. I don't give IVIG. So on the label or in the
16 insert, does the manufacturer state what the antibody
17 levels are? Is there some way to find out?
18 CHAIRMAN SIEGAL: I haven't read a package
19 within 30 years.
20 DR. QUIROLO: Would it help you, would it
21 help the clinician, to know because I noticed that in
22 one of the papers there was a huge difference between
23 the manufacturing processes as to how much antibody
24 there were in each of these different products? So
25 would it help the clinician to know whether the titers

1 were in these products?

2 CHAIRMAN SIEGAL: It would but it's never

3 provided and, of course, as has been pointed in this

4 meeting, there are other titers which would be much

5 more helpful than the measles titer because measles

6 hasn't been our clinical problem the way pseudomonas

7 antibodies would be or other encapsulated bacteria

8 antibodies and so on.

9 All right. So let's go around the table.

10 EXECUTIVE SECRETARY JEHN: Before we go

11 around the table, I just want to summarize the first

12 one. It was 13 yeas and one nay.

13 For question two, Dr. Berger.

14 DR. BERGER: Yes.

15 EXECUTIVE SECRETARY JEHN: Dr. Ballow.

16 DR. BALLOW: Yes.

17 EXECUTIVE SECRETARY JEHN: Dr. Colvin.

18 DR. COLVIN: Yes.

19 EXECUTIVE SECRETARY JEHN: Dr. Cryer.

20 DR. CRYER: Yes.

21 EXECUTIVE SECRETARY JEHN: Dr. Di

22 Bisceglie.

23 DR. DI BISCEGLIE: Yes.

24 EXECUTIVE SECRETARY JEHN: Dr. Edwards.

25 DR. EDWARDS: Yes.

1 EXECUTIVE SECRETARY JEHN: Dr. Finnegan.

2 DR. FINNEGAN: Yes.

3 EXECUTIVE SECRETARY JEHN: Dr. Glynn.

4 DR. GLYNN: Yes.

5 EXECUTIVE SECRETARY JEHN: Dr. Quirolo.

6 DR. QUIROLO: Yes.

7 EXECUTIVE SECRETARY JEHN: Dr. Schreiber.

8 DR. SCHREIBER: Yes.

9 EXECUTIVE SECRETARY JEHN: Dr. Szymanski.

10 DR. SZYMANSKI: Yes.

11 EXECUTIVE SECRETARY JEHN: Dr. Whittaker.

12 DR. WHITTAKER: Yes.

13 EXECUTIVE SECRETARY JEHN: Ms. Baker.

14 MS. BAKER: Yes.

15 EXECUTIVE SECRETARY JEHN: Dr. Siegal.

16 CHAIRMAN SIEGAL: No. I'm just being
17 contrary. Now the last question is please comment on
18 the need for -- I'll change my vote by the way.

19 Dr. Katz. I'm sorry.

20 EXECUTIVE SECRETARY JEHN: He's not a
21 vote, but it's just an opinion.

22 DR. KATZ: My guts tell me that we can
23 talking about measles and IGIV in the United States,
24 but I think it's hard to argue against getting this
25 data because the PK data is relatively easy. Trying

1 to define the correlates of protection and immunity
2 I don't think we have a clue and I think while 120
3 correlates with something. That does mean it's the
4 cause. So I'm not sure how far in a time of virtually
5 zero incidents in the U.S. we can go toward defining
6 what immunity really is.
7 CHAIRMAN SIEGAL: And again, in the Chen
8 study from which that number is derived, that was done
9 in healthy adults, not in kids without CD-8 cells.
10 Okay. So please comment on the need for
11 and feasibility of any alternative strategies that
12 CBER could consider to reduce the likelihood of failed
13 lots of IGIV and IGSC based on potency testing for
14 measles antibodies in order to ensure availability of
15 product for primary immunodeficiency patients. Mark.
16 DR. BALLOW: I have to assume that there
17 is variability from lot to lot, that some lots have
18 higher levels than other lots because from what we've
19 heard there are lots of failed and they are either
20 discarded or they are sent to Europe or elsewhere.
21 And I and my colleagues have been pushing actually to
22 look another group of antibodies and that is
23 antibodies to pneumococcal polysaccharides because
24 this causes significant clinical disease in this group
25 of patients. And one day we hoped that the bottle

1 would actually be labeled as to their antibody content
2 with regard to some of these important antibodies
3 again particularly pneumococcal polysaccharides but
4 one could do it also for measles antibodies. So
5 therefore one can visualize on the shelf. I know this
6 will be distribution nightmare, but one could
7 visualize that you would have bottles on the shelf
8 where you know the titers of measles and you know the
9 titers of pneumococcal antibodies and therefore you
10 could utilize those particular lots for patients with
11 primary immune deficiency disease where it's important
12 to have appropriate antibody titers to protect those
13 individuals and use the other lots for off-label.
14 DR. BERGER: I would also like to support
15 this idea. In the workshop, several examples were
16 brought up not only about pneumococcus but about, for
17 example, the problem of chronic Enteroviral
18 Meningoencephalitis in Bruton's patients and so on and
19 it's easy to see that the issue raised now about
20 measles because measles is the one that's written into
21 the law we're going to face the same issue with
22 Varicella zoster for example and that's going to be
23 much harder to control natural exposure because people
24 will get Shingles unless there's incredibly high
25 penetration of the new zoster vac.

1 So I would suggest two things at least be
2 considered some time in the future. One is the idea
3 of having some sort of agreed upon assays and labeling
4 lots or product according to their antibody content
5 against a variety of diseases and then the second
6 issue was raised which Mark also touched upon is the
7 issue raised by the tremendous use of IGIV for "off-
8 label uses." And it sounds very funny to say should
9 we label some of the lots to be used only for off-
10 label use but, in fact, we could label them for use in
11 ITP. Several of the products are labeled for ITP. Of
12 course, we have very little --
13 I think one of the most impressive things
14 out of the workshop and this session today is how
15 little we know about IVIG or IGG products and how they
16 work in the patients and however little we know about
17 it in PID patients is a lot more than we know about it
18 in the autoimmune and neurological diseases that
19 actually constitute the majority of the use. But at
20 least an interim strategy or as a strategy at some
21 point in answer to issue number three is to consider
22 the potential of labeling lots as not for use in PID.
23 Then those lots could still be on the market and could
24 be used for other indications.
25 CHAIRMAN SIEGAL: I hope we're taking

1 notes on this.

2 DR. CRYER: Yes, I have a similar comment.

3 I think if I have the process down right, then all of

4 these units have to be measured anyway. So it's just

5 a matter then of recording the antibody levels for the

6 various things on each unit. I think what that allows

7 is even if you didn't begin selecting out units for

8 certain things at the beginning you would at least

9 have a registry that allowed you to correlate the

10 levels of individual antibodies with the outcomes in

11 specific patients that you could then make

12 generalizations on later about what you need to do.

13 If you're already doing it anyway, it's just a matter

14 of writing it down and sticking it on the bottle or

15 the bag. It seems pretty simple to me.

16 CHAIRMAN SIEGAL: Dr. Szymanski.

17 DR. SZYMANSKI: We voted yes for the

18 number two, but even it's difficult to do the study

19 unless you know how much antibody you have. So even

20 for that purpose you had to have measured level in the

21 bag to know how much to increase the titers. So

22 labeling is important.

23 CHAIRMAN SIEGAL: I think one of the things

24 we don't know at all, really, is how much variation

25 there is in the repertoire from one batch of gamma

1 globulin to the next except insofar as the subclass
2 changes from one manufacturer to another which is
3 documented in one of the papers that we received.
4 DR. COLVIN: As a small aside, something
5 else from the FDA, if you look at how the labels are
6 on bottles like this, that tells us exactly how much
7 vitamin A. It sort of makes sense to me that we would
8 do the same thing in the case where it might actually
9 have a real impact as opposed to drinking this.
10 DR. DI BISCEGLIE: A little off track, but
11 I think perhaps important for the Agency to consider
12 is one of the uses of I think the intramuscular
13 preparation is post exposure prophylaxis of Hepatitis
14 A and the Agency may know the answer and I don't need
15 a response from them but I suspect that the titers of
16 antibody to Hepatitis A in lots are declining as with
17 measles and it's something that I think should be
18 looked at.
19 DR. YU: We do have some data which is not
20 yet published and the HAV levels indeed are a little
21 bit low and also depends on type of plasma, if it's
22 source plasma or versus recovered plasma. So
23 recovered plasma a little bit lower.
24 DR. GOLDING: Can I just mention that in
25 reference to a previous remark that in the Audet paper

1 that is part of the handout sheet, they studied 166
2 lots from seven manufacturers and the mean values or
3 the standard deviation are given there and they are
4 close to a threefold difference between the lowest
5 levels of measles titer and the lowest -- lots with
6 the lowest levels to the highest levels. It's about a
7 threefold difference.
8 CHAIRMAN SIEGAL: But we don't know the
9 pneumococcal antibody titers for Type 3 Pneumococcus
10 for example in those same lots, do we?
11 DR. GOLDING: No. I thought you were
12 talking about measles.
13 CHAIRMAN SIEGAL: I'm thinking in general
14 about the heterogeneity of antibodies that ones find
15 in a given pool and how that ends up in gamma globulin
16 and how different each lot is with respect to that
17 because we're really -- I mean gamma globulin is
18 essentially a black box and for off-label uses it's
19 certainly a black box unless we're talking about how
20 much anti-big D there is or how much isoglutinin there
21 is at random there. But we don't even understand how
22 it works as was pointed out, and for most of the off
23 label uses.
24 DR. GOLDING: We agree with you and there
25 was a paper published by the FDA by my group which

1 looked at titers of H. flu and Strep pneumoniae among
2 a large number of lots from different manufacturers.
3 So there was a paper last year where we looked at
4 that, but we have been talking to the manufacturers to
5 try and encourage them to develop their assays and to
6 use those assays for PK studies to try and get to the
7 point that I think you're aiming at and we have the
8 same goal.

9 DR. BALLOW: One thing we haven't talked
10 about is education. So if we move forward with this,
11 I think we have to educate at least those individuals
12 who use gamma globulin and patients with primary
13 immune deficiency disease to make them aware that
14 there are circumstances like travel abroad or mini
15 epidemics that might come along in certain
16 geographical areas to be aware that they have to
17 increase the dose or give extra doses of gamma
18 globulin in order to protect our patients based on
19 some of the data that we've heard. I think a lot of
20 my colleagues probably don't appreciate that at this
21 point. So there may have to be some education or
22 maybe an addendum to the package insert of these
23 products.

24 CHAIRMAN SIEGAL: One strategy that we
25 could use as clinicians is just to send off titers for

1 14 serotypes of pneumococcus in our patients and see
2 what we're getting. All right. Are there any other
3 comments in this third question?
4 DR. QUIROLO: I think your statement
5 underlies the fact that there should be labeling for
6 the titers because the clinicians say who was in a
7 measles epidemic would know which product to use. If
8 you have no idea what you're giving, how can you
9 decide whether you're going give 400 or 800 mg of
10 product that maybe has a low titer?
11 DR. BERGER: In all fairness certainly
12 seeing a higher titer might lead you to use a certain
13 product in a certain situation, but as we also see
14 with measles, understanding the correlate of a titer
15 done with any given assay doesn't necessarily directly
16 translate into predicting the clinical efficacy of
17 that preparation. So this whole issue, I think, is a
18 little bit more complicated than just measuring titers
19 by ELISA and putting them on the bottle like the
20 vitamin level.
21 CHAIRMAN SIEGAL: Anyone else? All right.
22 Dr. Epstein, do you have any other comments or needs
23 from us?
24 DR. EPSTEIN: No. I wanted to make a very
25 small comment in the current context because the

1 question was asked about is 0.48 times CBER standard
2 good enough for the future looking forward five years
3 or ten years from now and we have a little bit of
4 information about that which is the neutralizing titer
5 of plasma pools in the birth cohort 1968 to 1972.
6 That's close to 40 years post vaccination and there is
7 gravitation toward a level of 1 IU/mL or 1,000 mIU/mL
8 in the pool which correlates with the level that Dr.
9 Golding said is what you would need in order to end up
10 with projected trough titer of 120 per mL in the
11 recipient. So I think that suggest to us that it is in
12 fact a level that would remain robust over time.
13 But I couldn't agree more that if we have
14 actual studies on administered dose and trough levels
15 obtained, we'll be in a much better position to
16 predict where things will end up. But that's just a
17 small comment in the larger context.
18 I appreciate the deliberation of the
19 committee and I think that FDA has obtained the
20 feedback that we need to go forward.
21 CHAIRMAN SIEGAL: In that case I thank you
22 all for coming and this meeting stands adjourned. Off
23 the record.
24 (Whereupon, at 4:29 p.m., the above-
25 entitled matter was concluded.)