PROTECTING THE NATION'S BLOOD SUPPLY FROM INFECTIOUS AGENTS: NEW STANDARDS TO MEET NEW THREATS

HEARINGS

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS

OF THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

HOUSE OF REPRESENTATIVES

ONE HUNDRED FOURTH CONGRESS

FIRST SESSION

OCTOBER 12, AND NOVEMBER 2, 1995

Printed for the use of the Committee on Government Reform and Oversight

U.S. GOVERNMENT PRINTING OFFICE

22-844 CC WASHINGTON : 1996

For sale by the U.S. Government Printing Office
Superintendent of Documents, Congressional Sales Office, Washington, DC 20402
ISBN 0-16-052441-5

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

WILLIAM F. CLINGER, JR., Pennsylvania, *Chairman*

BENJAMIN A. GILMAN, New York
DAN BURTON, Indiana
J. DENNIS HASTERT, Illinois
CONSTANCE A. MORELLA, Maryland
CHRISTOPHER SHAYS, Connecticut
STEVEN SCHIFF, New Mexico
ILEANA ROS-LEHTINEN, Florida
WILLIAM H. ZELIFF, JR., New Hampshire
JOHN M. McHUGH, New York
STEPHEN HORN, California
JOHN L. MICA, Florida
PETER BLUTE, Massachusetts
THOMAS M. DAVIS, Virginia
DAVID M. McINTOSH, Indiana
JON D. FOX, Pennsylvania
RANDY TATE, Washington
DICK CHRYSLER, Michigan
GIL GUTKNECHT, Minnesota
MARK E. SOUDER, Indiana
WILLIAM J. MARTINI, New Jersey
JOE SCARBOROUGH, Florida
JOHN B. SHADEGG, Arizona
MICHAEL PATRICK FLANAGAN, Illinois
CHARLES F. BASS, New Hampshire
STEVEN C. LATOURETTE, Ohio
MARSHALL "MARK" SANFORD, South Carolina
ROBERT L. EHRLICH, JR., Maryland

CARDISS COLLINS, Illinois
HENRY A. WAXMAN, California
TOM LANTOS, California
ROBERT E. WISE, JR., West Virginia
MAJOR R. OWENS, New York
EDOLPHUS TOWNS, New York
JOHN M. SPRATT, JR., South Carolina
LOUISE McINTOSH SLAUGHTER, New York
PAUL E. KANJORSKI, Pennsylvania
GARY A. CONDIT, California
COLLIN C. PETERSON, Minnesota
KAREN L. THURMAN, Florida
CAROLYN B. MALONEY, New York
THOMAS M. BARRETT, Wisconsin
GENE TAYLOR, Mississippi
BARBARA-ROSE COLLINS, Michigan
ELEANOR HOLMES NORTON, District of Columbia
JAMES P. MORAN, Virginia
GENE GREEN, Texas
CARRIE P. MEEK, Florida
CHAKA FATTAH, Pennsylvania
BILL BREWSTER, Oklahoma
TIM HOLDEN, Pennsylvania

BERNARD SANDERS, Vermont (Independent)

JAMES L. CLARKE, *Staff Director*
KEVIN SABO, *General Counsel*
JUDITH McCOY, *Chief Clerk*
BUD MYERS, *Minority Staff Director*

SUBCOMMITTEE ON HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS

CHRISTOPHER SHAYS, Connecticut, *Chairman*

MARK E. SHOUDER, Indiana
STEVEN SCHIFF, New Mexico
CONSTANCE A. MORELLA, Maryland
THOMAS M. DAVIS, Virginia
DICK CHRYSLER, Michigan
WILLIAM J. MARTINI, New Jersey
JOE SCARBOROUGH, Florida
MARSHALL "MARK" SANFORD, South Carolina

EDOLPHUS TOWNS, New York
TOM LANTOS, California
BERNARD SANDERS, Vermont (Ind.)
THOMAS M. BARRETT, Wisconsin
GENE GREEN, Texas
CHAKA FATTAH, Pennsylvania
HENRY A. WAXMAN, California

EX OFFICIO

WILLIAM F. CLINGER, JR., Pennsylvania
CARDISS COLLINS, Illinois

LAWRENCE J. HALLORAN, *Staff Director*
ANNE MARIE FINLEY, *Professional Staff Member*
ROBERT NEWMAN, *Professional Staff Member*
THOMAS M. COSTA, *Clerk*
KEVIN DAVIS, *Minority Professional Staff*
CHERYL PHELPS, *Minority Professional Staff*

CONTENTS

	Page
Hearing held on October 12, 1995	1
Hearing held on November 2, 1995	99
Statement of:	
DeFilippi, Patricia, National Hemophilia Foundation; Corey Dubin, the Council of 10,000 and the National Hemophilia Federation; John Penner, M.D., Michigan State University, College of Human Medicine; and, Ronald Gilcher, M.D., Oklahoma Blood Center	36
Fournel, Michael A., vice president, research and development, Bayer Corp.; Edward Gomperts, Baxter Healthcare Corp.; Fred Feldman, vice president, technical development, Armour Pharmaceutical Co.; Gene F. Tutwiler, Alpha Therapeutics Corp.; James Reilly, president, American Blood Resources Association	157
Lipton, Karen Shoos, chief executive officer, American Association of Blood Banks; Toby Simon, president, Council of Community Blood Centers; and Richard J. Davey, chief medical officer, American Red Cross Biomedical Services	122
Philip, Mark A., chief executive officer, Immuno-U.S., Inc.	214
Satcher, David, Director, Centers for Disease Control and Prevention; and Paul McCurdy, National Heart, Lung, and Blood Institute, National Institutes of Health	102
Shalala, Donna, Secretary, Health and Human Services, accompanied by Dr. Phillip Lee; and, Hon. Porter J. Goss, a Representative in Congress from the State of Florida	8
Zoon, Kathryn, Ph.D, Director, Center for Biologics, Evaluation and Research, Food and Drug Administration; accompanied by Jay Epstein, an M.D., Acting Director, Office of Blood Research and Review	86
Letters, statements, etc., submitted for the record by:	
Clinger, Hon. William F., a Representative in Congress from the State of Pennsylvania, prepared statement of	7
Collins, Hon. Cardiss, a Representative in Congress from the State of Illinois, prepared statement of	101
Davey, Richard J., chief medical officer, American Red Cross Biomedical Services, prepared statement of	144
DeFilippi, Patricia, National Hemophilia Foundation, prepared statement of	38
Dubin, Corey, the Council of 10,000 and the National Hemophilia Federation, prepared statement of	43
Feldman, Fred, vice president, technical development, Armour Pharmaceutical Co., prepared statement of	172
Fournel, Michael A., vice president, research and development, Bayer Corp., prepared statement of	159
Gilcher, Ronald, M.D., Oklahoma Blood Center, prepared statement of	55
Gomperts, Edward, Baxter Healthcare Corp., prepared statement of	166
Goss, Hon. Porter, a Representative in Congress from the State of Florida:	
April 27, 1993, letter to and response from Ms. Shalala	33
Prepared statement of	32
Green, Hon. Gene, a Representative in Congress from the State of Texas, prepared statement of	7
Lipton, Karen Shoos, chief executive officer, American Association of Blood Banks, prepared statement of	124
McCurdy, Paul, National Heart, Lung, and Blood Institute, National Institutes of Health:	
Additional information on research	121

Page

Letters, statements, etc., submitted for the record by—Continued
McCurdy, Paul, National Heart, Lung, and Blood Institute, National Institutes of Health—Continued
Prepared statement of 111
Penner, John, M.D., Michigan State University, College of Human Medicine, prepared statement of 51
Philip, Mark A., chief executive officer, Immuno-U.S., Inc.:
Prepared statement of 217
Response to questions 232
Reilly, James, president, American Blood Resources Association, prepared statement of 184
Satcher, David, Director, Centers for Disease Control and Prevention, prepared statement of 105
Shalala, Donna, Secretary, Health and Human Services, prepared statement of 12
Shays, Hon. Christopher, a Representative in Congress from the State of Connecticut:
Company responses to IOM recommendations 200
July 12, 1995 letter to Dr. Kessler 3
Prepared statement of 2
Responses from panelists 77
Simon, Toby, president, Council of Community Blood Centers, prepared statement of 137
Towns, Hon. Ed, a Representative in Congress from the State of New York, prepared statements of 6, 101
Tutwiler, Gene F., Alpha Therapeutics Corp., prepared statement of 179
Zoon, Kathryn, Ph.D, Director, Center for Biologics, Evaluation and Research, Food and Drug Administration, prepared statement of 90

PROTECTING THE NATION'S BLOOD SUPPLY FROM INFECTIOUS AGENTS: NEW STANDARDS TO MEET NEW THREATS

THURSDAY, OCTOBER 12, 1995

U.S. HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RESOURCES AND
INTERGOVERNMENTAL RELATIONS,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:10 a.m., in room 2154, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Davis, Souder, Chrysler, Towns, Barrett, and Green.

Ex officio present: Representative Clinger.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley and Robert Newman, professional staff; Thomas M. Costa, clerk; Kevin Davis and Cheryl Phelps, minority professional staff members; Ellen Rayner, minority chief clerk; and Jean Gosa, minority staff assistant.

Mr. SHAYS. I would like to call this hearing to order and to welcome our witnesses, and to also welcome our guests as well and, in particular, thank the Secretary of HHS for coming to this hearing. And we will obviously be very eager to hear what she has to say and grateful that you are here.

Each year, approximately 4 million patients in the United States receive transfusions of whole blood and blood components derived from 12 million units of blood from more than 8 million individual donors. When receiving a transfusion, each of those patients forms a very personal bond of trust with one or more blood donors and with all those responsible for the collection, processing, storage, distribution and administration of potentially life-saving therapies. Those patients have a right to know their trust is well placed.

On behalf of those patients, we asked the Department of Health and Human Services to assure us that our public health agencies, particularly the Food and Drug Administration, are aggressively maintaining safeguards to detect emerging infectious agents and eliminate bloodborne pathogens from the Nation's blood supply.

We are very grateful that Secretary Shalala asked to testify today to provide that assurance and to discuss those steps the Department will take to improve the coordination and implementation of blood safety measures. We welcome her testimony on this vital issue.

Vigilance is the only sure barrier against nature's relentless and ingenious army of potential contaminants. We know from hard experience that any lapse of regulatory watchfulness, any scientific complacency, any absence at the sites of leadership, can lead to the loss of life. In the early 1980's, 10,000 people with hemophilia, fully 50 percent of all U.S. hemophiliacs at the time, as well as 20,000 other transfusion recipients, were infected with HIV through blood products. And I emphasize that was in the 1980's.

Many, in turn also infected their spouses, leaving children without parents. Some families lost an entire generation of children who relied on blood products to fight the deforming effects of hemophilia.

Today, we ask how the lessons of that 1980's tragedy will be applied to prevent new threats—Chagas' Disease, prions, parvovirus, and the bloodborne pathogens not yet known to us—from entering the national bloodstream.

One lesson should be an increased willingness to adopt intermediate testing measures to reduce the risks of infections entering the blood supply. For HIV, that risk arises during the 20-day window period during which infection in donated blood is not detected by the current antibody test. Use of an HIV antigen test would detect infected blood sooner, closing the risk window by approximately 10 days.

We applaud the FDA Commissioner's decision to recommend HIV antigen testing and will look to the FDA for the development of additional screening tests to reduce the already low risks of window period exposure to hepatitis and other infections.

Today our blood supply is safer than ever. Our goal is to assure the public that the safe supply of blood and blood products will remain as safe from infectious agents as good science and strong leadership can insure.

Testimony today from consumers, physicians, and the FDA will help us achieve that goal. We welcome our distinguished witnesses this morning and look forward to a thorough discussion of any issue critical to the public health.

At this time, I would like to invite the ranking member of this committee, formerly the chairman of this committee who has spent a lot of time on this issue, to offer any statement he would like.

[The prepared statement of Hon. Christopher Shays, and the July 12, 1995, letter to Dr. Kessler follow:]

PREPARED STATEMENT OF HON. CHRISTOPHER SHAYS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CONNECTICUT

Each year, approximately four million patients in the United States receive transfusions of whole blood and blood components derived from 12 million units of blood from more than eight million individual donors. When receiving a transfusion, each of those patients forms a very personal bond of trust with one or more blood donors and with all those responsible for the collection, processing, storage, distribution and administration of potentially lifesaving therapies. Those patients have a right to know their trust is well-placed.

On behalf of those patients, we asked the Department of Health and Human Services (HHS) to assure us that our public health agencies, particularly the Food and Drug Administration, are aggressively maintaining safeguards to detect emerging infectious agents and eliminate blood-borne pathogens from the nation's blood supply.

We are grateful that Secretary Shalala asked to testify today to provide that assurance and to discuss those steps the Department will take to improve the coordi-

nation and implementation of blood safety measures. We welcome her testimony on this vital health issue.

Vigilance is the only sure barrier against nature's relentless and ingenious army of potential contaminants. We know from hard experience that any lapse in regulatory watchfulness, any scientific complacency, and absence of decisive leadership can lead to the loss of life.

In the early 1980s, ten thousand people with hemophilia, fully 50% of all U.S. hemophiliacs at the time, as well as 20,000 other transfusion recipients, were infected with HIV through blood products. Many in turn also infected their spouses, leaving children without parents. Some families lost an entire generation of children who relied on blood products to fight the deforming effects of hemophilia.

Today, we ask how the lessons of that 1980s tragedy will be applied to prevent new threats—Chagas' Disease, prions, parvovirus, and the blood-borne pathogens not yet known to us—from entering the national bloodstream.

One lesson should be an increased willingness to adopt intermediate testing measures to reduce the risks of infections entering the blood supply. For HIV, that risk arises during the twenty day "window period" during which infection in donated blood is not detected by the current antibody test. Use of an HIV-antigen testing and will look to the FDA for the development of additional screening test to reduce already-low the risks of window period exposure to hepatitis and other infections.

Today our blood supply is safer than ever. Our goal is to assure the public that the supply of blood and blood products will remain as safe from infectious agents as good science and strong leadership can ensure. Testimony today from consumers, physicians, and the FDA will help us achieve that goal.

We welcome our distinguished witnesses this morning, and look forward to a thorough discussion of an issue critical to the public health.

July 12, 1995

David A. Kessler, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DEAR DR. KESSLER:

The Subcommittee has been investigating issues affecting the safety of the nation's blood supply. In the course of the investigation, it was learned that on June 23, the Food and Drug Administration's Blood Products Advisory Committee (BPAC) recommended against routine HIV–1 antigen screening of donor units. I urge you not to accept that recommendation but take immediate action to license HIV–1 antigen tests for donor screening.

These tests will reduce the average infection "window," the period between HIV infection of a donor and antibody detection in the blood. The window is now estimated to average 20 to 25 days. Antigen testing will reduce the window by 10 days, resulting in detection of up to 20 infected (antigen positive/antibody negative) donation cases per year which are now missed. Since each donation collected undergoes separation into at least two units, antigen testing will prevent up to 40 individuals from exposure to HIV-tainted blood products. That in turn could prevent transmission to an additional estimated 1.7 individuals per infected case, meaning that at least 68 individuals per year will be protected from HIV infection through licensing of antigen tests as a screening tool!

The June 23 decision by the BPAC was illogical. The committee first voted unanimously (15–0) that antigen testing was proven effective in "HIV–1 prevention . . . based on incidence and window period reduction." But the BPAC then voted (6–9) against a finding that antigen screening is "likely to provide a significant public health benefit which outweighs the potential risks." Based on that contradictory conclusion, the BPAC then voted (6–8, with 1 abstention) against recommending licensure of the antigen test as a donor screen. Those attending the meeting describe a heated discussion of the cost of antigen testing per avoided death. Cost appears to be the only potential risk considered by the BPAC, and it was cost alone that prompted the BPAC to recommend against implementation of routine donor antigen screening, despite their own unanimous finding of the test's effectiveness.

Yet the cost of antigen testing is not the primary concern of those who would have to conduct the screening. Both the American Association of Blood Banks and the American Red Cross, who together collect 98 percent of the nation's blood supply, support licensure of the HIV–1 antigen test. Given that fact, I hope you agree that

the FDA's primary concerns under the Federal Food, Drug and Cosmetic Act (FFDCA) ought to be the safety and effectiveness of a product or device. Highly speculative cost estimates should not outweigh scientific evidence of the effectiveness of antigen testing to save lives.

You have every reason to act boldly. Timidity in confronting the AIDS threat has already exacted a tragic toll. The FDA failed to take effective action against HIV infection in the 1980s and 10,000 hemophiliacs became infected through blood products, including 90% of patients with Type A Hemophilia and 50% of all hemophiliacs. I understand that an Institute of Medicine Report will be released today which is very critical of the agency's failure during that period to prevent transmission of HIV through the blood supply. Please do not allow that to happen again.

Decisive action on your part is long overdue. As the Subcommittee discovered in its investigation of the premarket review processes for food additives, the agency views statutory time frames as mere guidelines or goals. The Product Licensing Applications for the short-duration antigen tests were initially filed in 1990 and are still not approved. The FFDCA requires the agency to review and make a decision on biologic products within 180 days. The statute requires action by the agency, not endless deliberation by an advisory committee.

Also, I suggest that you disband the Blood Products Advisory Committee immediately and replace it with an Advisory Committee on the Safety of the Nation's Blood Supply. The critical mission of this advisory committee should be reflected in its title. At least one-third of the total membership of the new advisory committee should be individuals who have received blood products (but not in connection with a professional or commercial activity) and representatives of consumer organizations with expertise in blood products, as proposed in a bill introduced by Rep. Porter Goss (FL–14), H.R. 1021, of which I am a cosponsor.

You stated at the September 26, 1994 FDA Conference on The Feasibility of Genetic Technology to Close the HIV Window in Donor Screening that you believe that as a public health agency the FDA has an obligation to foster the development of new technologies—especially if these technologies hold the promise of a blood supply that is even safer. This is especially true for detecting HIV—the AIDS virus." You also said, "We need to close the window." You now have the opportunity to do just that.

Dr. Kessler, you have the responsibility and the authority as Commissioner to protect the nation's blood supply. Please approve the HIV–1 antigen test for screening of blood donors immediately and institute a new Advisory Committee on the Safety of the Nation's Blood Supply so that the American blood supply remains as free from infectious agents as strong leadership and good science can assure.

Sincerely,

CHRISTOPHER SHAYS
Chairman

Mr. TOWNS. Thank you very much, Mr. Shays, for holding this hearing and for your leadership on this particular issue. This is an issue that knows no particular constituency. Blood and blood products are not characterized by political party, and the level of safety that we aspire to should not reflect any political agenda.

Mr. Chairman, each year 4 million people rely on the quality and integrity of the blood supply, and no one knows when their mother, father, sister, brother, or child will be faced with some medical emergency requiring the transfusion of blood or blood products.

Clearly, the safety of the Nation's blood supply can touch the life of any American. For this reason alone, today's oversight hearing is critically important. I look forward to the testimony of each of today's witnesses and would like to especially commend Health and Human Services Administrator Donna Shalala for—or Secretary, I should say, for appearing before this subcommittee to present her agency's strategy for protecting the blood supply for our evaluation.

Madame Secretary, your presence significantly enhances our ability to understand the complexities of the task of insuring a blood supply free of contaminants, and demonstrates the highest level of commitment on the part of your agency and the adminis-

tration to maintaining a safe blood supply. And we thank you for that.

This hearing provides the subcommittee with the opportunity to reveal the recommendations to improve the safety of the blood supply that are set forth in a 1995 Institute of Medicine report. In addition, this hearing will enable us to assess HHS's plans for implementing these recommendations.

Toward that end, these fundamental questions, I hope, will be answered: Do HHS' plans show an understanding of the kinds of threats that exists to the safety of blood supply? For example, does the plan contemplate the risks of Hepatitis G or CJD in the blood supply? Has HHS improved coordination between the Public Health Service, FDA, NIH, and CDC in the detection and elimination of bloodborne infectious agents?

Should HHS adopt intermediate measures to assure greater protection of the blood supply and, if so, what is HHS's strategy for employing these measures?

So I would like, Mr. Chairman, and I hope that before the hearing is over that these questions will be asked. Thank you very much, and I yield back the balance of my time.

Mr. SHAYS. I thank the gentleman. At this time I welcome any comment that the chairman of the full committee, Mr. Clinger, would like to make.

Mr. CLINGER. Thank you very much, Mr. Chairman. I just want to commend you and your staff for the hard work you have put in in convening this oversight hearing on an issue which affects, or could affect, each and every one of us, which is the safety of the Nation's blood supply.

Each year, 4 million patients receive transfusions and over 20,000 units of blood are donated for patients in need. It is appropriate today for the first day of the National Hemophilia Foundation's Conference in my home State of Pennsylvania, to underscore the plight of the thousands of hemophiliacs who were infected with HIV through contaminated blood.

The question raised today is: What happens if we are faced with another crisis? Are we prepared to cope? We need to insure that this tragedy will not happen again. There seems to be general agreement that we need constant monitoring and testing with the best technology available to insure the safety of our blood supply.

But there is more that needs to be done than just the obvious, as detailed in the Institute of Medicine's report. We must have better coordination between the numerous agencies involved with monitoring the blood supply and to aggressively use every resource available.

Monitoring and testing our blood supply is a shared responsibility among different agencies and outside groups, which makes coordination even more difficult. We cannot have agencies competing for turf at the expense of patients, and we cannot have long delays in approving new technology which will help us protect blood supplies. We cannot continue to rely on inadequate or unreliable information.

So I want to welcome Secretary Shalala this morning, and hope that you can provide us with some insights today with the anticipated announcement that the Department will be implementing

many of the recommendations offered by the Institute of Medicine. We must, and can, do better to insure the safety of patients.

So I look forward to hearing the testimony of the witnesses and again welcome Secretary Shalala.

Mr. SHAYS. Madame Secretary, I know that you need to leave at 11 o'clock and that Dr. Lee will be able to stay, and we are going to honor that request. I know you have to meet with the President.

Mr. Chrysler and Mr. Souder, would either one of you like to make an opening statement?

Mr. SOUDER. I would say, just in respect to the Secretary's time, welcome.

Mr. CHRYSLER. The same.

Ms. SHALALA. Thank you very much.

Mr. SHAYS. As is our custom, we swear in our witnesses in this committee, and we will be swearing everyone in. If you would just stand and raise your right hand.

[Witnesses sworn.]

Mr. SHAYS. For the record, I will note that both witnesses have answered in the affirmative.

And if I could just ask unanimous consent that all members of the subcommittee be permitted to place any opening statements in the record and that the record remain open for 3 days for that purpose.

Without objection, so ordered.

[The prepared statements of Hon. Edolphus Towns, Hon. William F. Clinger, and Hon. Gene Green follow:]

PREPARED STATEMENT OF HON. EDOLPHUS TOWNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

I thank you, Chairman Shays, for scheduling this hearing which I know you have planned as a candid examination of the safety of the Nation's blood supply. As evidenced by this cover story in U.S. News and World Report, questions have been raised about blood safety that are in need of resolution. Mr. Chairman, this is an issue that knows no particular constituency. Blood and blood products are not characterized by political party, and the level of safety that we aspire to should not reflect any political agenda.

Mr. Chairman, each year, four million people rely on the quality and integrity of the blood supply. And no one knows when they, their mother, father, sister, brother, or child will be faced with some medical emergency requiring the transfusion of blood or blood products. Clearly, the safety of the Nation's blood supply can touch the life of any American. For this reason alone, today's oversight hearing is critically important.

I look forward to the testimony of each of today's witnesses, and would like to especially commend Health and Human Services Secretary Donna Shalala for appearing before this subcommittee to present her agency's strategy for protecting the blood supply for our evaluation.

Madame Secretary, your presence significantly enhances our ability to understand the complexity of the task of ensuring a blood supply free of contaminants, and demonstrates the highest level of commitment on the part of your agency and the administration to maintaining a safe blood supply.

This hearing provides the subcommittee with the opportunity to review recommendations to improve the safety of the blood supply that are set forth in a 1995 Institute of Medicine report. In addition, this hearing will enable us to assess HHS's plans for implementing these recommendations. Toward that end, these fundamental questions must be answered:

(1) Does HHS's plan show an understanding of the kind of threats that exist to the safety of blood supply?

For example, does the plan contemplate the risks of hepatitis G or C.J.D. in the blood supply.

(2) Has HHS improved coordination between the Public Health Service, N.L.H., and C.D.C in the detection and elimination of blood-borne infectious agents?

(3) Should HHS adopt intermediate measures to assure greater protection of the blood supply, and if so, what is HHS's strategy for employing these measures?

For example, does the plan include antigen testing.

Again, Secretary Shalala's presence here will significantly inform our discussion of these issues.

I welcome you Madame Secretary, and all of our witnesses, and look forward to a productive hearing.

PREPARED STATEMENT OF HON. WILLIAM F. CLINGER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF PENNSYLVANIA

I want to thank Subcommittee Chairman Shays and his staff for their hard work in convening this oversight hearing on an issue which affects or could affect each and every one of us—the safety of our nation's blood supply. Each year four million patients receive transfusions and over 20 million units of blood are donated for patients in need. It is appropriate today, the first day of the National Hemophilia Foundation's conference in my home state of Pennsylvania, to underscore the plight of the thousands of hemophiliacs who were infected with HIV through contaminated blood.

The question raised today is what happens if we are faced with another crisis? Are we prepared to cope? We need to ensure that this tragedy will not happen again. There seems to be general agreement that we need constant monitoring and testing with the best technology available to ensure the safety of our blood supply.

But there is more that needs to be done than just the obvious as detailed in the Institute of Medicine's report. We must have better coordination between the numerous agencies involved with monitoring the blood supply, and to aggressively use every resource available. Monitoring and testing our blood supply is a shared responsibility among different agencies and outside groups which makes coordination even more difficult. We can not have agencies competing for turf at the expense of patients. We can not have long delays in approving new technology which will help us to protect blood supplies. We can not continue to rely on inadequate or unreliable information.

I hope that Secretary Shalala will provide us with some insights today with the anticipated announcement that the Department will be implementing many of the recommendations offered by the Institute of Medicine. We must and can do better to ensure the safety of patients.

I look forward to hearing the testimony from the witnesses today.

PREPARED STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Thank you, Mr. Chairman for calling this hearing. This subcommittee has a heavy responsibility in discussing this issue seriously without stoking fears in the public. I believe there needs to be concern among the public about the safety of the blood supply, not because the safety is worse than in the past, but because it could be better than it is now. I would like to commend the Chairman for his ability to tackle another sensitive issue in a balanced and responsible way.

I would like to welcome our witnesses today, especially Secretary Shalala. I am very interested in hearing what HHS has decided to do about improving the safety of our national blood supply.

Finally, there has been some concern noted about the behavior of the Blood Products Advisory Committee (BPAC) in not recommending some intermediate action be taken to screen blood for HIV-1 antigens. Hopefully, today we will learn why they did not recommend any action be taken and whether this calls into question whether this standing committee should be disbanded.

Again, I thank the Chairman.

Mr. SHAYS. And, also, that our witnesses be allowed to summarize and offer any other material that they would like as well. And that will, without objection, be so ordered.

Madame Secretary, welcome. It is nice to have you before our committee again.

STATEMENT OF DONNA SHALALA, SECRETARY, HEALTH AND HUMAN SERVICES, ACCOMPANIED BY DR. PHILLIP LEE; AND, HON. PORTER J. GOSS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Ms. SHALALA. Thank you very much, Mr. Chairman. I am very pleased to be here. I am accompanied by Dr. Phillip Lee, the Assistant Secretary for Health, who is one of the Nation's leading authorities on public health. Good morning to you, Mr. Chairman and members of the subcommittee. Thank you for the opportunity to discuss the Department's program for insuring the safety of the Nation's blood supply.

I know that you are conducting this hearing because of your commitment to reducing the risks of contamination of blood and blood products, and I am here today because we share your commitment. The 3.5 million Americans a year who receive blood or blood products can be assured that the United States has one of the safest blood supplies in the world. No one should hesitate to receive blood when required.

The Department of Health and Human Services plays multiple roles in helping to insure the safety and availability of our blood supply. The Food and Drug Administration regulates the blood industry by licensing products, as well as issuing and enforcing safety rules. FDA also conducts research as an essential part of its science-based decisionmaking.

The Centers for Disease Control and Prevention use their nationwide surveillance system to identify and monitor bloodborne diseases. CDC advises the appropriate government officials when known or newly recognized diseases are identified as potential threats to the safety of the blood supply. CDC does research related to the risk of transmission of diseases directly through blood, as well as secondary transmission.

The National Institutes of Health is engaged in the ongoing research to improve blood banking operations and blood safety. For example, NIH is supporting work to develop methods of destroying infectious agents in blood components and is developing physician guidelines for the appropriate use of blood products.

Blood is human tissue and a natural vehicle for the transmission of infectious diseases. Putting someone else's blood into a person is an inherently risky medical procedure.

The greatest risk and our greatest fear is of the unknown. We dread newly emerging infectious diseases that can be transmitted through blood. Just such a disease became the blood supply's biggest threat and the Public Health Service's most difficult challenge in 1981 when AIDS was first recognized and initial cases were reported.

Within a year, we were all confronted by the risk of AIDS. Among those at acute risk was anyone dependent on the life-sustaining power of blood and blood products.

In the early 1980's, the research community had not identified the AIDS virus and could not test for its presence in blood. It was not until 1985, that blood banks could confidently screen blood for the HIV virus and all but eliminate the risk to the blood supply.

This did not occur soon enough to prevent a true human tragedy. More than half of America's 16,000 hemophiliacs were infected by

the HIV virus through blood products, such as a coagulant known as Factor VIII. Thousands of others, including persons without hemophilia, were infected by blood transfusions.

Mr. Chairman, I would be remiss if I did not attempt to put a human face on these statistics that we sometimes cite too quickly. These thousands of cases represent fathers and mothers and sons and daughters, and our hearts go out to them. We do not consider the Department's responsibilities regarding blood safety without thinking of the human faces behind the statistics.

Indeed, in my own office are the pictures drawn by children, some of whom were infected during this period, to remind me of the Public Health Service's responsibility in this area.

In response to congressional and other public concerns about the events of the 1980's, 2 years ago I asked the Institute of Medicine to undertake a comprehensive study of the events surrounding HIV transmission to people with hemophilia. The Institute's report, published last July, covers the period of 1982 to 1986, and the decision-making process during that time. The Institute of Medicine did not review blood regulation after 1986.

The Institute stated that it undertook its assignment "with the intent to prepare the guardians of the blood supply for future threats concerning blood safety." Upon issuance of the report, IOM cautioned: "The danger of hindsight is unfairly finding fault with decisions that were made in the context of great uncertainty."

I agree. We are interested in exploring the past only so the present and future blood supplies will be safer. As the Institute of Medicine noted, the report deals with a period of uncertainty when medical providers and researchers grappled with a disease of unknown origin with unpredictable outcomes. As early as 1982, there were cases of AIDS in persons who received blood products, suggesting that some components of the blood supply might be contaminated.

These suspicions created a major dilemma for the public health community. In the case of people with hemophilia, the quandary was especially difficult. Blood-clotting factors were miracle products primarily responsible for nearly doubling the life span of people with hemophilia. When questions arose about possible contamination of these products, patients and their doctors had legitimate concerns that any attempts to safeguard clotting factors could also jeopardize their availability.

The IOM report notes that recommendations about donor screening, viral inactivation, and recalls of blood products were considered in the early 1980's. According to the Institute of Medicine, it took some time before sufficient scientific and political support was in place to facilitate the implementation of such safeguards.

Perhaps the Department could have moved more quickly to adopt those proposals. I believe the IOM report shows that our entire public health system missed opportunities to intervene and to save lives.

On July 13, 1995, the day the IOM report was issued, I created a task force of seven senior public health officials to assess the IOM's recommendations and report their conclusions to me. The task force was chaired by the Assistant Secretary of Health and comprised of the Commissioner of the FDA, the Director of the

CDC, and the Director of the National Institutes of Health. Three senior career officers from each of the Public Health Service Agencies also served on the task force.

I am pleased to present the task force report to the subcommittee today. But before I discuss the task force recommendations, I want to emphasize that the Department had already learned much from the AIDS experience long before we received the IOM's findings. Many of the IOM recommendations had already been implemented and in place for several years.

Our public health system is better prepared today to deal with an emerging infectious agent than it was in 1981. There is better science resulting from intensive research into bloodborne diseases. Nationwide disease surveillance systems cast wider and deeper nets today. There is greater oversight of blood manufacturing. There is extensive donor screening which is required, as well as routine testing for such diseases as HIV, hepatitis, and syphilis.

In order to maintain the safety of America's blood supply, it is important to be prepared to meet new challenges. If another infectious disease emerges, we want the Department to be fully prepared to deal with it quickly and effectively. Therefore, today I am directing that the recommendations of the Task Force on Blood Safety be implemented.

A great deal of thought and study went into these recommendations, first by the Institute of Medicine and then by the Department's Task Force on Blood Safety. I believe that implementation of the recommendations will enhance the Department's blood safety operations.

The first recommendation addresses one of IOM's more serious conclusions, that there was a lack of leadership in the Department in the early 1980's, a time when Federal public health officials differed about the appropriate safeguards for the blood supply. During this period, some key political leaders were openly hostile to massive Federal intervention in the AIDS crisis, according to the Institute of Medicine.

Blood safety must never again be handled as a secondary issue. I am elevating it to the highest level of the Department. I will designate the Assistant Secretary for Health to be the Department's Blood Safety Director, with overall responsibility for coordination and oversight of the Public Health Service's blood safety programs.

Reporting to the Blood Safety Director will be a Blood Safety Committee. The committee's membership will include the Commissioner of FDA, the Director of CDC, and the Director of the National Institutes of Health. The committee will be serviced by the Advisory Council on Blood Safety and Availability. The advisory group will include representatives of industry, consumers, scientific experts, and ethicists.

The Advisory Council will provide a forum in which to examine broad public health and societal implications of blood safety issues. These include availability, informed consent, social choice, the allocation of research resources, and the impact of economic factors on availability.

The Public Health Service Agencies have separate responsibilities in the blood safety areas, but they will serve together on the Blood Safety Committee. We will transform a system that has

sometimes been plodding into one that can reach decisions and implement them quickly.

The Blood Safety Director and the committee will not supersede the authority of the FDA. The Commissioner of FDA will continue to be ultimately responsible for regulatory decisions regarding blood safety. The Commissioner should continue to seek scientific advice and expertise from his FDA Blood Products Advisory Committee.

The FDA Advisory Committee's role will be directed to matters pertaining to FDA. All issues outside of FDA's purview will be considered by the new Blood Safety Committee operating at the Department and Secretarial level.

The purpose of appointing the Director and committee is to facilitate leadership and give priority to blood safety issues at the highest level during times of crisis and disagreement. For example, had there been a Blood Safety Director and the committee in the 1980's, I believe the Federal Government would have acted sooner and more responsively to early suspicions about HIV contamination of the blood supply.

The task force agreed with IOM that the Department must be responsive to CDC's early warning system about threats to public health. CDC will maintain its internal working group of blood safety. This group coordinates blood safety issues and evaluates any new or potential threats to the blood supply.

CDC will also continue to refine and upgrade its comprehensive surveillance system as technological advances occur. CDC will emphasize research on the risk of transmission of newly recognized or emerging infectious diseases in the blood supply and CDC will now have a permanent seat on the FDA Blood Products Advisory Committee.

In regard to the Advisory Committee, the task force recommends that it reflect a better balance between industry and consumers. In fact, FDA expanded consumer representation of the Advisory Committee last year. Now the agency is going even further. Anyone with the appearance of a conflict of interest resulting from their connection to the blood industry will no longer have voting privileges on the Blood Products Advisory Committee. They will, however, continue to provide scientific support as consultants.

IOM also expressed concern that the public did not receive sufficient information about risks to the blood supply in 1981 and 1982. The task force agrees. The new Blood Safety Committee will coordinate information about emerging risks of bloodborne diseases transmitted to any potential users of blood products as quickly as possible and the committee will report directly to me on its activities.

In order for the Department to keep the public informed and base regulatory decisions on sound science, our experts must have current and complete data on the blood supply. The task force recommends that the Department consider new options for expanding the authority of the Public Health Service to collect data. This effort will be one of the first responsibilities of the new Blood Safety Committee.

The implementation of these major recommendations of the IOM and other reforms proposed by the Task Force on Blood Safety will

give blood safety the highest possible priority in the Department. There will be strong leadership on blood safety issues. There will be coordination. There will be identification of resource needs. Consumers will have a larger voice and there will be additional scientific expertise.

The transmission of HIV by blood and blood products in the 1980's was a catastrophe, but we have learned something from that experience and we are using those lessons to enact safeguards that will make our blood supply safer than ever before.

Blood will always be capable of transmitting disease, Mr. Chairman, and its use will never be completely free of risk. But for everyone who relies on blood to sustain life, the Federal Government must and will do everything in its power to reduce risk and assure availability.

I look forward to working with the subcommittee as it pursues its review of blood safety. We greatly appreciate the opportunity to testify here this morning and we would be happy to answer any questions you may have.

[The prepared statement of Ms. Shalala follows:]

PREPARED STATEMENT OF DONNA SHALALA, SECRETARY, HEALTH AND HUMAN SERVICES

Good morning, Mr. Chairman and members of the subcommittee.

Thank you for the opportunity to discuss the Department's program for ensuring the safety of the Nation's blood supply. I know you are conducting this hearing because of your commitment to reducing the risks of contamination of blood and blood products. I am here today because I share your commitment.

The three and one half million Americans a year who receive whole blood or blood products can be assured that the United States has one of the safest blood supplies in the world. No one should hesitate to donate blood or receive blood when required.

The Department of Health and Human Services plays multiple roles in helping to ensure the safety and availability of our blood supply.

The Food and Drug Administration (FDA) regulates the blood industry by licensing products as well as issuing and enforcing safety rules. FDA also conducts research as an essential part of its science-based decision making.

The Centers for Disease Control and Prevention (CDC) use their nationwide surveillance system to identify and monitor blood-borne diseases. CDC advises the appropriate government officials when known or newly recognized diseases are identified as potential threats to the safety of the blood supply. CDC does research related to the risk of transmission of diseases directly through blood, as well as secondary transmission.

The National Institutes of Health (NIH) are engaged in ongoing research to improve blood banking operations and blood safety. For example, NIH is supporting work to develop methods of destroying infectious agents in blood components and is developing physician guidelines for the appropriate use of blood products.

Blood is human tissue and a natural vehicle for the transmission of infectious diseases. Putting someone else's blood into a person is an inherently risky medical procedure. The greatest risk, and our greatest fear, is of the unknown. We dread newly emerging infectious diseases that can be transmitted through blood.

Just such a disease became the blood supply's biggest threat and the Public Health Service's most difficult challenge in 1981, when AIDS was first recognized and initial cases reported. Within a year, we were all confronted by the risk of AIDS. Among those at acute risk was anyone dependent on the life-sustaining power of blood and blood products.

In the early 1980s, the research community had not identified the AIDS virus and could not test for its presence in blood. It was not until 1985 that blood banks could confidently screen blood for the HIV virus and all but eliminate the risk to the blood supply.

This did not occur soon enough to prevent a true human tragedy. More than half of America's sixteen thousand hemophiliacs were infected by the HIV virus through blood products, such as the coagulant known as Factor Eight. Thousands of others, including persons without hemophilia, were infected by blood transfusions.

Mr. Chairman, I would be remiss if I did not attempt to put a human face on these statistics that we sometimes cite too quickly. These thousands of cases represent fathers and mothers and sons and daughters. Our hearts go out to them, and we do not consider the Department's responsibilities regarding blood safety without thinking of the human faces behind the statistics.

In response to Congressional and other public concerns about the events of the 1980s, two years ago, I asked the Institute of Medicine (IOM) to undertake a comprehensive study of the events surrounding HIV transmission to people with hemophilia. The Institute's report, published last July, covers the period 1982–1986 and the decision-making process during that time.

IOM did not review blood regulation after 1986. The Institute stated that it undertook its assignment "with the intent to prepare the guardians of the blood supply for future threats concerning blood safety." Upon issuance of the report, IOM cautioned: "The danger of hindsight is unfairly finding fault with decisions that were made in the context of great uncertainty."

I agree. We are interested in exploring the past only so the present and future blood supplies will be safer.

As IOM noted, the report deals with a period of uncertainty, when medical providers and researchers grappled with a disease of unknown origin, with unpredictable outcomes. As early as 1982, there were cases of AIDS in persons who received blood products, suggesting that some components of the blood supply might be contaminated. These suspicions created a major dilemma for the public health community.

In the case of people with hemophilia, the quandary was especially difficult. Blood clotting factors were miracle products primarily responsible for nearly doubling the life span of people with hemophilia. When questions arose about possible contamination of these products, patients and their doctors had legitimate concerns that any attempts to safeguard clotting factors could also jeopardize their availability.

The IOM report notes that recommendations about donor screening, viral inactivation, and recalls of blood products were considered in the early 1980s. According to IOM, it took some time before sufficient scientific and political support was in place to facilitate the implementation of such safeguards.

Perhaps the Department could have moved more quickly to adopt those proposals. I believe the IOM report shows that our entire public health system missed opportunities to intervene and save lives.

On July 13, 1995, the day the IOM report was issued, I created a task force of seven senior public health officials to assess the IOM's recommendations and report their conclusions to me. The Task Force was chaired by the Assistant Secretary for Health, and comprised of the Commissioner of FDA, the Director of CDC, and the Director of NIH. Three senior career officers from each of the Public Health Service agencies also served on the Task Force.

I am pleased to present the Task Force's report to the subcommittee today. Before I discuss the Task Force's recommendations, I want to emphasize that the Department had already learned much from the AIDS experience long before we received the IOM's findings. Many of the IOM recommendations had already been implemented and in place for several years.

Our public health system is better prepared today to deal with an emerging infectious agent than it was in 1981. There is better science resulting from intensive research into blood-borne diseases. Nationwide disease surveillance systems cast wider and deeper nets. There is greater oversight of blood manufacturing. Extensive donor screening is required, as well as routine testing for such diseases as HIV, hepatitis, and syphilis.

In order to maintain the safety of America's blood supply, it is important to be prepared to meet new challenges. If another infectious disease emerges, we want the Department to be fully prepared to deal with it quickly and effectively. Therefore, today I am directing that the recommendations of the Task Force on Blood Safety be implemented.

A great deal of thought and study went into these recommendations, first by IOM, and then by the Department's Task Force on Blood Safety. I believe implementation of the recommendations will enhance the Department's blood safety operations.

The first recommendation addresses one of IOM's more serious conclusions, that there was a lack of leadership in the Department in the early 1980s, a time when Federal public health officials differed about safeguards for the blood supply. During this period, some key political leaders were openly hostile to massive Federal intervention in the AIDS crisis, according to TOM.

Blood safety must never again be handled as a secondary issue. I am elevating it to the highest level of the Department. I will designate the Assistant Secretary for Health to be the Department's Blood Safety Director, with overall responsibility for coordination and oversight of the Public Health Service's blood safety programs.

Reporting to the Blood Safety Director will be a Blood Safety Committee. The Committee's membership will include the Commissioner of FDA, the Director of CDC, and the Director of NIH. The Committee will be served by the Advisory Council on Blood Safety and Availability. The advisory group will include representatives of industry, consumers, scientific experts, and ethicists.

The Advisory Council will provide a forum in which to examine broad public health and societal implications of blood safety issues. These include availability, informed consent, social choice, the allocation of research resources, and the impact of economic factors on availability.

The Public Health Service Agencies have separate responsibilities in the blood safety area, but they will serve together on the Blood Safety Committee. We will transform a system that had sometimes been plodding into one that can reach decisions and implement them quickly.

The Blood Safety Director and the Committee will not supersede the authority of FDA. The Commissioner of FDA will continue to be ultimately responsible for regulatory decisions regarding blood safety. The Commissioner should continue to seek scientific advice and expertise from the FDA Blood Products Advisory Committee.

The FDA Advisory Committee's role will be directed to matters pertaining to FDA. All issues outside FDA's purview will be considered by the new Blood Safety Committee operating at the Departmental level.

The purpose of appointing the Director and Committee is to facilitate leadership and give priority to blood safety issues at the highest level during times of crisis and disagreement. For example, had there been a Blood Safety Director and Committee in 1981, I believe the Federal Government would have acted sooner and more responsively to early suspicions about HIV contamination of the blood supply.

The Task Force agrees with IOM that the Department must be responsive to CDC's early warning system about threats to public health.

CDC will maintain its internal working group on blood safety. This group coordinates blood safety issues and evaluates any new or potential threats to the blood supply.

CDC will also continue to refine and upgrade its comprehensive surveillance systems, as technological advances occur. CDC will emphasize research on the risk of transmission of newly recognized or emerging infectious diseases in the blood supply.

CDC will now have a permanent seat on the FDA Blood Products Advisory Committee. In regard to the Advisory Committee, the Task Force recommends that it reflect a better balance between industry and consumers. In fact, FDA expanded consumer representation on the Advisory Committee last year. Now the Agency is going even farther. Anyone with the appearance of a conflict of interest resulting from their connection to the blood industry will no longer have voting privileges on the Blood Products Advisory Committee. They will, however, continue to provide scientific support as consultants.

IOM also expressed concern that the public did not receive sufficient information about risks to the blood supply in 1981 and 1982. The Task Force agrees. The new Blood Safety Committee will be responsible for the coordination of information about emerging risks of blood-borne diseases transmitted to any potential users of blood products as quickly as possible. The Committee will report directly to me on its activities.

In order for the Department to keep the public informed and base regulatory decisions on sound science, our experts must have current and complete data on the blood supply. The Task Force recommends that the Department consider new options for expanding the authority of the Public Health Service to collect data. This effort will be one of the first responsibilities of the Blood Safety Committee.

The implementation of these major recommendations and other reforms proposed by the Task Force on Blood Safety will give blood safety the highest possible priority in the Department.

There will be strong leadership on blood safety issues. There will be coordination. There will be the identification of resource needs. Consumers will have a larger voice. There will be additional scientific expertise.

The transmission of HIV by blood and blood products in the 1980s was a catastrophe. But we have learned something from that experience, and we are using those lessons to enact safeguards that we believe will make our blood supply safer than ever before.

Blood and blood products will always be capable of transmitting disease, and their use will never be completely free of risk. But for everyone who relies on blood to sustain life, the Federal Government will do everything in its power to reduce risk and assure availability

I look forward to working with the subcommittee as it pursues its review of blood safety. I greatly appreciate the opportunity to testify here this morning. I will be happy to answer any questions.

Thank you.

REPORT TO THE SECRETARY—TASK FORCE ON BLOOD SAFETY

INTRODUCTION

In July, 1993, at the request of Senators Kennedy and Graham and Representative Goss, Secretary Donna Shalala asked the Institute of Medicine (IOM) to review the events of the early 1980s, relating to the transfusion of HIV through blood products to more than half of the 16,000 hemophiliacs in the U.S. While recognizing that the blood supply in the United States is among the safest in the world, the Secretary believed that the results of such a study could be helpful in strengthening capacities to ensure the safety of the Nation's blood supply against new challenges in the future. The IOM convened an expert panel, which released its report on July 13, 1995.

Consistent with the HHS request, the panel did not review the existing blood safety program or the current safety of the blood supply, but rather, studied the events and public health organizational and decision-making structures of the early 1980s as they affected blood safety. Based upon this historical review, the panel developed 14 recommendations "that might have moderated some of the effects of the AIDS epidemic," and urged government and private organizations responsible for blood safety "to evaluate their current policies and procedures to see if they fully address the issues raised" by the recommendations. To conduct such an evaluation, including an overall review of HHS blood safety activities, Secretary Shalala appointed this Task Force.

After reviewing the IOM recommendations in the context of the existing blood safety system, the Task Force concluded that most of the recommendations had been addressed by improvements introduced since the mid-1980s. In light of the goals embodied in the IOM recommendations, however, the Task Force identified aspects of the Department's organizational structure surrounding blood safety decision making that could be strengthened. The proposed improvements involve broadening the formal avenues of advice available to FDA for certain decisions and improving high-level coordination among PHS agencies on blood safety issues. The Task Force also agreed with the IOM that FDA needs better information on blood availability and supply issues, but believed more study would be necessary before proposals could be made in that regard.

The Task Force's comments and recommendations follow the format of the IOM recommendations 1–14. In preparing this report, the Task Force met with representatives of a variety of organizations interested in blood safety issues. The Task Force believes that the report fully addresses the issues raised in the IOM report, and contains proposals that will further improve the safety of the U.S. blood supply.

Recommendation 1:

> The Secretary of Health and Human Services should designate a Blood Safety Director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.

The Task Force recommends that the Secretary designate the Assistant Secretary for Health to serve as the Blood Safety Director. The Task Force notes that the Assistant Secretary for Health has been broadly responsible for coordination and oversight of the blood safety program among the many responsibilities of this position; however, the Task Force believes it would be valuable to support and enhance this important function by clearly highlighting this responsibility within the Department's administrative structure. The Blood Safety Director would be responsible for coordination and oversight of the overall blood safety program of DHHS, and would serve as Chair of the Blood Safety Committee (see Recommendation #2). The Blood Safety Director would periodically report to the Secretary on issues of importance regarding blood safety and availability.

The Assistant Secretary for Health brings accountability at a senior level within the Department, and extensive professional experience and administrative expertise in coordinating interagency issues. Established working relationships between the Assistant Secretary for Health and PHS agencies around blood safety issues would facilitate quick implementation of the goals of this recommendation.

Recommendation 2:

The PBS should establish a Blood Safety Council to assess current and potential future threats to the blood supply, to propose strategies for overcoming these threats, to evaluate the response of the Public Health Service to these proposals, and to monitor the implementation of these strategies. The Council should report to the Blood Safety Director (see Recommendation 1). The Council should also nerve to alert scientists about the need, and opportunities for research to maximize the safety of blood and blood products. The Blood Safety Council should take the lead to ensure the education of public health officials, clinicians, and the public about the nature of threats to our nation's blood supply and the public health strategies for dealing with these threats.

Prior to the organizational changes now pending within the Department, the Assistant Secretary for Health had general responsibility for coordination and oversight of the Department's overall blood safety program, with the FDA Commissioner as the final decision maker on all regulatory matters. Surveillance efforts have been led by CDC and research on blood and blood products has been shared by the NIH, FDA and CDC. An interagency group, with representatives of FDA, CDC, NIH, HRSA, and the Department of Defense, constitutes the Public Health Service Interagency Working Group on Blood Safety and Availability. This group meets monthly by conference call. The conference call is an effective mechanism for sharing information and coordinating activities among the various government agencies involved in blood safety issues. Each agency is represented on the Working Group by public health officials with expertise in these issues.

FDA receives outside advice through its Blood Products Advisory Committee (BPAC), a scientific advisory group that includes representatives from interest groups in the blood safety arena. Outside groups also communicate informally with FDA and the other agencies, all of which maintain ongoing relationships with interested outside groups, including some formal liaisons.

While this arrangement has worked well and helped produce one of the safest blood supplies in the world, the goals embodied in the IOM's first two recommendations could be furthered by certain changes.

First, the Task Force recommends the formation of a PBS Blood Safety Committee, chaired by the Blood Safety Director and made up of the FDA Commissioner, the CDC Director, and the NIH Director, with the Public Health Service Interagency Working Group on Blood Safety and Availability reporting to this committee.

Under the Department's new organizational structure, the Public Health Services agencies will not routinely report to the Assistant Secretary for Health. The PHS Blood Safety Committee, with the Assistant Secretary for Health as its chair, will ensure the necessary coordination of policy and actions by the PHS agencies.

The PHS Blood Safety Committee would strengthen the interagency efforts that constitute the PHS blood safety program. Currently, the monthly interagency conference calls provide an effective forum for communication of information and ideas between PHS agencies. The Task Force believes it is important to create a forum for decision-making, priority setting, and high-level interagency coordination on key issues. The Blood Safety Committee would accomplish this.

The PHS Blood Safety Committee would meet several times each year on a scheduled basis, and would also meet at the request of any individual member, to accomodate quick action on priority issues. It would consider issues arising out of the monthly PHS Interagency Working Group on Blood Safety and Availability conference calls, assure that issues raised there were addressed, and allow for high-level, expeditious, interagency action on such issues where appropriate. The Interagency Working Group would routinely provide a report of the proceedings of this Group to the Chair of the Blood Safety Committee.

The Blood Safety Committee would serve the following functions outlined by the IOM in Recommendation 2: assessing threats to the blood supply, proposing strategies to address these, and evaluating the implementation and effectiveness of these strategies over time. Primary responsibility for identifying research needs and opportunities and conveying these to the scientific community would continue to remain with individual agencies. However, the Blood Safety Committee would ensure that new research questions regarding blood safety (such as emerging infectious agents) and availability raised by the PHS Interagency Working Group or the PHS Advisory Council on Blood Safety and Availability (see following page) are directed to the appropriate agencies for further exploration.

The Department would continue to carry out the responsibility for communicating information about risks in the blood supply to the public.

The Task Force believes that the functions outlined by the IOM for the Blood Safety Council are governmental functions that should be performed by the Depart-

ment, not by outside private parties. The Task Force makes the following recommendation to address the important role and contributions of those outside of government.

Second, a PBS Advisory Council on Blood Safety and Availability representing the range of interests in the blood safety area, including industry, consumers, and ethicists, should be appointed to advise the Committee.

As demonstrated by the events of the 1980s, decisions concerning blood safety may implicate basic societal values or highly politicized public health issues. Currently, HHS receives advice on blood safety and availability through the FDA's Blood Products Advisory Committee (BPAC). The primary mission of the BPAC is to provide expert scientific advice to the FDA on regulatory matters relating to the blood supply. For example, the BPAC is asked to evaluate the quality and sufficiency of data which are submitted to the Agency as a basis to validate either safety or efficacy of a novel product which is pending licensure. Such issues typically are brought before the BPAC when there is controversy over the applicable scientific standard, the interpretation of clinical trial data, or the net benefit of product approval despite limited effectiveness or potential toxicities. Additionally, the BPAC is used to obtain outside scientific input into policy decisions affecting the blood supply, to assess the importance of emerging threats and to evaluate the potential benefits of new technologies.

While FDA can and does seek advice from a wide range of sources, a more standardized, formal mechanism for seeking advice from sources outside the FDA on sensitive issues process. The Task Force concluded that there are advantages to having a broader range of advisory viewpoints available when issues inherently raise broader societal concerns that cannot be resolved through the evaluation of scientific data alone. The PHS Advisory Council on Blood Safety and Availability would provide a forum in which to examine the broad public health and scoietal implications of issues impacting on the safety and availability of the blood supply. The Task Force recommends inclusion of industry representatives on the Advisory Council because of importance of input and expertise from this sector; however, no industry representative would vote on particular issues in which they have a conflict of interest.

The range of issues considered by the Advisory Council would be: implications for blood safety and availability of various economic factors affecting product cost and supply; defining societal parameters around safety of the blood supply; broad ethical and legal issues, including discussion of appropriate informed consent; and the setting of global priorities such as allocation of research resources.

The Task Force is aware that this recommendation may appear to add additional layers of complexity and bureaucracy to the blood safety program at the Department, however the Task Force believes it does not. The Advisory Council would have the specific charge of advising on broad societal issues affecting blood safety and availability, not those requiring immediate Departmental action. The Task Force sees an important role for providing decision-makers with broad-based consumer input to establish a societal context within which to consider blood safety and availability issues. In contrast, the role of the BPAC would remain as a forum in which complex scientific regulatory issues could be rigorously considered, keeping decision-makers fully informed around developing scientific and technical matters. The Task Force believes the Advisory Council would be valuable in conjunction with the BPAC to maximize the Department's ability to address all areas of concern in maintaining a safe blood supply.

Recommendation 3:

The federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products.

The IOM report provided as a basis for this recommendation a concern for the ability of individuals to seek legal remedies due to blood shield laws. There are a wide range of legal issues involved here, such as the degree to which sufficient remedies or alternative resources are available to persons with blood-product related injuries. These issues are beyond the purview and expertise of public health officials at the Department of Health and Human Services and should be considered in a broader context.

Although the IOM report did not address issues of cost and availability of care as the basis for a compensation proposal, the Task Force recognizes the substantial needs faced by many individuals with HIV disease who are also affected by hemophilia. Both conditions are chronic, devastating illnesses requiring complex and costly medical care over time. The availability of insurance to meet these costs is often predicated upon the ability to work, and many individuals with HIV eventually require federal support through the Medicaid program. The Department has a number

of programs targeted to address this burden, such as the hemophilia treatment centers and Ryan White CARE Act, recognizing that resources are straining to meet the need. The Task Force acknowledges the important role of these programs but could not undertake to re-examine them in the context of this report.

Recommendation 4:

Other Federal agencies must understand, support, and respond to CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.

The Task Force agrees with this recommendation, and all of the HHS agencies understand the value and quality of CDC's work. The key to assuring that this recommendation is carried out is interagency communication, so that CDC's information about potential threats is widely known and understood. CDC has pursued this goal by, for example, participating in the monthly interagency conference calls of the PHS Interagency Working Group on Blood Safety and Availability and participating in meetings of the FDA Blood Products Advisory Committee. CDC's participation in the recommended PHS Blood Safety Committee would further assure that CDC's views are well known to all HHS agencies responsible for the safety of the blood supply.

CDC has also developed an internal working group to address issues of blood safety. The working group ensures better coordination of the different groups at CDC that work on individual pathogens, by focusing attention and effort on blood safety issues related to these different pathogens. This group is also able to consider and evaluate any new or newly recognized known or potential threats.

Recommendation 5:

The PBS should establish a surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in recipients of blood and blood products.

The Task Force agrees that surveillance is vital. PHS now has comprehensive surveillance systems in place, and refinements are continuing. CDC has a number of different systems for surveillance of current or potential threats related to transfusion of blood/blood products. These include disease-specific surveillance systems (e.g. hepatitis viruses and AIDS), donor-based systems (for HIV), and recipient population-based systems (e.g. among hemophiliacs). Identification of previously unknown agents may occur through epidemic investigations or Emerging Infection projects. The CDC routinely provides input to the FDA's Blood Products Advisory Committee, affording the Committee the benefit of this surveillance expertise.

Special studies have also been used to assess the magnitude of the risk, if any, for transmission of agents by blood/blood products, such as variant HIV strains, idiopathic CD4+ T-lymphocytopenia (ICL), and hepatitis C from intravenous immunoglobulin (IVIG). Surveillance studies are enhanced by use of quantitative decision analyses which can contribute to appropriate evaluation of potential threats to the blood supply. In addition, applied research that enhances the safety of the blood supply is conducted both at FDA and at CDC. At NIH, the Retrovirus Epidemiology in Donors Study plays an important role in the Department's surveillance efforts.

The Task Force notes that the success of certain components of HHS' surveillance system is dependent in part upon the public health infrastructure at the state, local and provider level. This public health infrastructure for the reporting of new events maximizes the effectiveness of existing surveillance networks.

Recommendation 6:

Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

The Task Force agrees with this recommendation with reservations. FDA has already utilized the stated principle in its decision-making since 1986. For example:

Since 1987, FDA has approved product amendments for viral inactivation of clotting factor concentrates and immune globulins using solvent-detergent incubation procedures despite the fact that these methods are effective only for enveloped viruses, which account for all major known transmitted diseases.

In 1990, FDA approved the first donor screening test for antibodies to hepatitis C virus (HCV) despite estimates that the test could at best prevent only about 70% of non-A, non-B post-transfusion hepatitis.

In 1992, the FDA recommended donor screening for HIV–2 despite the rarity of HIV–2 infections in North America. This measure was taken when the avail-

ability of combination HIV–1/HIV–2 antibody tests made it possible to provide a preventive measure of uncertain benefit without the addition of risk.

The Task Force notes, with reservation, that risk analyses are not always possible, because of missing data or a lack of complete scientific understanding. It may be extremely difficult to develop a quantitative assessment of low risks. Also, it is not always possible to assure lack of harm from any intervention, and it can be dangerous to presume absence of harm where data are lacking.

Recommendation 7:

The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

The Task Force agrees with this recommendation. FDA has implemented such periodic review for numerous decisions made since 1986. For example:

FDA has recently reexamined the question whether to screen the blood supply for HIV–1 antigen. A decision against such screening was made in 1989 when the available data showed a lack of efficacy. Based on new information, the issue was brought to public discussion again in 1995. On the basis of this discussion, FDA now has decided to recommend donor screening for HIV–1 antigen, once the test becomes available for blood screening.

A test for antibodies to HIV–2 was first approved in 1990, but was not recommended for use in donor screening due to the rarity of HIV–2 infections in North America and the predicted negative impacts of adding a donor screening test. This decision was reexamined in 1991 after combination tests for HIV–1/HIV–2 antibodies, as well as results of additional surveillance studies, became available.

In 1978 an FDA Advisory Panel recommended discontinuation of the donor screening test for syphilis. FDA was about to publish a proposed rule to discontinue the test in 1985. This action was reconsidered in face of the AIDS epidemic, and the test was retained as a surrogate marker for risk of sexually transmitted diseases, including AIDS. The latter decision is now being reexamined.

Recommendation 8:

Because regulators must rely heavily on the performance of the industry to accomplish blood safety goals, the FDA must articulate its requests or requirements in forms that are understandable and implementable by regulated entities. In particular, when issuing instructions to regulated entities, the FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.

The Task Force agrees that FDA's communications should be clear, and believes that FDA has made many improvements in this regard since 1986. For example, FDA has increased its use of Advisory Committees, public meetings and workshops as means to communicate its expectations through public discussion, and has issued increasingly specific guidance to regulated industry through Guidelines, Points to Consider and Recommendations. In addition, FDA has made increasing use of compliance policy guidance documents to clarify its positions on enforcement. Guidance documents are used to provide clarification and education but are not legally binding on either the industry or the agency.

Under existing authorities, FDA can promulgate regulations either through notice and comment rulemaking or directly under its emergency authorities should an urgent public health need exist. Alternatively, FDA may issue guidance documents as a vehicle of rapid communication. As long as guidance documents are treated as non-binding, the federal Administrative Procedures Act does not require notice-and-comment rulemaking. FDA uses these alternative approaches as appropriate.

In the past, FDA communication to the blood industry has often taken the form of recommendations, rather than regulations, in part because of the length of the regulations development process and the resources required. It is also impractical for FDA to rely on its emergency rulemaking authorities routinely. The Task Force is aware of concerns within the blood products industry regarding FDA guidance issued outside of the rulemaking process. Industry views the rulemaking process as a comprehensive one with clear parameters for evaluation. One area for further consideration is whether the rule-making process could be expedited to allow more timely, formal FDA guidance on blood safety issues.

FDA will continue to strive to communicate the most recent information available, in the clearest manner possible, and specifically identify those requirements that are binding. Where the agency does not engage in formal rulemaking, the FDA will remain mindful of the need for public discussion and input.

Recommendation 9:

The FDA should ensure that the competition of the Blood Products Advisory Committee reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.

The Task Force agrees with this recommendation, and notes that FDA has been attentive in recent years to the issue of representation on its advisory committees. Responding in part to an earlier IOM report, FDA restructured the Blood Products Advisory Committee in 1994, expanding consumer representation through voting consultants. This status was reserved by FDA for individuals who bring specific expertise on an issue and who have no conflict of interest bearing on the issue under consideration. In 1995, the charter was revised to expand the possibility for voting representatives with consumer interests. Also, in 1995, FDA removed advisory committee members with any appearance of a conflict of interest, except for a single, designated, non-voting industry representative. The scientific expertise and input of industry are available to BPAC through invitations to industry representatives to participate as non-voting consultants on an ad hoc basis, and through industry participation in Open Public Hearings at all BPAC meetings.

The Task Force reviewed criticism of blood industry organizations that there is now insufficient technical expertise on the BPAC.

While FDA is considering changes in this regard, the Task Force believes that BPAC can fulfill its obligations in its current format, using industry consultants where necessary. Whereas the role of industry in voting on BPAC proceedings has been eliminated as a result of reforms, industry input in terms of scientific data and expertise must remain strong.

Recommendation 10:

The FDA should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.

The Task Force agrees with this recommendation, and notes that FDA, not BPAC itself, provides the agendas for discussion at the meetings. The Task Force believes that FDA currently manages the Blood Products Advisory Committee well and communicates expectations clearly. In particular:

FDA routinely provides members of the Advisory Committee with a summary of each issue to be discussed at the upcoming meeting, including all relevant publications and summaries of presentations. Additionally, FDA provides its own analysis of each issue, its policy position, and a set of options and/or questions for committee consideration. FDA formats such discussion items in a manner likely to sharpen the committee focus, such as by asking "yes or no" questions on critical points affecting FDA decisions.

FDA evaluates its committee members first through a selection process, and then through a review of their performance at the time of renewal of appointment. FDA considers such factors as participation in the meetings, contribution to the discussion of issues and other engagement with the business of the Agency, such as service on site visit teams.

Recommendation 11:

The PBS should develop reliable sources for the information that it needs to make decisions about the blood supply. The PBS should have its own capacity to analyze this information and to predict the effects of regulatory decisions.

The Task Force agrees with the premise of this recommendation, but believes that additional study is necessary to determine whether, or to what degree, it is feasible to implement. Although FDA gathers and analyzes data as needed to enhance decision making, the agency still lacks independent information in certain key areas bearing on product supply, distribution and cost which may affect the safety, efficacy or availability of products. The availability of such information to FDA and the rest of PHS would enhance decision making in the realm of blood safety. However, new data collection could be expensive and difficult for HHS.

One option to obtain this information would be through expanded PHS authority to access data, or through additional record keeping requirements. Another alternative would be to leave data collection on economic aspects of the blood industry to outside organizations, with PHS participation in the analysis and interpretation of such data. A third option is to rely on voluntary reporting of data by industry. A fourth option is for the Secretary to ask the Office of the Inspector General to do compliance audits to determine the accuracy or the data provided to FDA.

CDC has expressed interest in collaborating with FDA to assess the feasibility of implementing this recommendation. Such an assessment will continue over the next six months, and will include an evaluation of benefits to be obtained through addi-

tional information collection, weighed against the burdens and costs such activity would impose upon HHS and upon the blood industry.

Recommendation 12:

When faced with a decision in which all options carry risk, especially if the amount of risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.

The Task Force agrees, and believes that the level of informed discussion occurring between doctors and patients has risen since the early 1980s.

Recommendation 13:

The Department of Health and Human Services should convene a expert panel to inform the providers of care and the public about the risks associated with blood and blood products, about alternatives to using them, and about treatments that have the support of the scientific record.

While a standing expert panel might not be the most effective means available, the Task Force agrees that this type of clinically useful information should be communicated as it becomes available. As issues of importance arise, the PHS Blood Safety Committee and the Advisory Council on Blood Safety and Availability will evaluate the government's communication efforts, including the activities of the Agency for Health Care Policy and Research and its clinical guidelines program, to determine what additional efforts are needed.

Recommendation 14:

Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgment, and otherwise act so as to earn the confidence of the public and patients.

The Task Force agrees with the premise of this recommendation.

Mr. SHAYS. Madame Secretary, I thank you for your very thoughtful testimony. And given the importance of it, I am happy that it was given in its entirety. My questions can be directed to you as well as Dr. Lee.

First off, in your opening statement, you said we had one of the best, safest, blood supplies. Do you think it used to be the safest and now is one of the safest, or should I read anything into that?

Ms. SHALALA. No, you shouldn't read anything into it. The blood supply is as safe as the donors that give blood. And there are, in fact, Scandinavian countries that are considered stronger, not because they have a better oversight system but because of the nature of their donors in terms of the homogeneity of their donors. But in terms of the kind of safety and precautions that we have put in place.

Mr. SHAYS. Our process can match any process around the world?

Ms. SHALALA. Yes.

Mr. SHAYS. My sense is as I have been trying to understand this issue better, that the same kind of challenge that we faced in the early 1980's with HIV and the introduction of this dreaded disease, we could potentially end up with diseases that we have no concept of now that could match HIV in terms of its impact on society.

And is this the result of what, Doctor? I mean, why is this the case? I mean, is it the interaction that exists in our world? And, first off, one, is it true and, second, why?

Dr. LEE. Well, I would say definitely it is true. And with the newly emerging infections, and HIV was just one of those, we saw subsequent to that the Hontavirus outbreak in Arizona with very quick response from CDC, which really cut it off.

But we are at risk because of the global nature now of our transportation. We have got people moving globally constantly. An infec-

tion developing—the example of the Ebola Virus outbreak in Africa. Again, with CDC and WHO intervention, promptly controlled.

But we can expect, I think, and we must be prepared to anticipate, the emergence of new virus infections. Eternal vigilance is absolutely essential in this case, and that is one of the reasons that CDC and NIH both and the FDA are all working very aggressively in the area of newly emerging infections.

Ms. SHALALA. Mr. Chairman, if I might add, in our budgets we have tried to ask for new investments in these units that are related to emerging diseases.

And Dr. Lee and I have a particular concern about, if I might go to another area, about the debate about international organizations and the funding of the World Health Organization in particular because they are, in fact, our international partners.

And unless the World Health Organization has its funding on these emergency diseases, the rest of the world is totally dependent on the Centers for Disease Control. We need these international investments. And that is a perfect example of something that may have an impact on U.S. health.

Mr. SHAYS. I have no problem with you going into a little more depth on that. Is your concern that we, in fact, aren't providing our fair share to the World Health Organization?

Ms. SHALALA. No, I'm concerned because we are cutting back on the investments in international organizations with all the debate about the U.N. And I hope that people remember that some of these organizations, like the World Health Organization, are part of this international partnership.

I will be going to Africa to take a look at both the emerging diseases issue, as well as the AIDS issue, in December, first with the Vice President and then on my own.

But we have to make sure that we maintain this country's leadership capacity at the CDC, at the National Institutes of Health, as well as our partnership with organizations like the World Health Organization which has the strong lead around the world on these emerging diseases, both from a research point of view, as well as these quick response teams that get out there. I hope that as we see these issues as an international issue, not simply an American issue.

Mr. SHAYS. Your point is well taken. I think your point is absolutely right on target. Let me just respond to your proposal.

The first basic point that I am hearing you say in your testimony is that there was almost a belligerence on the part of the government to respond to the contamination of our blood supply. And you are raising—making sure that you have—that we respond by ensuring that there be someone at the highest level to monitor this and to organize it, and also in terms of your committee.

But let me just ask you this, and then I will get in more detail. First, it was the belligerence of our government to respond quickly—the people in power, political leaders and so on, well before your time. And, second, that we failed to get information out to the public.

Were those the only two basic challenges that you saw, because that is what I am reading in your testimony?

Ms. SHALALA. Well, in my testimony I also point out that for a whole group of people, hemophiliacs for example, a challenge that would reduce their access to blood, to blood supplies which extended their life, also led to the complexity of the issue.

It is clear cut from the point of view that we know that people did not make quick, effective decisions looking backwards, but it was a tremendously complicated debate. And it wasn't just the government. It was the oversight, obviously, during that period. So it was really all of us.

What we are trying to do is to put a system in place in which it can no longer be hidden in which one part of HHS will not be a voice in the wilderness about something emerging, in which they will have not only a seat at the table but will force the decision-making and at the highest levels of the Department.

But in the end, unless you have tough, courageous people in these positions—and let me point out, Mr. Chairman, I was never asked about the Nation's blood supply at my own confirmation hearing. If this is so important to us, if we need to raise this to this level, every Secretary of HHS ought to be asked about how they would make decisions, how they think about these issues about the blood supply, about emerging diseases because, in fact, this is not something one can push off on State government in which there is shared responsibility.

Dr. LEE. Also, just one added point, Mr. Chairman. The level of scientific uncertainty in the early and mid-1980's was very great. There was disagreement among the scientists and the physicians on a number of these issues. And that same problem we face today. I mean, the scientific uncertainty.

I think in moving to organize the approach as the Secretary has, we are trying to diminish that to the maximum extent possible and keep the process, as she points out, as open as possible.

Mr. SHAYS. From your statement, the Assistant Secretary of Health will be the Department's Blood Safety Director, and then you have reorganized the FDA's Blood Products Advisory Committee.

Ms. SHALALA. Yes.

Mr. SHAYS. Just explain before I go to you, Mr. Chrysler, how your statement that the Blood Safety Director and the committee will not supersede the authority of the FDA. Explain the significance of that statement, if you will.

Ms. SHALALA. Well, the FDA has the regulatory authority as an independent regulatory agency. That does not mean that the FDA Commissioner doesn't report to the Secretary, but just that we are protecting the independence of the regulatory authority of the FDA.

Mr. SHAYS. Fine, thank you.

Ms. SHALALA. But those regulations, as you know, must go to the Secretary for signature and to the Office of Management and Budget at the same time. But we need to preserve a regulatory agency at the same time.

Mr. SHAYS. Thank you. Actually, Mr. Green, if you don't mind, I will go to Mr. Chrysler and then we will go to you.

Mr. Chrysler.

Mr. CHRYSLER. Thank you. Mrs. Shalala, how will the National Advisory Council avoid duplication of the role of the Blood Products Advisory Committee?

Ms. SHALALA. Let me have Phil sort that out.

Dr. LEE. The BPAC, or the Blood Products Advisory Committee, will focus on the scientific and technical issues that relate specifically to FDA regulations. The Advisory Council, which is dealing with both blood safety and availability, will look at the broader ethical issues.

As the Secretary pointed out, there are legal questions, some raised in the IOM report. They are broader issues of social policy that they will address. They may relate to, for example, the CDC surveillance activities or the NIH research activities—are we investing sufficiently in those areas—as well as looking at the process for regulation. But the Advisory Council will not deal with the technical and scientific issues directly affecting FDA regulation.

Ms. SHALALA. Congressman Chrysler, one of the things that the IOM review made very clear is that there was lots of advice to the Department, but it was too fragmented. FDA needed a certain kind of technical advice and that we needed a broader committee with outside representation, in addition to getting the coordination done within the Department. And that is the recommendation that we responded to.

Mr. CHRYSLER. Do you support the compensation for the victims?

Ms. SHALALA. IOM didn't really take that up, and we have not reviewed that issue. I know there is some interest in Congress and we would be pleased to have further conversations, but we have not gone through a review on that issue.

Mr. CHRYSLER. Thank you.

Mr. SHAYS. Mr. Green.

Mr. GREEN. Thank you, Mr. Chairman. And I will submit a statement for the record, but I want to thank the chairman for calling the hearing because this is an issue that, like our Secretary said, you weren't asked at your confirmation hearings, but it is of great concern to all of our constituents. And it may not be on the top level. Obviously, Medicare, Medicaid, and lots of other issues are, but this is one that everybody is concerned about.

One of the interesting things I noticed was the committee, the Blood Product Advisory Committee, considered approval of the HIV antigen testing, but then they recommended against that screening despite a unanimous finding that the tests were effective. Ostensibly, this recommendation was made because of the concern over the cost of the test, even with that unanimous finding.

Is it within the BPAC's discretion to take cost considerations into account when making those recommendations, and how frequently do cost considerations influence approval of testing procedures that would improve the blood safety?

Ms. SHALALA. There is no statutory requirement to consider cost-effectiveness of products or methods designed to safeguard blood; however, the FDA is responsible for insuring the availability as well as the safety of blood and blood products.

And they think, and we do, that it is appropriate to consider cost only when it may impact on availability. In the case of the HIV antigen test, FDA did not accept the Advisory Committee's rec-

ommendation and approve use of the test. This is another example of a controversial matter that will, in the future, be brought before the Department's Blood Safety Committee.

Now, I don't know whether Phil wants to add anything.

Dr. LEE. No, I think that is just basically the issue. And in an open discussion, the committee can take up a lot of considerations. The Commissioner in his decision looked at safety and effectiveness, and that was the basis for the Commissioner's decision.

And, yet, in a discussion, the committee could consider that. But when the decision was made by the Commissioner it was safety and effectiveness, which is the legislation that governs the FDA's Commissioner's decisions.

Mr. GREEN. Did the committee find that the tests were effective?

Dr. LEE. Absolutely.

Mr. GREEN. And the Commissioner found that, but still the Commissioner made the decision not to require it?

Dr. LEE. The Commissioner is requiring it. The Commissioner, of course, did not accept the committee's recommendations. He has required it and there is one test that has been developed and another that is under the development for HIV antigen.

Mr. GREEN. The committee recommended against the screening and the Commissioner decided to start it?

Dr. LEE. Correct.

Mr. GREEN. The Institute of Medicine reports and suggests that political hostility earlier in the last decade may have slowed the response of Federal agencies to HIV threat in the blood supply. And you mentioned some, and my colleague mentioned some, of the tragedies that occurred. And many consumer blood products became infected then.

The blood safety is a fundamental and apolitical issue. It's a human issue. What measures do we propose, or do you propose, for depoliticizing the decisionmaking process? Again, whether it's HIV or some other disease that may become a political issue, it is still a disease and it strikes people no matter whether they are a Democrat or Republican or Independent.

Ms. SHALALA. I hope we have learned a lesson from HIV. Obviously, the issue of sexual orientation entered into the reluctance of officials and everybody else to act quickly. It is clear that the history is a sorry history that we do not want to repeat.

What we have clearly done is to elevate the importance of the decisions to put the top public health officials in the country, many of whom may or may not be political appointees at the time.

And, hopefully, we will learn from that history that diseases don't belong to one group, as Congressman Towns so eloquently pointed out. They don't know what party you are in or what your age is, what your economic group is. They may start off with one group, but they end up for all of us. And that we can simply never let this happen again in this country, or anyplace else in the world, I should point out.

Mr. GREEN. Thank you, Madame. Thank you, Mr. Chairman.

Mr. SHAYS. I thank the gentleman. Mr. Souder.

Mr. SOUDER. Pardon me, Madame Secretary, but I am confused a little on this safety-availability question. Could you and Dr. Lee

clarify that a little bit what you mean by that tradeoff between safety and availability that you don't want to have it just be safety?

Dr. LEE. Let me just say a word about that. If you had a test, for example, that would be very, very expensive for blood banks that might diminish the availability, or let's say you instituted some type of donor screening that would limit the availability of donors, you could reduce the availability of the blood supply.

Ms. SHALALA. And create another safety problem.

Dr. LEE. To such an extent that you would not have enough blood when you needed it. And that is the issue about availability. I mean, that is so that it isn't just the safety of the individual unit, but we have to have enough blood—we have to have enough Factor VIII—available.

Mr. SOUDER. And I understand that. I had another question, but let me ask—that I was going to ask. Are you saying if this test screens out blood that is unsafe, is that what it does?

Dr. LEE. No, I'm talking about if you have something that is very costly or if you have something that eliminates—for example, we are looking at certain diseases. And you eliminate those donors with those diseases, even though it hasn't been proven that that disease is transmitted through the blood supply.

Mr. SOUDER. So we're talking a level of risk that may not exist.

Dr. LEE. Exactly right, yes. And that is why the Advisory Council will be looking at the safety and availability issues.

Mr. SOUDER. So, in effect, you are saying that where the availability—I understand. And the question I was going to ask was directly related to that.

In other words, we always hear of the blood drives and the shortage of, in general, blood. And how much pressure is an increasing number of diseases, the number of the better screening tests we get, putting pressure on the blood supply itself?

And then that kind of backs into this other question of what is the acceptable level of risk and the precise testing, and how do we reassure people who are getting blood that it is safe and what that level of risk is in a society where there is no interest in really scientific data. They are willing to be scared on almost any allegation that is flying around.

I mean, it has been helpful and not helpful at the same time to have movies like Outbreak and the books that are going around, because just like we are dealing in environmental issues that we are not a very scientific-oriented society right now. We are a very emotional society.

And this is a very—what you are saying here is that, on the one hand, you have availability and you are willing to take a certain level of risk in that blood supply because you have to have this much blood.

How great is the pressure on the blood supply?

Dr. LEE. Well, it's also why it is important to try to increase the number of donors. I mean, we have a relatively small percentage of the population who are donors and they are regular donors. And if we could double the percentage we would then have a much better assurance with respect to the availability.

And so we have a job to do in educating the public. Many people think that they could get AIDS by donating blood. Of course, that

is not true at all. So we have a tremendous educational job to do with respect to the importance of donation.

Of course, the Red Cross has done a tremendous job in that area getting volunteers, as have other blood banks, so that the donor side of it is critically important. Educating potential donors and encouraging people to donate is very, very important.

Ms. SHALALA. Congressman Souder, Dr. Lee is referring to the fact that I have been chairing the Federal Employees Blood Drive to try to get the number of Federal employees to give regularly. If we can get that base, it would have a tremendous effect on the blood supply actually in the country.

So we are targeting specific groups—the military, civilian Federal employees—to see if we can get regular donors up. We'll take blood from any Congress person that would like to donate.

Mr. SOUDER. We're giving a lot already politically.

Staying away from the HIV virus, I don't even mean to get into this at all, but I would assume that the same pattern is true of almost any disease and the safety-availability question that there would always—how do you stay away from political pressures, particularly when you are just learning the risk variables that a group may be afraid that if they are labeled as unsafe to the blood supply it could have connotations on what kind of friendships, who is welcome, what kind of scare tactics?

And could not political pressures, in fact, affect a decision like this when safety factors could suggest something else?

Ms. SHALALA. I think the best way to answer that is that you start with the science. The best way of protecting the Nation's public health is to start with the best scientific advice you can possibly get and the best public health advice.

And it has got to be nonpartisan advice because a Secretary—essentially, you are asking me and Dr. Lee how we make these judgments. And we have to begin with our ultimate responsibility, which is to no political party but to the Nation's health.

And our job is to get the best scientific advice we possibly can. If that advice also leads to the point Dr. Lee was making, that if someone came up with a test that would take care of a certain disease but destroy the blood supply, then we would have that discussion. But we have not had that in that sort of way, but certainly at the margins that is the kind of decision.

We start by getting the best scientific evidence, the best public health evidence, and doing it as publicly as we possibly can so that the American people come along with us as part of the discussion. And it is elevated to the highest levels of the Department so that what you don't get is turf fighting between agencies over even the science.

Dr. LEE. I think the point that she made earlier about it has to be nonpartisan or bipartisan. This is not a partisan issue at all. It may be political in some sense. But if it is bipartisan or nonpartisan we avoid, I think, some of the problems that arose in the past.

Mr. SOUDER. Thank you very much.

Mr. SHAYS. I know Mr. Chrysler has another question. I do, as well. Do you have another question before the Secretary leaves?

Mr. GREEN. No, thank you.

Mr. SHAYS. If I could, I just want to—Mr. Chrysler, why don't you ask your question, then I will ask mine.

Mr. CHRYSLER. Thank you, Mr. Chairman. I just wanted to follow up with what Congressman Souder was asking. In this sound science concept, would that include recommending a reinfusion of community physicians into the management of what is considered the blood bank industry?

Dr. LEE. I think in terms of the management, one of the things that has caused some controversy recently has been our work with the Red Cross with respect to—and they have made major investments in improving their whole systems. And that has led to a more centralized approach by the Red Cross, which some of the local blood banks which have been affiliated with the Red Cross have been objecting to.

Now, the involvement of physicians is, in my view, critical in terms of local blood banks and also the process used by the National Red Cross. Exactly how that should be done, I think in the case of the Red Cross—which is about half of all the blood that is collected in the United States is done through Red Cross programs—that is really a decision for the leadership of the Red Cross to make.

Certainly, I would say that the leadership there has been outstanding in terms of what they have done over the last few years to give us greater assurance with respect to safety in the investments they have made, but I think it does cause them conflicts when you have had to centralize some of those processes to have the assurance that the blood supply is safe and the procedures are being followed in the appropriate way.

Ms. SHALALA. I think, Congressman Chrysler, Mrs. Dole, the president of the Red Cross, has made an extraordinary effort to upgrade the quality of management and of blood safety procedures, and in the process of setting higher standards. There may have been some conflict with some local communities. You have heard Dr. Lee and my attitudes about that.

But I can't say enough good about what the Red Cross has done. They have made a huge investment in improving the quality of their own oversight and of the blood supply. And it has been particularly Mrs. Dole's leadership and she has been very tough-minded about raising the standards.

Mr. CHRYSLER. Do you think, though, that centralization of the blood processing and the restrictive and sometimes inflexible regulations implemented by the FDA have the potential to destroy the system?

Ms. SHALALA. I can't answer the question as it is asked. What we have obviously been doing, both the Red Cross and the Department, is to raise and improve the standards so that no matter where you get blood in the United States the quality, the oversight, does not change.

I can imagine, knowing what I know about how difficult it is to run large complex organizations in which you are trying to get that kind of evenness. The only thing I would suggest to you is this is one area where you probably want us to be a little more rigid, a little more tough-minded, so that the quality of the blood supply in each part of the country is the same.

I think in terms of the management of the Red Cross, Mrs. Dole's effort has been to change the fundamental culture of that management so there is more accountability. And I would not describe that as more rigidly hierarchal, as opposed to spreading accountability throughout the system. So we have been partners in this effort and I am totally supportive of the steps that she has taken to do that.

Mr. SHAYS. If I could, I would like to ask this before you leave, and if you don't have the answer now I certainly understand. First, Dr. Lee, I want to make sure I am accurate on this. And I am asking this in response to testimony that is going to follow your testimony.

It is estimated between 100,000 to 200,000 people were infected with Hepatitis C virus prior to the licensing of the screening test in 1990. I get a little uneasy when I hear an estimate of 100,000 to 200,000 who are now presently unaware of their infection.

And I want to know if that is a legitimate statement, 100,000 to 200,000 people infected with Hepatitis C.

Dr. LEE. I think that is probably accurate. We can give it to you for the record from CDC, but I would say that it is rough estimate, yes.

Mr. SHAYS. OK. Now, the FDA's Blood Products Advisory Committee considered no notification issue seven times since 1989. Like in the case of HIV, we had Surgeon General Koop in 1985, say to those who had had blood transfusions that they needed to be tested for HIV.

And I guess the issue is, Madame Secretary, in light of I think your very important statement that, one, you needed to have the Assistant Secretary be in charge of this and you have a committee formed, the second was the whole issue of notification, I would want to know what criteria for HHS is—your mandated lookback procedures in public health notifications?

And I want to know how it would apply in this instance and whether you all would review whether or not those prior to 1990 shouldn't, in fact, be told that they should be tested for Hepatitis C.

Dr. LEE. We will actually review that again. As you know, the CDC and FDA have both reviewed that on more than one occasion. And our Blood Safety Committee, which I would chair with the Commissioner, with the Director of NIH, and with the Director of CDC, will review that issue. But that is the kind of issue that has to be addressed at that level.

Mr. SHAYS. Let me ask you though, this is an infectious disease. I mean, it can be transmitted to partners so if, in fact, we have 100,000 to 200,000 people who have Hepatitis C, shouldn't they be told about it and told to test for it to see if they, in fact, are one of those individuals?

Dr. LEE. Well, I think there is, again, a difference of view about that. And, again, the CDC has reviewed this. FDA has reviewed that. The decision has been made up to now not to do that lookback but, again, I think that is the kind of issue that needs to be reviewed.

Mr. SHAYS. Could I put that first on your list?

Dr. LEE. Absolutely.

Mr. SHAYS. I think that would be helpful.

Ms. SHALALA. Fair enough.

Mr. SHAYS. Thank you. We really appreciate your testimony and your statement and the answers to our questions.

Ms. SHALALA. Thank you.

Dr. LEE. Do you want me to stick around?

Mr. SHAYS. You know what, Dr. Lee, I think we are all set. I think that you have been very helpful to us and we are ready to proceed to our next panel.

But before I ask that next panel, we have our colleague, Mr. Porter Goss, who has been very interested in this issue, and I welcome him.

Is this for the purpose of an introduction primarily or a statement for the record? Just so you know, we would be happy to have you make that statement. No objection from our members. I would just need to tell you we will swear you in like all other members.

[Witness sworn.]

Mr. SHAYS. Thank you. It is nice to have you here, and we welcome your statement.

Mr. GOSS. Thank you, Mr. Chairman. Recognizing that I am under oath, I will tell you that I also am very glad that I am here. And that is heartfelt. I am delighted that this subcommittee is taking this step.

This has been a project of great concern for many years and this is a very positive step you are taking, and so I am thrilled. I apologize for being a little breathless getting here. I had another conflict. But this matters.

I would like to submit my prepared statement for the record, if I may?

Mr. SHAYS. Sure.

Mr. GOSS. And I will abbreviate very quickly because I know that you have others here.

Mr. SHAYS. You don't need to speak quickly though. You can speak at regular pace.

Mr. GOSS. Thank you very much, sir. This started some time ago for me when I found out, to my dismay, that there were an awful lot of victims out there who were going around, because they had relied on the U.S. Government to do its job in a way to protect what, in fact, was the Nation's blood supply, and that there was a failure; and that there were some terrible, terrible consequences to that failure.

I looked into some of the people who are part of that failure, and it is impossible not to be moved by their story or their plight. So I went back to see if there was any wrongdoing or what could we have done better. Was this just an accident? Was it circumstances recognizing that there are bad things in the world, and is this just one of those?

With the help of Senator Kennedy and Senator Bob Graham of Florida, we asked for some assistance from the administration. And the end result was we got a good response. And I am sorry I wasn't here to hear all that Secretary Shalala had to say.

They have made some changes, I know, as a result of what happened, based on the report from IOM, which is available to you. I believe that Secretary Shalala has spoken properly about looking

forward to making sure this never happens again and so forth. That is a very responsible position to take.

But it does not remove the fact that there are a bunch of victims out there, and it does not remove the fact that maybe we ought to try and figure out some way to help some of those people. This is not a small group. This is about 8,000 people who, through no fault of their own and through reliance on the process, on the system, and on the people who were paid to do the job right, became victims in the worst possible way.

Mr. SHAYS. Would you also include the 20,000 others who are not hemophiliacs as well?

Mr. GOSS. Of course I would. I have not gone into that into the same degree. Part of this has to do with the fact that this is somewhat constituent-driven in my own district.

We had an unfortunate situation where we had three victims, three young children, who became HIV infected. They were hemophiliacs. And the community where they lived in Florida, sadly, did not understand the implications of that or understand much about AIDS, and they burned them out.

I am happy to say that another nearby community in Florida, which is in my district, welcomed them with open arms and helped that family. And that is how I first got into this.

I have since discovered that there are people all over this country writing letters saying please give us some help, please give us some relief.

There are two things we have done in terms of positive legislation, to summarize this. One is the Advisory Committee, to try and rearrange what was clearly a conflict of interest, a too-close-for-comfort situation, between the people who were making the decisions about protecting the blood supply and the people who were producing the products that were being used. That was just crying for attention. It was an accident waiting to happen, and it happened.

The second area—and I understand that Secretary Shalala testified to some of the things that she has done to accommodate that problem—and I think that is a very positive step.

The second is a piece of legislation that we call the Ricky Ray Hemophilia Relief Fund Act, which is named after one of the young gentlemen who was an innocent victim. This is a 15 year-old Florida boy who got the disease well before he was 15, and I watched him disappear. It was not a happy process.

His family has been very involved. And what we have worked out is to try and find a compensatory fund, some relief for these families, because it turns out that there is not only a tremendous pain and suffering involved; there is an additional cost.

It is a practical thing. This will never make up for what these people have suffered, but it will begin to help them a little bit. And it is a recognition that we failed in our responsibility as the U.S. Government. That is the essence of it.

I would be happy to respond to any questions. We have many cosponsors, including you, as you know, and I am very thankful for that kind of leadership and support.

[The prepared statement of Hon. Porter Goss, and the April 27, 1993, letter to and response from Ms. Shalala follow:]

PREPARED STATEMENT OF HON. PORTER GOSS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Mr. Chairman: thank you for this opportunity to discuss my concerns about blood and blood product safety and the work that my staff and I have done in this area over the past 7 years.

As you may know, I have been working with a community of individuals—many of them children—who suffer from hemophilia-associated aids as a direct result of their use of contaminated blood products during the 1980's. The hemophilia community in the United States has been devastated by this tragedy—with approximately 8,000 people (or half the hemophilia population) afflicted by this terrible disease. They are dying at a rate of one each day.

Since coming to Congress I have come to know the families of many victims of this medical disaster—and have come to believe that the Federal Government has an obligation to assist them. In my view, the unique status blood products have enjoyed within the regulatory and legal framework, established and maintained by the Federal Government, makes this a unique situation that demands our attention.

In 1993, I joined with Senators Bob Graham and Ted Kennedy in asking the Secretary of HHS to review the events of the 1980's to understand how such a tragedy could have happened. In response, Secretary Shalala commissioned a study by the Institute of Medicine at the National Academy of Science.

After nearly two years, in July 1995 the distinguished panel of experts at IOM released its report, entitled "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking."

The IOM report catalogues a series of missed opportunities and failures of institutional leadership—pointing to the multi-faceted network of organizations (public and private) and individuals that share responsibility for protecting the safety of the Nation's supply of blood, and specifically blood products.

The IOM levelled strong criticism against the Federal Government—underscoring that Federal authorities "consistently chose the least aggressive option that was justifiable" and that the FDA "did not adequately use its regulatory authority and therefore missed opportunities to protect the public health."

The IOM also raised serious concerns about the make-up of the advisory panel upon which the FDA relied to make decisions concerning blood and blood product safety—the blood products advisory committee, better known as the BPAC. The report states that "the prominence of representatives from blood banks and blood products manufacturers on the BPAC, with no balancing influence from consumers and no process within the FDA to evaluate its recommendations, is a failure of advisory committee management."

The IOM panel made a series of recommendations stemming from this review in the interest of ensuring that a blood-products related tragedy like this one does not happen again. I am most pleased that HHS and the FDA have, in principle, embraced the conclusions of the IOM report and are in the process of instituting change along the lines of those recommendations.

I have introduced two bills dealing with this subject. The first, HR 1021, requires a change in the make-up of the FDA's BPAC, to ensure that at least one-third of the voting members of that panel are actual consumers of blood products. The intent of this legislation was to ensure that a better balance exists on that panel, providing an opportunity for those individuals whose lives are at stake to have a voice in the formulation of policy. We certainly understand the FDA's oft-stated concern that all members of that panel must have a minimum scientific understanding of the very complex issues involved, but my experience suggests that people with hemophilia have made themselves scientific experts because for them it is a matter of life and death.

We applaud the FDA for its recent decision to reconstitute the BPAC, asking all members with affiliations with blood banks to resign their voting positions. We do not yet know what the newly designed BPAC will look like—but we hope the FDA will take the recommendation of the IOM, and HR 1021, and ensure true balance of interests and perspectives.

The other legislation I have sponsored deals with the victims of this tragedy. As we make sure that the proper safeguards are in place to prevent another blood-borne disaster, we must not forget about the victims of the 1980's. HR 1023 authorizes a government compensation trust fund from which each victim could claim $125,000 in compassionate assistance. The premise behind this bill is that government failed to fulfill its unique responsibility for protecting the safety of blood products—and thus has an obligation to assist the victims.

I understand the concerns that some people have about setting a precedent with this bill. However, I am convinced that blood products are unique, and so establish-

ing a compensation program for victims of hemophilia-associated aids would not open the door for future liability in other cases involving other products. In addition to the unique regulatory structure that exists for blood and blood products, there is also a unique legal structure in place, one that the Federal Government has helped to maintain for many years by deferring to state blood shield laws, which grant blood products special status as a "service." These laws place a much larger burden of proof on victims of blood products—making it virtually impossible to seek damages through the court system. This is also a point the IOM discussed in its report.

Mr. Chairman, I know that the provisions of HR 1023 are outside the jurisdiction of this panel. But I wanted to discuss the bill briefly here today because I think it is important that we not forget those who have suffered from this tragedy as we work to prevent future disasters in this area. We have more than 135 bi-partisan cosponsors on HR 1023, and we hope to have hearings in the Judiciary Committee soon.

In the meantime, I applaud you for the work you are doing and hope that we can have in place proper safeguards to make such a tragic episode truly a thing of the past.

Thank you.

UNITED STATES SENATE
WASHINGTON, DC
April 27, 1993

The Honorable Donna Shalala
Secretary, Department of Health and Human Services
Room 614G, Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, DC 20201

DEAR SECRETARY SHALALA:

We respectfully request that the Department of Health and Human Services Office of the Inspector General investigate the issue of HIV transmission among hemophiliacs through contaminated blood products.

There are approximately 20,000 hemophiliacs in the United States. Tragically, at least half this population contracted HIV between 1982 and 1984 from contaminated blood product transfusions.

We ask that you review the events which led to this widespread transmission of HIV among hemophiliacs, including knowledge within the public and private sector regarding the possibility of transmission through blood products and the availability of other non-contaminated products. After your study, we ask that you provide us with a report on this issue.

If you should require further information regarding this request, please contact Susan Emmer (Sen. Graham) at 224–1535, or Michael Iskowitz (Sen. Kennedy) at 224–5880.

Sincerely,

EDWARD M. KENNEDY
BOB GRAHAM
PORTER GOSS

July 1, 1993

The Honorable Porter Goss
House of Representatives
Washington, D.C. 20510

DEAR MR. GOSS:

Thank you for your letter, also signed by Senators Kennedy and Graham, requesting that this Department's Office of the Inspector General investigate events leading to HIV transmission to hemophiliacs through contaminated blood products between the years 1982 and 1984.

I agree that it would be useful to gain a more complete understanding of the events that occurred in that period regarding the use of blood and blood products for transfusion and for treatment of those with hemophilia. Such a review would give us better insight into how medical knowledge and practice contribute overall to public health decisions regarding disease transmission in the earliest stages of an epidemic.

I am sure you appreciate that the blood supply in the United States is the safest in the world. But at the same time, I believe the results of a study could be helpful

in strengthening capacities to insure the safety of the Nation's blood supply against new challenges in the future.

Because a high level of scientific and medical expertise is required to conduct a thorough study, I have asked that the project be undertaken by the Institute of Medicine of the National Academy of Sciences, an external organization with proven experience in conducting studies of a similar nature. I have requested that my senior staff develop the necessary scope of work and make arrangements with the Institute to conduct this evaluation.

I am sending similar letters to Senators Edward Kennedy and Bob Graham.

Sincerely,

DONNA E. SHALALA

Mr. SHAYS. Well, let me just say that you were not an assigned witness here, and I apologize that, in fact, we didn't have you on our agenda right away to testify.

We did not ask the Secretary this issue and really we are talking about what we would do from this point on. And I don't know if—and it is something that this committee will, in fact, look into in some detail. I don't know if any of my colleagues on either side want to just comment or ask a question.

Mr. Souder.

Mr. SOUDER. I wanted to make a brief comment and then a side question or two. I had also a very emotional meeting with a number of people in my district office, including one lady whose husband was a hemophiliac and had died, one whose brother had died, and one young man who is in the process of dying who has three small children.

And part of the cost compensation question comes is that he is in danger of losing his home because he can't keep his job. The Ricky Rays were children, but this also has an effect on hemophiliacs who are adults and are at direct risk of being unable to support themselves. And that is when we get into the compensation question.

Part of our concern is that, particularly when you hear some of the numbers we just heard, is how do you put a dollar value and how do we do this equitably in our budget crunch? And we have many needs and I am very supportive of the legislation, and I hope to be able to talk to you about that in particular.

Now, also, I know Dr. Lee is still here. It would be very helpful in the process of us being able to work with his legislation, and others that may come up on this 100,000 to 200,000 people who are out there potentially that could be affected, to get more actual data on what has historically happened so we know what kind of potential liability we would get in.

Because if we start addressing some, potentially that would become a legal argument that we are acknowledging guilt in others. And we need to know what we are dealing with a little more precisely than saying that there are disagreements over who and how many.

Mr. GOSS. The question of committee jurisdiction is well known to me, and I agree with your comments. Indeed we are trying with the Judiciary Committee to do move this forward.

The chairman asked me the question about the hemophiliacs, and we are talking about the difference between blood products and whole blood. I think in terms of the jurisdiction of this committee, the question of the safety of the blood, of all blood products,

is critical. And I understand that distinction. And so that is why I answered the question that I did.

But with regard to the question of providing some kind of compensation, some kind of relief, which I admit is primary to the Judiciary—and I assure you I am headed there—I think we need to look backward there to deal with these people, which is why I brought it up here. Primarily, it is a plea for your support. And I know I already have yours and I appreciate that.

How we are going to pay for it, I promise you we are not going to suggest raising taxes. If I can't find the money someplace else in a lower priority or a waste, fraud and abuse situation, you will not be hearing from me.

Mr. SHAYS. Mr. Goss, we know you have been involved in this from day one and really thank you.

And I do want to correct the record. I did misspeak because you, in fact, did ask the Secretary about how we might deal with this. And she had left a pretty open response to neither have—the agency hasn't made—the Department has made a decision for or against this issue.

Is that correct, Dr. Lee?

Dr. LEE. We would be very glad to work with you.

Mr. SHAYS. Do you mind just coming up? The only purpose for asking you, I want to make sure that I am being very accurate in the Department's position and so on.

Dr. LEE. The Institute of Medicine report proposed a no-fault prospective system of compensation. The legislation, of course, proposes compensation for the victims of past practices. The Department, of course, would have to work with Justice, with Treasury, and others.

But we would be very pleased, as the Secretary indicated, to work with you, work with other committees, to work out some fair and equitable solution to what is a tragic situation.

Mr. SHAYS. Thank you. And that was, in fact, the sense of what the Secretary had said, so I'm sorry for the record I didn't acknowledge that.

Mr. GOSS. Mr. Chairman, I am very glad you asked that question and I am very pleased to hear that response. I am sorry I missed what the Secretary herself said but we, in fact, had made that request some time ago and I do not think we have gotten an answer yet. So I am much encouraged by what you have said.

Mr. SHAYS. I thank you, Mr. Goss, for being here.

Mr. GOSS. Thank you, Mr. Chairman.

Mr. SHAYS. We will get to our second panel. Our second panel is Patricia DeFilippi, Corey Dubin, John Penner, and Ronald Gilcher. Patricia DeFilippi is with the National Hemophiliac Foundation; Corey Dubin is the Council of 10,000 and the National Hemophiliac Federation; John Penner is the Michigan State University College of Human Medicine; and, Ronald Gilcher is Oklahoma Blood Center.

And I will swear in all the witnesses, so you can remain standing.

[Witnesses sworn.]

Mr. SHAYS. I welcome all of you here and appreciate very much your coming to testify. We will start as the order is in your seating, and we will start first with you, Mrs. DeFilippi.

STATEMENT OF PATRICIA DEFILIPPI, NATIONAL HEMOPHILIA FOUNDATION; COREY DUBIN, THE COUNCIL OF 10,000 AND THE NATIONAL HEMOPHILIA FEDERATION; JOHN PENNER, M.D., MICHIGAN STATE UNIVERSITY, COLLEGE OF HUMAN MEDICINE; AND, RONALD GILCHER, M.D., OKLAHOMA BLOOD CENTER

Mrs. DEFILIPPI. Mr. Chairman and members of the subcommittee, my name is Penny DeFilippi and I am here today on behalf of 20,000 persons with hemophilia, von Willebrand's disease, and other clotting deficiencies. Today, I am speaking as a member of the National Hemophilia Foundation, a voluntary health agency working to improve the health and welfare of people with bleeding disorders.

Today, I would like to tell you about my family's story and our exposure to hepatitis and other contaminants still found in blood and blood products. My family has probably been unknowingly affected by hemophilia and its repercussions for many generations. My grandmother used to say that, in our family, when a baby was born another child died.

Thanks to advances in modern medicine, that is no longer so. My sons are dependent on a blood-derived product known as clotting factor to supply the missing protein that allows their blood to clot normally. While this treatment means that our sons are no longer at risk of being crippled or dying of untreated bleeding, the products used to control their hemophilia continue to expose them to other diseases that are killing them.

My husband and I have two sons with hemophilia. I am an affected carrier of hemophilia, which means that I too can have problems with bleeding, though very rarely. My father grew up as an undiagnosed mild hemophiliac, attended West Point where he played football, was a veteran of the Pacific theater in World War II, and had a 30-year career as an Air Force officer. I remember that he suffered with continuous knee problems, diagnosed as water on the knee, and had major problems with his dental work and his tonsillectomy. Still, he was relatively healthy.

Our family, including my father, discovered we were affected by hemophilia when my older son, Geoffrey, had a routine blood test at age 2. He did not stop bleeding for 2 hours. Two years later, James was born and he, too, was diagnosed with hemophilia.

In 1981, when James was 2, he became extremely ill. He was diagnosed with Hepatitis B, transmitted to him through contaminated clotting factor. He spent much of the next 2 years in and out of the hospital. He was so ill at one point that he decided that he wanted to die so he could be reborn as our daughter. He thought that way he would no longer be sick.

The family stayed relatively healthy after James recovered and remained so until my father had major surgery and James went back for a new routine hemophilia check at about age 13. My father had developed gall bladder trouble and he had to have surgery and neglected to tell his physician that he had hemophilia. The re-

sult was a substantial amount of bleeding. He was heavily transfused, first with regular blood and then with cryoprecipitate and clotting factor.

Following his surgery, my father was diagnosed with Hepatitis non-A, non-B, a new disease that was being seen in the blood pool and was transmitted to him through blood products. Today, we call this disease Hepatitis C.

Three years later, after becoming sicker and sicker, he was admitted to the hospital with advanced liver failure. He was bleeding so heavily, in effect, he was drowning in his own blood. Despite an experimental procedure to bypass his liver, he died 2 weeks later at the age of 72.

Throughout my father's severe illness that preceded his death, my husband and I remained concerned about the chronic symptoms of Hepatitis B that James was exhibiting. His lab tests indicated he had no other form of hepatitis, so the doctors told us that if he avoided alcohol and drugs and was careful about his diet and was not further exposed to hepatitis, he might be fine.

But within 3 months of his grandfather's death, James was diagnosed with Hepatitis C, transmitted through the products he continued to use to treat his hemophilia. And it was time to pay the piper.

James' treating physicians at the University of North Carolina suggested that he begin a series of treatment with Alpha-Interferon. This drug was not licensed for use in children, but there was an experimental program being run here in Washington, DC, that James could participate in.

James had a closed liver biopsy, which showed that he had triaditis, a scarring of the ducts in his liver. He definitely needed Interferon therapy, and that required James to give himself painful injections in his thighs three times a week. James rows crew on the high school team so he has no body fat. That meant that the shots went directly into his muscle.

He eventually used all the sites on his upper thigh and was going to have to go elsewhere on his body, but it turned out to be unnecessary, as he developed an autoimmune reaction to this drug. Basically, he became allergic to it and he was forced to quit the therapy before it could cure him.

Although he was relieved not to have any more shots, James was concerned about his future and his ability to expose others. The doctors at Walter Reed Army Medical Center told James that the risk of transmitting his hepatitis was minimal and that he could live a normal life while he was healthy. This was not what we had heard from NHF, but it was what we wanted to hear.

At age 16, James fell in love with a lovely young lady I would like to call Allison. One night when they were kissing, his lip split and he bled into her mouth. He was concerned when he came home. I repeated what the doctors had told him, but James decided to double-check just to find out if Allison would be fine.

He called the doctors and they told him that they had not been completely honest: He had exposed her. She needed to call her doctor and begin treatment immediately.

It is unlikely that James will ever have as difficult a call to make as the one he made to Allison and her family that night. In the

end, although they did not blame James, she was not allowed to see him again.

Last winter, just to make the terrible even worse, we learned that these vials of Factor VIII that you see sitting here were contaminated with Creutzfeldt-Jakob Disease, or CJD, a fatal disease that can cause severe brain damage. James was exposed to CJD from this product which he had received from Walter Reed.

Six months before we were notified that the product James was using was contaminated, Walter Reed had destroyed their hospital supply of the product. Clearly, they knew it was dangerous, but they had not notified the patients who had a supply at home.

James is now a high school senior. He is 6 feet, 2 inches tall, captain of the crew team, a National Merit commended scholar, a lifeguard, and a swimmer. He has an offer from the Ford Agency to model next summer. He is applying to colleges. He dreams of early admission, a seat on the crew team, and a scholarship to Princeton.

James has hemophilia, Hepatitis B, Hepatitis C, and possibly CJD. He doesn't want to mention this in his college applications. He asked me directly, "Mom, does everything in my life have to be affected by hepatitis?"

I, too, soon face surgery for possible cancer, and I no longer trust the blood pool. I don't know yet how I will handle the potential need for blood. I add this to ongoing thoughts of how much more time we have until James' liver fails.

In my written testimony I have submitted details of NHF's recommendations, and I support those. The question asked by my son is the same as the one for every member of the hemophilia community and the bleeding disorder community: When the discussion is either hepatitis, CJD, or HIV, are the blood and blood products we depend on safe?

The question is no longer isolated to our community but does have national significance. Ask yourselves, do you know anyone who has a knowledge of the blood supply who would not donate their own blood prior to surgery? Are we fulfilling our responsibilities to Americans to maintain a safe blood supply?

I ask this panel to help other families so that they do not have to watch their family members go through what our family has gone through. Thank you for your patience and your compassion.

[The prepared statement of Mrs. DeFilippi follows:]

PREPARED STATEMENT OF PATRICIA DEFILIPPI, NATIONAL HEMOPHILIA FOUNDATION

Mr. Chairman and Members of the Subcommittee, my name is Penny DeFilippi, and I am here today on behalf the 20,000 persons with hemophilia, von Willebrand's disease and other clotting deficiencies. Today I am speaking as a member of the National Hemophilia Foundation a voluntary health agency working to improve the health and welfare of people with bleeding disorders. You are probably familiar with the hemophilia community in relation to our exposure to HIV in the early eighties leading to the infection of more than 8000 individuals. Today I would like to tell you my family's story and our exposure to hepatitis, and other contaminants still found in blood and blood products.

My family has probably been unknowingly affected by hemophilia and its repercussions for many generations. My grandmother used to say that in our family when a baby was born, another child died. We suspect that was due to untreated internal bleeding. Thanks to advances in modern medicine that is no longer so. My sons are dependent on a blood derived product known as clotting factor, to supply the missing protein that allows their blood to clot normally. While this treatment means that our sons are no longer at risk of being crippled or dying of untreated bleeding,

the products used to control their hemophilia continues to expose them to other diseases that are killing them.

I am married to George DeFilippi, a pilot in the Air Force. We have four children; two grown daughters, Joycelyn and Gwen, and two sons with hemophilia, Geoffrey and James, named for my father, who also lived with hemophilia. I am a third grade teacher at Abingdon Elementary in Arlington County, Virginia. I am an affected carrier of hemophilia, which means that I too can have problems with bleeding, though very rarely.

My father grew up as an undiagnosed, mild hemophiliac, attended West Point where he played football, was a veteran of the Pacific theater in W.W.II, and had a 30 year career as an Air Force officer. I remember that he suffered with continuous knee problems, diagnosed as water on the knee, and had major problems with dental work and his tonsillectomy. He was often irritable- probably because he was bleeding in his joints and in pain. Still, he was relatively healthy.

Our family, including my father, discovered we were affected by hemophilia when my older son, Geoffrey, had a routine blood test at age two. He did not stop bleeding for two hours. At that time we researched our family history and discovered the pattern. Two years later James was born, he too was diagnosed with hemophilia.

Both boys were generally healthy except, of course, for the bi-weekly trips to the emergency room for infusions of clotting factor used to treat their hemophilia. In 1981, when James was two, he became extremely ill. He was diagnosed with hepatitis B, transmitted to him from contaminated clotting factor. He spent much of the next two years in and out of the hospital. He was so ill at one point that he decided that he wanted to die so that he could be reborn as our daughter. He thought that in that way he would no longer be sick.

At the time when he was most seriously ill and we thought he was going to die, a liver transplant was first considered. His father and I decided that we would rather have James live a shorter, happy life rather than have him suffer the problems a transplant patient suffers. James recovered and everything seemed to be going well for a time. This changed when my father had to have major surgery, and James had a normal hemophilia check up.

My father developed gall bladder trouble. He had to have surgery and neglected to mention his hemophilia to his physician. The result was a substantial amount of bleeding. He was heavily transfused with regular blood and later with cryoprecipitate and clotting factor. Following his surgery, my father was diagnosed with hepatitis non-A-non-B, a new disease that was being seen in the blood pool and transmitted to him through blood products. Today we call this disease hepatitis C. He and my mother adjusted their life style so that he would have as little chance as possible of exposing the family he loved. During this time, he began having massive nose bleeds on a regular basis. These nose bleeds very likely exposed everyone around him to hepatitis because it is contagious through exposure to the affected person's blood. Three years later, after becoming sicker and sicker, he was admitted to the hospital with advanced liver failure. He was bleeding so heavily, in effect, he was drowning in his own blood. Despite an experimental procedure to by-pass his liver, he died two weeks later at the age of 72.

Throughout my father's severe illness that preceded his death, my husband and I remained concerned about the chronic symptoms of hepatitis B that James exhibited. His lab tests indicated that he had no other form of hepatitis, so the doctors told us that if he avoided alcohol and drugs, was careful about his diet and was not further exposed to hepatitis he might do fine. Within three months of his grandfather's death James was diagnosed with hepatitis C, transmitted through the products he continued to take to treat his hemophilia. It was time to pay the piper. All I could think was that we had been given some wonderful years of health and joy but had only succeeded in learning to love our son more desperately. How could we stand to lose this boy who had shown such courage and had such a beautiful soul?

James' treating physicians, the pediatric Hematologists and Gastroenterologists at University of North Carolina, suggested that he begin a series of treatments with Alpha-Interferon. This drug was not licensed for use in children, but there was an experimental program being run here in Washington D.C. that James could participate in. My husband received an emergency reassignment from the Air Force and James and Geoffrey became patients at Walter Reed Army Medical Center.

James had a closed liver biopsy which showed that he had triaditis, a scaring of the ducts of his liver. He definitely needed the Interferon therapy which required James to give himself painful injections in his thigh three times a week. James rows crew on the high school team so he has no body fat. That meant that the shots went directly into his muscle. He eventually had used all the sites on his upper thighs and was going to have to go elsewhere on his body. That turned out to be unneces-

sary as he developed an auto-immune reaction to the drug. Basically, he became allergic to it. He was forced to quit before the therapy could cure him.

Although he was relieved to not need anymore shots, James was concerned about his future and his ability to expose others. The doctors at Walter Reed told James the risk of transmitting hepatitis was minimal and that he could live a normal life while he was healthy. This was not what we had heard elsewhere, but it was what we wanted to hear . . . .

At sixteen, James fell in love with a lovely young lady I will call Allison. She also rowed crew, was a top scholar and was truly lovely. One night when they were kissing, his lip split and he bled into her mouth. He was concerned when he came home. I repeated what the Army doctors had told him. James decided to double check just to be sure that Allison would be fine. He called and the doctors told him that they had not been completely honest—he had exposed her. She needed to call her doctor and begin treatment immediately. It is unlikely that James will ever have to make a more difficult call than he had to make to Allison and her family. In the end, though they said they did not blame James, Allison was not allowed to see him again. He now believes that he will never have a normal relationship with a woman.

Last winter just to make the terrible even worse we learned that these vials of factor VIII that you see sitting here were contaminated with Creutzfeldt-Jakob Disease or CJD, a fatal disease causing severe brain damage. James has been exposed to CJD from this product which he received from Walter Reed. Six months before we were notified that the product James was using was contaminated, Walter Reed had destroyed the hospital's supply of the product. Clearly, they knew that it was dangerous, but had not notified patients who had a supply at home.

James is now a senior in high school. He is six feet two inches tall, captain of the crew team, a National Merit commended scholar, a life guard and swimmer. He has an offer from the Ford Agency in New York City to model next summer. He is applying to colleges. He dreams of early admission, a seat on the crew team and a scholarship to Princeton. James has mild hemophilia A, hepatitis B, hepatitis C and possibly CJD. He doesn't want to mention this in his college applications. He asked me directly, "Mom, does everything in my life have to be affected by hepatitis?"

I do not feel that the government needs to run everything or even correct every problem. Yet, in my mind the government does have a clear responsibility in setting the standard for the safety of blood and blood products. The government must also be responsible for informing the general public about the risks of receiving blood and products that may be contaminated. At a minimum, information should be given to anyone who has had a blood transfusion or taken blood products and anyone who has been exposed to the blood or body fluids of someone who was transfused. Only then can individuals be screened for hepatitis and determine their status so they can make informed decisions about their future behavior.

I am soon facing surgery for possible cancer and I for one no longer trust the blood pool. I don't know yet how I will handle the potential need for blood. I add this to ongoing thoughts of how much more time we have until James' liver begins to fail.

I join with the National Hemophilia Foundation and the hemophilia community in urging this committee to take action to implement the recommendations of the recent Institute of Medicine Study to improve the safety of blood and blood products. Specifically, NHF recommends that:

- FDA work with manufacturers to expedite the development of new viral inactivation techniques for product sterilization.
- A system be developed and enforced by FDA for notifying providers, potential purchasers, and known consumer groups about potential threats to blood products from infectious diseases.
- Smaller plasma pools be used in the production of clotting factor to minimize the effect of product withdrawal and recalls on supply.
- Consumers of blood products be vesting participants in regulatory commissions or meetings on blood policy including equal representation on a Blood Safety Committee.
- Accurate warning labels should be developed for blood products because current labels are hopelessly inaccurate and outdated.
- A blood and blood products fund be established to address injury for those infected by contaminates in the blood supply.

The question asked by my son is the same for every member of the hemophilia and bleeding disorder community whether the discussion is hepatitis, CJD or HIV. Are the blood and blood products we are dependent on safe? This question is no longer isolated to our community but has national significance. Ask yourselves do you know anyone who has knowledge of the blood supply who would not donate

their own blood before surgery. Are we fulfilling our responsibility to Americans to maintain a safe blood supply? I ask this panel to help other families so that they do not have to watch their family members go through what our family has gone through. Thank you for your patience and compassion.

Mr. SHAYS. I just want to say you must have a magnificent son.

Mrs. DEFILIPPI. Yes.

Mr. SHAYS. That phone call he made was a very courageous phone call, obviously the one he had to make. But it also says something about his parents, who encouraged him to make that call.

Mrs. DEFILIPPI. Thank you.

Mr. SHAYS. Mr. Dubin, thank you for being here.

Mr. DUBIN. Mr. Chairman, your staff said that at the beginning I should ask that this be included in the record. This is an appendix to my written testimony of documents.

Mr. SHAYS. Let me say if the choice is having you read that or put it in the record, we will definitely put it in the record.

Mr. DUBIN. I have no intentions of reading it, Mr. Chairman.

Mr. SHAYS. So ordered.

Mr. DUBIN. Thank you.

Mr. SHAYS. I'm sorry, I erred in not announcing that Mr. Barrett, a very active member of this committee, Tom Barrett, from Wisconsin, is also in attendance now.

Mr. DUBIN. Thank you. Just to clear the record, I am Corey Dubin of the Committee of 10,000. We represent the nearly 10,000 people with hemophilia infected by HIV. I am a voting consultant to the FDA Blood Products Advisory Committee and also represent the Hemophilia Federation, which is distinct from the National Hemophilia Foundation.

Mr. Chairman and members of the committee, I appreciate the opportunity to be here today. And as I listen to the discussion, I think there is some very important points to be taken up.

The HIV contamination of the blood supply is the result of regulatory failure and industry inaction; however, it is only a result. The real story is hepatitis. The real story is three decades of the hepatitis contamination of the American blood supply and the indifference and inaction of government, the blood banking industry, and the manufacturers of blood products to this contamination.

In the Institute of Medicine report, one of the things they cited that I think is most important to focus in on, is the prevailing assumptions about medically accepted risks. For three decades, this was considered a medically accepted risk.

I think in hindsight we are beginning to look at what that meant. I am a person with severe hemophilia, HIV, Hepatitis C, probably Hepatitis G, which was raised which I think many of us are going to find that we have in our bodies.

And I think it is important to understand the real story. The core of the story is hepatitis. What have we done about hepatitis? What have we not done about hepatitis? And I think we need to focus.

HIV is a much more explosive, media attention kind of issue but if we are going to begin to truly get down to the business of addressing the blood supply and addressing the safety of this country's blood supply, then we must look at hepatitis because therein is the core issue. Why for three decades were thousands of Ameri-

cans infected with hepatitis? Why for three decades was there industry and government inaction in hepatitis?

In 1974, the then-Commissioner of the FDA in the Federal Register, which is included in our appendices, made some very strong statements about hepatitis and the danger. In 1975 FDA promulgated new regulations. Those were good regulations. Unfortunately, those regulations were—the enforcement of them were lax and sometimes nonexistent.

And this is what set the stage for the HIV epidemic. Had, in fact, industry and government mandated the application of technologies which existed and were patented by 1978 to 1989, then HIV would have certainly been a footnote in the hemophilia community because solvent detergent viral inactivation and heat treating would have worked.

Now, we have heard today that there was scientific debate, there was uncertainty. Nobody knew quite what was happening. I would propose to you that we did know hepatitis was contaminating the blood supply, we did have the technology to do something about it, and we knew enough about HIV for the CDC to be, by late 1982, warning the FDA, the National Hemophilia Foundation, and hemophilia treaters by early 1983 that they might have a problem.

The complacency that existed around hepatitis carried over into the early days of HIV. The indifference to what was happening carried right through into the beginning of HIV epidemic and it left us with an explosive situation.

This is not a discrete moment in history when the regulatory structure broke down. Many of the problems that were operative in 1980, 1981, and 1982, and many years before, as I have said, are operative today. We must begin to look at them. We must begin to reconstruct the picture.

Because I think one of the things we have failed to do is reconceptualize this question of emerging threats to the blood supply. We have a certain construction of how we look at this. I heard much of it today in testimony previously and I think there are some real problems with it.

I think it is a mistake to juxtapose safety and availability. I do not believe for a moment that we need to do that. There were treatment options in the early 1980's for hemophilia that were never discussed—cryo, single donor cryo, cryoprecipitate, not treating with Factor VIII. I am a 40 year-old person with severe hemophilia and there are many bleeds I do not have to treat.

We conceptualize this issue in one way, and then we come up with a set of conclusions that I think are problematic. I urge the committee not to look at it through this prism of juxtapositioning safety here and availability here.

Now, on the question of cost and cost-benefit analysis, as a member of the BPAC I sat in on the P–24 decision. I was one of the six votes for antigen testing. I felt a very strong sense of deja vu and felt like we had learned nothing.

If we are going to include cost-benefit then, for God's sakes, why are we not looking at the cost to this Nation of treating 8,000 people with hemophilia who have AIDS, of treating 29,000 other Americans who have HIV infection from whole blood, of treating the cases of hepatitis, which we don't know how many?

Again, we conceptualize cost and how much it will cost per unit to institute the P–24 test, what it would have costed per unit to institute heat treatment in the early 1980's. And yet nowhere in this cost-benefit analysis have I heard anyone assess what the cost is to this Nation of the thousands of people infected.

I would propose to you, members of the committee and Mr. Chairman, that we could save hundreds of millions of dollars in health care expenditures if we reconceptualized this concept and looked at cost in the larger picture. That is something we are not doing.

And, again, it speaks to the way we construct emerging threats to the blood supply. It will never be a zero sum game. We will never have a completely safe blood supply, yet I still think we are missing the boat in some fundamental way in terms of understanding the way to move.

I don't think we have learned from what happened in the 1980's because I have yet to hear officials in the Federal Government really air out the hepatitis question in hindsight. Risk statistics bear out the bigger cost of treating infected people. And I think that is absolutely critical.

I will wrap up. Thank you. The last thing I want to say is that I think Secretary Shalala said it, but I want to underline it because I come at this as an investigative reporter, as well as a person with hemophilia and HIV.

But there is a human face. Behind me Dr. Kuhn and my daughter, Kaile. Dr. Kuhn and I have investigated this issue for 6 years. This is where we have come to these conclusions. He lost his wife because he did not know he was infected. My daughter many nights was awakened in the middle of the night wondering if I would survive. That is the human face.

But I don't want the human face to end in sympathy and just compassion; I want us to challenge ourselves to reconceptualize this issue and look at the big picture and really begin to address what blood safety means today and in the future. Thank you, Mr. Chairman.

[The prepared statement of Mr. Dubin follows:]

PREPARED STATEMENT OF COREY DUBIN, THE COUNCIL OF 10,000 AND THE NATIONAL HEMOPHILIA FEDERATION

Chairman Shays, gentlemen and gentlewomen of the committee, my name is Corey S. Dubin, I am the vice-president of the Committee Of Ten Thousand and a voting consultant to the FDA Blood Products Advisory Committee. I am a person with severe hemophilia who has been infected with HIV and hepatitis C through tainted blood products, specifically anti-hemophilic factor or factor VIII as it is more commonly known.

I am a member of a community that has been devastated by HIV/AIDS and is currently seeing one death each and every day from AIDS transmitted through tainted blood products. Fifty-percent of the American hemophilia community, nearly ten thousand people, were infected with HIV during the 1980's. This holocaust, we were told, was a "tragic, yet unavoidable mistake". A construction of events that we now know is and was patently false and misleading.

I stand before this committee to address the issue of emerging threats to the blood supply and the preparedness of the federal government to confront those threats. In assessing the competency of the federal regulatory system one must understand what occurred during the 1970's and 1980's regarding contamination of the blood supply if we are to undertake the changes necessary to ensure the future safety of this nation's blood supply. The HIV infection of nearly ten thousand persons with hemophilia and twenty nine thousand other Americans through transfusions was

not a discrete moment in history without relevance to the current discussion. Many of the problems that led to the disaster remain operative today and without a clear understanding of those problems we are certainly consigned to a repeat performance.

The HIV contamination of the blood supply is the result of regulatory failure and industry inaction. However it is a result and not the real story. The real story lies in two decades of hepatitis transmission through blood and blood products. It is the story of industry indifference and FDA unwillingness or inability to aggressively address hepatitis contamination of the nation's blood supply.

BY 1974 the FDA clearly understood the dangers of transfusion associated hepatitis transmission. In that year the FDA Commissioner stated that, "approximately three thousand deaths and more than twenty thousand overt cases of illness have been estimated to have been caused by the transfusion of hepatitis carrying blood in this country annually". On July 15, 1975 the FDA adopted new regulations regarding blood and blood products. Those rules called for the testing of all collected blood for the presence of hepatitis B surface antigen. The rules also mandated that any, "blood, plasma or serum that is reactive when tested for hepatitis B surface antigen shall not be used in the manufacturing of injectable biologic products".

While the FDA was correct in imposing new regulations for blood and blood products, the enforcement of the regulation adopted was lax at best and in many cases non-existent. Bad blood continued to enter the system while large pools of collected plasma contaminated with hepatitis were fractionated to produce factor VIII and IX concentrates which were marketed for the treatment of hemophilia.

Meanwhile in 1977 Dr. Ed Shanbrom, the former medical director of Hyland Laboratories, developed and patented the solvent/detergent method for virally inactivating lipid envelope viruses present in blood products. Shanbrom took this new process to the manufacturers of factor concentrates in the hope that they would adopt it and greatly reduce the danger of hepatitis transmission through blood products. For a variety of reasons the four major manufacturers declined to adopt solvent/detergent and or heat treatment until after the onset of the AIDS epidemic.

While the FDA clearly understood the scope and danger of hepatitis contamination they did not require industry to adopt viral inactivation during the late 1970's or early 1980's. In fact, is was not until 1988 that that FDA mandated viral inactivation for factor VIII and IX. For many years we, in the hemophilia community, have agonized over this history. For us the inaction on the part of industry and government resulted in the hemophilia/AIDS epidemic. Had industry and their federal regulators aggressively responded to hepatitis contamination of the blood supply, HIV would have been no more than a footnote in the hemophilia community.

The problems with hepatitis contamination of blood products have persisted right up to the present with a series of blood product recalls occurring over the last two years. In January of 1994 a major recall occurred of Intravenous Immune Globulin or IVIG due to hepatitis C contamination. The recall was instituted by the manufacturers after fourteen suspected transmissions in Spain, Sweden and the United States. All the products recalled were produced in the United States by Baxter/Hyland and distributed by them and the American Red Cross.

Ironically, for the last thirty years immune globulin has been considered one of the safest blood products on the US market. The FDA had never mandated that IVIG be subjected to viral inactivation techniques, believing that this product was safe. What we found surprising was the lack of theories about why this had happened at the FDA. After one month of research myself and Greg Haas published a lengthy investigative article on the history of IVIG and why this hepatitis C outbreak occurred. We were informed by officials at the FDA that we had proposed some interesting theories. Obviously, FDA's response led us to question what was occurring while leaving us with a sense that nothing had changed since the early 1980's and the AIDS disaster.

What relevance does this history have for this committee and today's discussion about protecting the blood supply from emerging threats? We know that there will always be new and continuing threats to the blood supply. The important question is how to prepare for and respond to those threats. When addressing this question it is necessary to address how the federal government, the manufacturers of blood products and the blood banking industry conceptually views ongoing threats to blood safety. Historically the baseline has been, "lets wait until all the data is in". This is what occurred in the early 1980's and the result has been the devastation of an entire community as well as thousands of others. Government and industry must be prepared to respond before all the data is in if we are serious about protecting the health and safety of the users of blood and blood products.

Many of the decisions made regarding viral contamination and the response of industry and government have been rooted in economic concerns at the expense of

safety. Decisions regarding threats to the blood supply must always be made with safety as the highest priority; not cost/benefit analysis and what the cost will be to the manufacturers of blood products and the blood banking industry. For three and one half decades we have been far too focused on the cost side of the equation and in every instance people, human beings, have been harmed.

We, as a nation, must understand that when we fail to prioritize safety over economic concerns, that ultimately the cost to the taxpayers is much higher in terms of treating those infected with virus' such as hepatitis C and HIV. Applying the highest degree of technology available to gain the greatest degree of safety possible, in the end result, will save this nation hundreds of millions, if not billions of health care dollars over the long haul. A substantive economic analysis, not based on short term cost and industry profits will surely demonstrate the long-term benefits to be gained from prioritizing safety over economic concerns.

This was vividly demonstrated recently when the FDA, Blood Products Advisory Committee, of which I am a member, voted to recommend against mandating P–24 antigen testing of all collected blood.. Adopting this test would close an existing window whereby an HIV infected donor could donate plasma that would be infectious yet go undetected by antibody testing.

This decision was made solely on the basis of what it would cost the nation's blood banks to institute this testing. The committee was presented with a cost/benefit analysis prepared by the director of a large San Francisco blood bank, His conclusions were that the test was more costly than it was worth, a conclusion I certainly did not agree with. The discussion centered on whether this was the best expenditure of the shrinking monies available for AIDS. The BPAC, dominated by blood bankers, was clearly in violation of its mandate regarding the safety of the blood supply. I do not believe that it is the job of the FDA and its BPAC to be considering how AIDS dollars are spent and then basing what should be a purely safety driven decision on that economic analysis.

The only substantive issue that should have been considered was and is, will instituting P–24 antigen testing improve the overall safety of this nation's blood supply and will it reduce the risk of HIV transmission for the users of blood and blood products. I was absolutely stunned by the vote and felt a real sense of history repeating itself. Only this time, I was sitting on the committee when it prioritized cost/benefit concerns over safety. I now had an insiders view of what occurred during the early and mid 1980's.

What was even more troubling than the vote was the apparent comfort of the FDA staff with this decision that would ultimately result in the devastation of more individuals and families from the nightmare that is AIDS. The only conclusion open to me after the vote was that very little had been learned from the HIV disaster of the 1980's and that conflict of interest remains alive and well at the FDA.

Another example of economics taking precedence over safety is the issue of plasma pool size. Plasma derivatives such as factor VIII are fractionated from pools containing the plasma of up to twenty thousand donors. One infected donor can contaminate an entire pool and anyone using products produced from that pool. The inherent danger of pooled plasma has been known since the second world war when the army began pooling plasma to be shipped to the Pacific theater.

The only reason for these very large pools is industrial economies of scale. The smaller the pool, the lesser the risk to the users of blood products. This is a given and the only point that should be debated is what is the optimal pool size in terms of safety, not in terms of what is economical for industry. However when this issue was debated at the March 1995 meeting of the BPAC, economic concerns again took precedence. The result was that the BPAC decided to again delay any action regarding this critical safety issue. Again it is hard not to conclude that the process is in large part driven by conflict of interest as it is the industry supplying the data on this issue.

The revolving door between the FDA and the business of blood must be closed if we are to seriously protect the users of blood and blood products. The agency remains beholden, in many ways, to the very entities it is charged with regulating. The BPAC must be organized to reflect all concerned with blood safety and not just the interests of the blood banks and the manufacturers of blood products. We must legislate an independent FDA that is no longer totally dependent on those it regulates for analysis of data and modeling of decision problems.

How can the FDA effectively regulate blood and blood products without independent data and analysis regarding issues that critically impact the lives of the 3.5 million Americans who use blood and blood products each year. It is naive and dangerous to believe that we can depend on industry for data that is not influenced by industry's economic bottom line. Conflict of interest significantly contributed to the hemophilia AIDS disaster, played a key role in the BPAC's P–24 decision and will

continue to be a barrier to improved blood and blood product safety if it is not aggressively addressed by the Congress and those in the Administration tasked with being the guardians of the nation's blood supply.

Another area of grave concern is the nation's blood and plasma collection system which is plagued by "accidents and errors" on a daily basis. Over the last 3 years we have seen numerous investigative reports in the nation's media regarding the ongoing and dangerous problems at the American Red Cross and the private blood banks. What is even more troubling is that these credible reports represent only the tip of the iceberg. According to the June 27, 1994 US News & World Report, "Blood banks know that more than 100,000 individuals may have received blood harboring the virus that causes hepatitis C but have not alerted them". The report also stated that the number of FDA logged accident and error reports from the nation's blood banks had dramatically jumped from 1,000 in fiscal year 1989 to 10,456 three years later in FY 1992.

Meanwhile in 1993 the FDA sued the American Red Cross in the federal courts in an attempt to improve safety at ARC blood centers. The court issued a consent degree that covered all aspects of ARC blood collection and distribution operations. As we speak, two years after the court acted, the American Red Cross remains in non-compliance with serious problems continuing throughout the ARC system. This while the ARC continues to operate without a national computerized blood tracking system which would greatly increase ARC's ability to track blood and plasma that was donated by an infected individual. A national tracking system could by housed at the FDA with terminals at every blood collection and processing facility in the country. The computer technology certainly exists yet the FDA, the ARC and the private blood banks continue to drag their feet on this important issue.

A good example of this tracking nightmare is the American Red Cross facility in Miami. In response to an anonymous letter sent to Senator Bob Graham of Florida by a lab technician at the Miami facility, an FDA inspector was dispatched to investigate allegations of substandard lab conditions and the shipping of blood with positive viral markers for HIV and hepatitis C. The inspector's report contained one entry that stated that there was no final disposition paperwork for 2850 units of several blood components, 197 of which had positive viral markers. When queried by a reporter from the Wall St. Journal about how they knew this bad blood had not been shipped to area hospitals the regional ARC director stated that, "we know that bad blood was not shipped because we count the shipping labels each day". If this is how we are tracking bad blood then clearly the users of blood and blood products remain in serious danger.

We must create a truly independent FDA if we are to prevent an ongoing reoccurrence of the hepatitis and HIV disasters. We must begin to learn from past mistakes rather than continuing with business as usual in the regulation of blood and blood products. The FDA must wield the power given to it by the Congress rather than always attempting to gently move industry toward higher standards. Over the last year I have consistently heard from FDA staff that changes will take many years to accomplish given the relationship with industry. From where I sit, we do not have years to wait unless we believe that consigning thousands of Americans to the nightmare of blood borne viruses is an acceptable option.

The Institute Of Medicine Report, "HIV & The Blood Supply; An Analysis Of Crisis Decision Making" did an adequate job of identifying where and some of the why regarding the breakdown of the regulatory system in the 1980's. They cited conflict of interest, lack of regulatory independence and the glaring lack of coordination between the different federal agencies that comprise the regulatory puzzle. They also cited a lack of independence on the part of the clinicians treating persons with hemophilia.

The expert IOM panel also found that within industry, government and the medical community that, "prevailing assumptions about medically accepted risks, especially hepatitis, led to a complacency and a failure to act upon reports of a new infectious risk". This cuts to the core of what troubles this nation's blood supply; a complacency to act that resulted in the devastation of nearly ten thousand persons with hemophilia from a blood borne pathogen that could have been prevented had the government and industry acted aggressively and with only one concern a priority, safety. If we learn nothing else from this report, we must learn that safety must always be the priority and if we are to err, we must err on the side of protecting the users of blood and blood products rather than saving monies that ultimately will have to be spent many times over to cope with-those harmed by these misguided decisions.

The recommendations of the IOM panel are, for the most part, sound and should be implemented. However, if they are implemented without the direct participation of the users of blood and blood products then we are right back where we started.

We support the establishment of a national blood safety council at the level of the HHS Secretary but again this council must contain representation of all of the interested parties; government, industry, the Red Cross, and all of the communities that depend on blood and blood products. From our perspective this point is non-negotiable and imperative if we are to create the necessary changes in the business of blood. The council must also have the authority to ensure that federal agencies are cooperating and listening to one another when confronted with emerging threats. If the FDA had not ignored the repeated warnings of the Centers For Disease Control that the causative agent for AIDS was a blood borne pathogen, thousands in the hemophilia community would have been spared this nightmare that is HIV/AIDS.

We must create an environment within which all of the interested parties can come together to ensure that this nation has the safest blood supply that is humanly possible. Along these same lines the FDA Blood Products Advisory Committee must also contain all of the communities that use blood and blood products. We believe that both the BPAC and the new HHS council should contain one third consumers if this process of change is to be successful. Without this we will continue to barred form the forums where decisions are made that critically impact our very existence. The panel also called for the establishment of no-fault compensation funds to compensate those harmed by tainted blood and blood products; A recommendation we strongly support and are actively pursuing through the Ricky Ray Hemophilia Relief Act Of 1995, HR 1023.

We must never forget that the issue of blood safety is about human beings, individuals and families, fathers, mothers, brothers and sisters. The hemophilia holocaust is not an abstract construction. It is about families devastated by bad decisions in industry and government. Decisions that prioritized economics over safety decisions that left this community feeling as if it were considered expendable by the industry, federal regulators and the medical community. We in the hemophilia community are the early warning system for the nation's blood supply. If it is contaminated it will first surface in our community. This is exactly what occurred in the 1980's and it was fundamentally ignored by all parties except the CDC which no one cared to listen to. My family and thousands of other American families have been devastated and our lives can never be returned to what they were. However we can learn from this nightmare and use this opportunity to fundamentally reform the business of blood in this country. This is the challenge that we have undertaken, it is our hope that industry, the medical community, and government, especially the Congress will join us in this most important endeavor.

Mr. SOUDER [presiding]. Thank you. Dr. Penner.

Dr. PENNER. Mr. Chairman, members of the subcommittee, I want to thank you for inviting me to participate in these hearings on the topic of protecting the blood supply from infectious agents. My name is John Penner. I am professor of medicine and pathology at Michigan State University and a full-time academician with responsibilities for patient care, research, and teaching in the field of hematology.

In this respect, my experience over the past 40 years has involved me in the management of the hemophilia program in Michigan, a comprehensive hemophilia clinical center funded by the U.S. Department of Health and Human Services, a sickle cell program for mid-state Michigan, and various aspects of transfusion medicine.

In addition, I have engaged in research on elements of blood coagulation, including blood derivatives. These projects have been funded by the National Institutes of Health and private as well as State-owned industries. Also, until recently, I have served as a medical director and principal officer of a Regional Red Cross Center as a part-time position contracted through my university. I believe my experience relates closely to the topic in question and encompasses all aspects of the problem under discussion.

This past Saturday, funeral services were held for a 32 year-old hemophiliac patient that I had cared for since he was 5 years old.

He died of the consequences of AIDS, 1 of some 30 of my patients who has succumbed to the bloodborne HIV infection.

The explosive nature of HIV and other retroviruses after entering the blood supply has exposed many of the inadequacies in the blood banking practices throughout the country and has created the crisis atmosphere which now attends the production and use of all blood and blood derivatives.

It is a tragic situation fueled by complacency in blood banking centers and industry. Many of our blood banking centers were created over 40 years ago as small community volunteer programs and were ill-equipped to respond to the HIV threat.

Industry, on the other hand, failed to respond for other reasons, notably a lack of medically knowledgeable management and emphasis on profit with a need to maintain productivity in a competitive market.

The public has long enjoyed the sense that blood provided through the best of intentions by many volunteers, their neighbors in the communities, is not only life-saving but essentially risk-free. Physicians also have left the burden of knowledgeable use of blood products to other and have avoided careful evaluation of these products.

Although the public and health care workers have been disillusioned by events over the past 15 years, they unrealistically expect and demand complete, safe, and risk-free blood and blood products.

In this context, the topics for this committee's deliberation can be discussed. I have reviewed the report of the committee to study "HIV transmission through blood and blood products" and agree wholeheartedly with the contents and recommendations.

Before addressing the issues framed by the subcommittee in its correspondence, however, I wish to bring to your attention a concern that I believe has been overlooked in attempts to produce a rapid correction of previous practices in blood banking programs.

From the outset, it should be recognized that blood and its derivatives are human resources derived from a volunteer blood donor population and cannot be considered in the same term as a manufactured product. This resource is dependent on the fragile relationship between the blood center and the community.

Any action that disrupts the relationship eventually will result in disappearance of the resource, as donors no longer give freely of their blood and time to volunteer. The centralization of blood processing and the restrictive and sometimes inflexible regulation implemented by the Food and Drug Administration have the potential to destroy this system.

Furthermore, in disagreement with Secretary Shalala, as regulations have become the driving force, business managers have been placed in charge of blood centers and have virtually eliminated input from the physicians and the medical community.

This lack of medical leadership will, in my opinion, lead to the alienation of the volunteer community and provide the opportunity for inappropriate decisions in the use of blood products. I would strongly recommend, and I mean strongly, a reinfusion of a community's physicians into the management of what is considered the blood banking industry.

I believe also that attention must be paid to physician and patient education to assure that appropriate use of all blood products is made. And in this matter there has been a long history of neglect with little, if any, encouragement for the development of programs to inform physicians and the public of the risks associated with blood products and the need to determine therapeutic requirements.

With a grant from the National Institutes of Health we attempted to alter physician practices in relation to the use of platelet concentrates and fresh frozen plasma. We met with only partial success when we applied a variety of interventions in selected areas of Michigan.

It was possible to obtain improvement in platelet concentrate use when physicians reduced their orders from 10 to 12 bags of platelets to a recommended 6 bags for patients with decreased numbers of circulating platelets who were at risk for bleeding complications.

On the other hand, physicians failed to improve the appropriateness of their ordering practices and often administered concentrates unnecessarily when platelet levels were decreased, but not to a degree that would require support.

To return to the issues outlined by your committee, emerging infectious agents of the blood supply, bacterial infections, although rare, continue to claim victims. One death in Detroit recently resulted from bacteria that can grow in the cold and remain unrecognized until infused. Yersinia Enterocolitica is the agent that I am speaking of. Bacterial growth also occurs frequently in platelet concentrates maintained at room temperature.

A contaminated platelet concentrate claimed a victim in Detroit. Excuse me, bacterial growth recently claimed a victim in Detroit, also as well in another city in Michigan, as a result of the growth occurring at room temperature in a platelet concentrate. A contaminated platelet concentrate then represents a basic growth area for bacteria and represents a culture medium.

Viral infection by Hepatitis C and new variants of hepatitis, cytomegalic and parvovirus and other retroviruses similar to HIV, to a limited degree, persist in the blood products and, despite attempts to screen and inactivate, will remain.

Preventive measures to eliminate risk of infectivity have been implemented and appear to be effective in blood centers and industry. It is necessary, however, to continue to maintain a commitment to the following:

One, a program of careful attention to blood drawing techniques and donor exclusion, with enforced guidelines and oversight; two, use of direct and surrogate tests to identify the presence of infective agents; and, three, support for new initiatives to inactivate infective agents in blood and blood products.

Now with respect to the HIV antigen kit: despite a very modest reduction in bloodborne HIV infections that could be achieved by implementing the HIV antigen assay, as described by the Advisory Committee, the public, as well as treating physicians, are unwilling to accept any risk that can be eliminated.

The need to reassure the public that all measures are being taken to maintain blood safety is paramount and supersedes cost. Thus, the availability of an antigen test that will improve screening

of blood products cannot be disregarded. Public concerns must be met in order to exclude any additional loss of human life, as well as to improve the public image of the blood supply. I strongly support the implementation of the HIV antigen kit and urge its acceptance.

Third, reorganization of the Blood Products Advisory Committee. It is apparent that the physicians and physician treaters have not had the opportunity to affect bureaucratic decisions and that industry and non-physician input in an advisory committee has not represented the public well. A broader membership with inclusion of physicians knowledgeable in blood banking practices, as well as patient care and representation from users, including members of the hemophilia and sickle cell communities, is required.

Finally, the committee should have more than an advisory role and, perhaps, decisionmaking powers that can directly affect regulatory efforts. Such a committee would be cognizant of concerns for maintaining the volunteer aspects of the blood supply.

Fourth, Hepatitis C, transmission through blood and blood products. Second and third generation Hepatitis C antibody testing has been employed effectively at the donor level; however, other related hepatitis viruses, although less common in the population, will require screening when testing has been developed. Antigen testing also should be implemented to reduce the potential window period if and when assay kits can be developed.

In addition, efforts must be made to identify all blood recipients at risk from donors' previous blood collections once a positive hepatitis test has been obtained. Therefore, lookback procedures must be given priority with full disclosure to the individual exposed to potentially contaminated blood.

Finally, a need not addressed by the IOM report relates to the non-labeled use of blood by-products by physicians. Cryoprecipitate, for example, is employed for Fibrinogen as well as for the von Willebrand factor replacement. There is no standardization of this product, and an alternative industry-produced concentrate of the von Willebrand factor has been approved only for its Factor VIII content.

Presently, most of the patients with severe von Willebrand disease are receiving these products as their only means of controlling hemorrhagic episodes. In my practice, I allow surgery to be performed on such patients, despite the fact that I am unsure of the quality and the content of the product that I have ordered. The potential for serious complications exists under these conditions and surely requires a solution that must be addressed by the FDA.

In summarizing my comments, I would like to state that the safety of the blood supply has improved dramatically during the past 5 years; however, continued aggressive regulation of blood banking services and blood derivative industry is needed with the application of any and all new procedures that will screen infectious agents from the blood supply.

To assure effective supervision of the blood products, a representative committee should be selected for the purpose of guiding the FDA in its oversight of the blood products.

Thank you for your attention.

[The prepared statement of Dr. Penner follows:]

PREPARED STATEMENT OF JOHN PENNER, M.D., MICHIGAN STATE UNIVERSITY, COLLEGE OF HUMAN MEDICINE

I wish to thank the subcommittee for inviting me to participate in hearings on the topic "Protecting the Blood Supply from Infectious Agents: New Standards to Meet New Threats". My name is John A. Penner. I am a Professor of Medicine and Pathology at Michigan State University, and a full-time academician with responsibilities for patient care, research, and teaching in the field of Hematology. In this respect, my experience over the past 40 years has involved me in the management of the Hemophilia program in Michigan, a Comprehensive Hemophilia Clinical Center funded by the U.S. Department of Health and Human Services, a Sickle Cell Program for midstate Michigan and various aspects of transfusion medicine. In addition, I have engaged in research on elements of blood coagulation including blood derivatives. These projects have been funded by the National Institutes of Health and private as well as State owned industries. Also, until recently, I have served as a Medical Director and Principal Officer of a Regional Red Cross Center in a part-time position contracted through my University. I believe my experience relates closely to the topic in question, and encompasses all aspects of the problem under discussion.

This past Saturday, funeral services were held for a 32 year old hemophilic patient that I had cared for since he was five years old. He died of the consequences of AIDS, one of some 30 of my patients who have succumbed to the blood borne HIV infection.

The explosive nature of HIV and other retro viruses after entering the blood supply has exposed the many inadequacies in blood banking practices throughout the country, and has created the crisis atmosphere which now attends the production and use of all blood and blood derivatives. It is a tragic situation fueled by complacency in blood banking centers and industry. Many of our blood centers were created over 40 years ago as small community volunteer programs and were ill equipped to respond to the HIV threat. Industry on the other hand failed to respond for other reasons, notably a lack of medically knowledgeable managers, and emphasis on profit with the need to maintain productivity in a competitive market.

The public has long enjoyed the sense that blood provided through the best of intentions by many volunteers, their neighbors in the community, is not only life saving but essentially risk free. Physicians also have left the burden of knowledgeable use of blood products to others and have avoided a careful evaluation of these products. Although the public and health care workers have been disillusioned by events over the past 15 years, they unrealistically expect and demand completely safe and risk free blood and blood products. In this context, the topic for this committee's deliberation can be discussed.

I have reviewed the report of the committee to study "HIV transmission through Blood and Blood Products" and agree, for the most part, with the content and recommendations.

Before addressing the issues framed by the Subcommittee in its correspondence, I wish to bring to your attention a concern that I believe has been overlooked in the attempts to produce a rapid correction of previous practices in blood banking programs.

From the outset, it should be recognized that blood and its derivatives are a human resource, derived from a volunteer blood donor population, and cannot be considered in the same terms as a manufactured product. This resource is dependent on the fragile relationship between the blood center and the community. Any action that disrupts that relationship eventually will result in the disappearance of the resource as donors no longer give freely of their blood and time to volunteer. The centralization of blood processing and the restrictive and sometimes inflexible regulations implemented by the Food and Drug Administration (FDA) have the potential to destroy this system.[1]

Furthermore, as regulations have become the driving force, business managers have been placed in charge of blood centers and have virtually eliminated input from physicians and the medical community. This lack of medical leadership will, in my opinion, lead to further alienation of the volunteer community and provide opportunity for inappropriate decisions in the use of blood products. I would strongly recommend a reinfusion of community physicians into the management of what is considered a blood banking industry.

[1] Destruction of some 500 units of blood, occurred in one of the Red Cross Centers as a result of an altered sentence in a laboratory procedure for syphilis testing that differed by five words from the manufacturers description. The manufacturer and the medical advisors agreed that the assay results were not affected. A recall required notification of several thousand recipients.

I believe also, that attention must be paid to physician and patient education to assure appropriate use of all blood products. In this matter, there has been a long history of neglect with little if any encouragement for the development of programs to inform physician and the public of the risks associated with blood products and the need to determine therapeutic requirements.

With a grant from the National Institutes of Health, we attempted to alter physician practices in relation to the use of platelet concentrates and fresh frozen plasma. We met with only partial success when we applied a variety of interventions in selected areas of Michigan.[2] It was possible to obtain improvement in platelet concentrate use when physicians reduced their orders from 10 to 12 bags of platelets to a recommended six bags for patients with decreased numbers of circulating platelets at risk for bleeding complications. On the other hand, physicians failed to improve the appropriateness of their ordering practices and often administered concentrates unnecessarily when platelet levels were decreased, but not to a degree that would require support. Use of fresh frozen plasma did not appear to improve with our approach, and definitely a strong educational program with frequent reinforcement will be needed before any significant reduction in inappropriate use can be obtained.

I. "EMERGING INFECTIOUS AGENTS OF THE BLOOD SUPPLY"

Bacterial infections although rare, continue to claim victims. One death in Detroit recently resulted from bacteria that can grow in the cold and remain unrecognized until infused (Yersinia Enterocolitica). Bacterial growth also occurs frequently in platelet concentrates maintained at room temperature. A contaminated platelet concentrate claimed a victim in another Michigan city. Viral infection by Hepatitis C and new variants of Hepatitis, Cytomegalic and parvo virus and other retroviruses similar to HIV persist to a limited degree in blood products, despite attempts to screen and or inactivate them.

Preventative measures to eliminate risk of infectivity have been implemented and appear to be effective in blood centers and industry. It is necessary, however, to continue and maintain a commitment to the following:

1. A program of careful attention to blood drawing techniques and donor exclusion with enforced guidelines and oversight.
2. Use of direct and surrogate tests to identify the presence of infective agents.
3. Support for new initiatives to inactivate infective agents in blood and blood products.

II. "HIV ANTIGEN KIT"

Despite very modest reduction in blood borne HIV infections that could be achieved by implementing the HIV antigen assay, as described by the Advisory Committee, the public, as well as treating physicians are unwilling to accept any risk that can be eliminated. The need to reassure the public that all measures are being taken to maintain blood safety is paramount and supersedes cost. Thus the availability of an antigen test that will improve screening of blood and blood products cannot be disregarded. Public concerns must be met in order to exclude any additional loss of human life, as well as to improve the public image of the blood supply. I strongly support the implementation of the HIV antigen kit and urge its acceptance.

III. REORGANIZATION OF THE "BLOOD PRODUCTS ADVISORY COMMITTEE"

It is apparent that the public and physician treaters have not had the opportunity to affect bureaucratic decisions, and that industry and non-physician input in an advisory committee has not represented the public well. A broader membership with inclusion of physicians knowledgeable in blood banking practices, as well as patient care and representation from users, including members of the hemophilia and sickle cell communities, is required. Finally the committee should have more than an advisory role and perhaps decision making powers that can directly affect regulatory efforts. Such a committee would be cognizant of concerns for maintaining the volunteer aspects of the blood supply.

---

[2] J.A. Penner, R. G. Bridgham, Intervention/Education to Improve Hemostatic Product Use, Final Progress Report for Nat. Heart Lung & Blood Inst., Grant #HL33922-05, Submitted Feb. 1992.

IV. "HEPATITIS C TRANSMISSION THROUGH BLOOD AND BLOOD PRODUCTS

Second and third generation hepatitis C antibody testing has been employed effectively at the donor level. However, other related hepatitis viruses, although less common in the population, will require screening when testing has been developed. Antigen testing also should be implemented to reduce the potential window period, if and when assay kits can be developed. In addition, efforts must be made to identify all blood recipients at risk from a donor's previous blood collections, once a positive hepatitis test has been obtained. Look back procedures must be given priority with full disclosure to the individual exposed to potentially contaminated blood.

CONCLUSION

Finally, a need not addressed by the IOM report relates to the non-labelled use of blood by-products by physicians. Cryoprecipitate, for example, is employed for Fibrinogen as well as for von Willebrand factor replacement. There is no standardization of this product and an alternative industry produced concentrate of the von Willebrand factor has been approved only for its factor VIII content. Presently, most of the patients with severe von Willebrand disease are receiving these products as their only means of controlling hemorrhagic episodes. In my practice, I allow surgery to be performed on such patients despite the fact that I am unsure of the quality and content of the product I've ordered. The potential for serious complications exists under these conditions and surely requires a solution that must be addressed by the FDA.

In summarizing my comments, I would like to state that continued aggressive regulation of blood banking services and the blood derivatives industry is needed with application of any and all new procedures that will screen infectious agents from the blood supply. To assure effective supervision of blood products, a representative committee should be selected for the purpose of guiding the FDA in its oversight of blood products.

[NOTE.—Due to high publication costs, the "Intervention/Education to Improve Hemostatic Product Use" final progress report can be found in subcommittee files.]

Mr. SOUDER. Thank you. Dr. Gilcher, I want to say that I have been pretty liberal with the 5-minute rule thus far. And you have a fairly lengthy statement. So if you—I don't think I have any more bones in my body to be more liberal than I have been. But if you can summarize some and we will be flexible with you.

Dr. GILCHER. Mr. Chairman, committee members, and other participants, I am Dr. Ron Gilcher, president of the Sylvan N. Goldman Center Oklahoma Blood Institute and have been involved in transfusion medicine for over 20 years.

I am pleased to testify today on issues concerning the safety of our Nation's blood supply. In particular, I will focus on the first two questions asked of me regarding the emergence of infectious agents into the blood supply and HIV antigen test kit review issues. I will also briefly comment on Hepatitis C transmission through blood products.

A number of infectious agents, including Chagas Disease, new forms of hepatitis such as Hepatitis G, and other parasites and bacterial agents, are emerging in our blood supply as the world's population becomes more global in their travels. Other infectious agents such as HIV–1 and II, HTLV–I and II, and Hepatitis B and C, still continue to be transmitted through blood product transfusions, although at a very low rate.

Other emerging transfusion-related issues, as of yet unclear as to their cause, include immunologic suppression and susceptibility to malignancy diseases not yet proven to be transmitted through transfusions include the prion diseases, of which Creutzfeldt-Jakob

Disease, a fatal neurologic disease, is now of concern to plasma derivative manufacturers.

Careful and strategic planning now may prevent a repeat scenario of the past which resulted in devastating AIDS morbidity and mortality in transfusion recipients and hemophiliacs.

A safety model developed and used at the Oklahoma Blood Institute for over 10 years and outlined as Enclosures 1 and 2 in my written testimony, focuses on six broad categories for enhancing blood product quality and safety. Although each is pertinent, the fourth category of new or improved testing relates to the issues of HIV–I antigen testing.

Antigen detection based tests make scientific sense when the antigen is detectable by current technology because it allows for earlier detection of the infectious agent since it is a direct test. Antibody detection based tests are indirect measures of an infectious agent and have a longer window of infectivity until the antibody is detectable.

This is true for Hepatitis B and is the reason why Hepatitis B surface antigen testing is done along with the antibody to the Hepatitis B core antigen, an antibody detection based test. The same is potentially true for detection of the human immunodeficiency virus where the antigen detection based test will allow earlier detection of HIV in donated blood.

The Oklahoma Blood Institute identified and documented an HIV window donation by testing a repository sample of a July 19, 1989, HIV antibody-negative donation with the HIV antigen test. That sample tested positive for HIV–I antigen and the recipient was confirmed HIV–I positive.

A prospective HIV–I antigen donor testing study was then begun in May 1991, and it confirmed a second donor positive for HIV–I antigen and negative for HIV antibody in May 1994. This time transmission of HIV was prevented.

This data and other investigators' data on HIV antigen testing was presented at the Blood Products Advisory Committee meeting on June 23, 1995, at which time the BPAC concluded that HIV–I antigen testing was not a cost-effective public health measure and that closing the HIV window was, in fact, not cost-effective at all.

When cost becomes the major concern and controlling force, medical progress is impeded. Inappropriate cost-benefit analysis may impede or stop consideration of a procedure, process, or test before a complete assessment of the benefits versus the risks has occurred. Clearly, this was the case with respect to the BPAC decision to not support licensing for the HIV-I antigen test for donor screening.

The decision on August 10, 1995, by the Food and Drug Administration to institute HIV–I antigen testing is clearly a first step toward closing the window on transfusion-associated HIV.

The Oklahoma Blood Institute has extensively evaluated the Abbott Laboratories short incubation HIV–I antigen test over the last 4 years by prospective testing under an IND granted through the FDA and has demonstrated its effectiveness in detecting donors infected with HIV. This test kit is one of several currently under licensure evaluation by the FDA.

The overall impact of this test on our routine laboratory operations has been minimal. Implementation of this test for mass donor screening can be successfully accomplished using similar compatible testing systems.

Another disease, Hepatitis C, still remains a major transfusion transmitted disease and is not likely to be decreased further by the current antibody detection based test kits. This is because of the long window of 11 to 12 weeks before antibody is detectable.

Conversely, an antigen detection based test kit such as Hepatitis C Virus polymerase chain reaction testing may shorten that window to 3 weeks. Cost modeling should not be used to impede research with PCR or PCR-like techniques.

In summary, the decision to use cost as the reason not to do something must ultimately be decided by the patient as a consumer and Congress.

Thank you.

[The prepared statement of Dr. Gilcher follows:]

PREPARED STATEMENT OF RONALD GILCHER, M.D., OKLAHOMA BLOOD CENTER

This testimony is in response to the letter received October 4, 1995 requesting my response to: (1) emerging infectious agents in the blood supply, (2) the status of HIV antigen test kit review by the FDA, (3) reorganization of the Blood Products Advisory Committee, and (4) Hepatitis C transmission through blood and blood products. The comments which follow will address these issues as well as general issues on blood safety.

I. GENERAL COMMENTS:

The evolution of transfusion and blood product safety in the United States over the last 25 years clearly demonstrates the need for a proactive process to enhance safety as opposed to the typically reactive posture that has and continues to drive safety issues. Better planning and less crisis intervention medicine possibly could have reduced the mortality and morbidity of blood product recipients from both HIV (AIDS) and hepatitis (Hepatitis B and C). Careful and strategic planning now may obviate similar outcomes in the future.

The health care forces of the 90's are cost, access to medical care, and quality of care, whereas in transfusion medicine the driving forces are cost, regulation, availability of blood products, and quality/safety of blood products. When cost and regulation become the primary focus and controlling forces, medical progress is impeded. Inappropriate cost benefit-analysis may impede or stop consideration of a procedure, process, or test before a complete assessment of the benefits versus risks has occurred. Inappropriate regulatory constraints may also impede the quality of care while driving up costs unnecessarily.

As an example, it is illogical today to allow certain blood products (irradiated blood and leukocyte reduced blood products) to be shipped intrastate but not be permissible to be shipped interstate because the FDA still has not defined the licensing standards for quality and content. This has resulted in unnecessary delays and reduced quality of care. A blood product not safe for interstate shipment and transfusion is not safe for intrastate shipment and transfusion. This is just one example of how patient care is impeded and costs are increased by unnecessary regulatory delays and complexities. Another example is the absence of donor reentry criteria for clearly false positive tests which leads to a loss of the best repeat donors (e.g. false positive antibody tests to Hepatitis B core antigen).

The closure of the HIV infection "window" is another example of how a primary focus on cost could have shut down all attempts to close "window" HIV transmissions through blood transfusion. On June 23, 1995 the Blood Products Advisory Committee decided it was not a cost effective public health measure to screen donor blood for HIV-1 antigen even though the members voted unanimously on the validity of the test. In fact, the general conclusion of the BPAC was that any measure to close the HIV "window" was not cost effective.

The decision to use cost as the reason not to do something must ultimately be decided by the consumer and congress.

A model for transfusion and blood product safety was developed by the Oklahoma Blood Institute in 1985 to allow strategic planning for the future with regard to

these issues. That model is seen in Enclosure 1 with examples in Enclosure 2. This model has allowed our blood center to develop an approach to transfusion and blood product safety that has and continues to provide safer and higher quality blood products as well as being cost effective. All plasma and platelets supplied to Oklahoma member hospitals are from pedigreed (frequent repeat) donors with a full transfusion dose being collected from one donor.

The creation of a repository of donated blood samples since September 1987 has allowed our research staff to evaluate new reagents such as the HIV–1 antigen test which has been under investigation since May 1991 at the Oklahoma Blood Institute. This blood sample repository has allowed our blood center to test a blood product previously donated in 1989 and confirm the first documented "window" transmission (Enclosure #3). Blood research under BB–IND #3894 to do prospective HIV antigen testing detected a donor on May 10, 1994 who was HIV antigen reactive and HIV antibody negative. This prevented transmission of HIV–1 to potentially multiple recipients. (Enclosure #4)

The model continues to be valid and changes are made to continue the focus on safety and quality. The concept of erring on the side of safety is continually used in the modeling process.

II. SPECIFIC COMMENTS:

A. Emerging infectious agents in the blood supply: A number of infectious agents are emerging and will continue to emerge as the populations of the world become more global in travel. New infectious agents as of yet unknown, but suspected to be in blood and possibly transmissible by blood elements are gaining recognition. Some of these are as follows:

(1) Chagas Disease: Chagas disease is caused by a blood parasite called Trypanosome Cruzli and is common in Latin America and Mexico, and is clearly transmissible by blood products.

(2) Creutzfeld-Jakob Disease: CJD is thought to be a prion disease (Scientific American, Vol. XVIII, pages 48–57; January 1995). Transmission through blood remains unproven.

(3) Babesiosis: This is a tick bom parasite that is transmitted through transfusion in certain parts of the United States.

(4) Other Viruses: Cytomegalovirus, Epstein Barr Virus, and Human Parvo Virus B–19 are occasionally transfusion associated.

(5) Bacteria: Contaminated blood due to inadequate arm sterilization preparation or bacteremia within a donor is a potentially serious problem in some blood products such as red blood cells and platelets.

(6) Malaria: Malaria is a serious problem in other parts of the world but not in the USA, although I have seen two cases of transfusion transmitted malaria from African immigrants, who passed all FDA and MBB criteria for blood donation.

(7) Immunologic Suppression: Immunologic suppression has not been adequately documented in human models but clearly has been documented in animal models. Existing animal data suggests that the mononuclear cells within blood are responsible and when removed by leukocyte reduction strategies the immunologic suppression does not occur. It is unknown whether this is due to a transmissible agent.

(8) Oncogenic Potential: There may be, as of yet, undefined tumor producing viruses or other agents which may cause malignancy in susceptible transfusion recipients. Animal models suggest that white blood cells (mononuclear cells) within the blood product may be associated with this tumor producing potential.

(9) Hepatitis: New forms of hepatitis such as Hepatitis G, have now been identified and have clearly been shown to be transmitted through blood.

The approach to recognize, remove or prevent infectious agents in blood intended for transfusion purposes is critical. Testing may be able to recognize the agent directly (antigen based tests including polymerase chain reaction) or indirectly (antibody based tests). Leukocyte reduction through filtration or other means may remove enough of the infectious agent to prevent recipient infection. Viral inactivation technology may prevent transmission of some viruses but not others, depending on the virus inactivation technology used.

When the agent remains unidentified, strategies to remove sources of potentially infected elements of blood may be prudent and cost effective in the future. For example, leukocyte reduction (removal) of white blood cells may prevent transmission of infectious agents totally contained within white blood cells. The retroviruses HTLV–I and II are completely contained within mononuclear cells. Removal of those cells could add an additional measure of safety because current testing has been documented to miss some infected individuals. The use of viral inactivation technologies to inactivate free and intracellular viruses as well as combining white cell

removal technology or technology to inactivate cells containing viral genomes will soon be possible.

If prions are proven to be the transmissible agent for diseases like CJD and if prion diseases are transmissible by blood, new technologies will be required to inactivate prions. On the other hand, use of single donor blood products to reduce recipient donor exposure and reduction of pool size during commercial processing of plasma into plasma derivatives will reduce the chance of this type of disease transmission.

Current viral inactivation technologies such as solvent detergent treatment could become a two edged sword, however. Although solvent detergent technology has proven useful for viral inactivation of viruses with lipid envelopes, it does not inactivate viruses without lipid envelopes and would not inactivate prions. To use solvent detergent processes to treat pooled plasma as replacement of current fresh frozen plasma (a single donor product) could prove to be a mistake. Erring on the side of safety must be a part of the strategic planning process with respect to transfusion and blood product safety.

B. Status of HIV–1 Antigen Test Kit Review by FDA

The use of "antigen" based tests makes scientific sense when the antigen is detectable by current technology, because it allows for earlier detection of the infectious agent. Such is the case with the current use of Hepatitis B surface antigen testing. Multiple technologies that can screen for viruses and other infectious agents directly now exist and include enzyme immunoassay (EIA) systems, polymerase chain reaction (PCR), and other technologies. The decision to use a particular test methodology for mass screening is dependent on the sensitivity and specificity of the test, the ability to automate the test, length of time to perform the test, and ultimately the cost of the test. All of this is true for HIV–1 antigen testing.

The consideration to use the current HIV–1 antigen detection based test is only the first step in "closing" the infectious window for HIV–1 transmission through blood. Recent studies have shown that DNA–PCR is no better than the HIV–1 antigen based test with respect to sensitivity whereas RNA–PCR is a more sensitive test. However, HIV–1 antigen based testing can be automated and is relatively inexpensive compared to PCR and can be done now..

A long incubation (24 hours approximately) HIV–1 antigen test (Abbott Laboratories HIVAG–1) was licensed by the FDA (July 1989) for the detection of Human Immunodeficiency Virus type 1 (HIV–1) antigens in human serum or plasma. It is intended to be used to aid in the diagnosis and prognosis of patients with HIV–1 infections but is not intended as a screening test for donated blood or plasma. This test is not practical for blood bank/transfusion medicine use because of the delays imposed on blood product release (e.g. platelets) when a research based shorter incubation (3½ hours) HIV–1 antigen test could be licensed and made readily available. The Oklahoma Blood Institute has used the short incubation HIV–1 antigen test of Abbott Laboratories under IND #3894 since May 5, 1991 to do prospective testing to determine the incidence of "window" donations, i.e. HIV antigen positive HIV antibody negative donation..

This short incubation test was used by OBI to document an HIV–1 "window" transmission from a repository sample of a donation made in 1989. This report was the first documented window transmission in the world. (Enclosure #3) Prospective testing with the Abbott short incubation HIV–1 antigen test detected a donation on May 10, 1994 that was non reactive for antibody to HIV–1, but reactive by the antigen based test to HIV–1. This resulted in prevention of transmission of HIV–1 to any potential recipient and again documented for the second time within our blood center system the value of HIV–1 antigen testing. The number of donations between the first and second antigen positive donations was approximately 676,000. If this was representative of the incidence in the United States, then the HIV–1 antigen test would detect approximately 21 HIV–1 positive donations out of the 14 million whole blood donations made per year. The number of transmissions however would be greater based on approximately 1.5 products per donation. Clearly, some of these transfusion recipients would die from their primary disease before HIV could be manifested as AIDS, but others, not realizing they were infected with HIV–1, would unknowingly infect other individuals. However, to use this as a reason not to test is flawed thinking in my opinion.

There is currently only one licensed test (Abbott Laboratories HIVAG–1) to perform HIV–1 antigen testing. In addition, Abbott Laboratories, Organon Teknika, and Coulter/Ortho have unlicensed short incubation HIV antigen tests. At least two of these tests (Abbott and Coulter/Ortho) have been submitted to the FDA for licensure. None of the short incubation tests have been licensed as of October 10, 1995.

Critical to licensing one or both of these tests is the availability of an adequate number of reagent test kits produced in a timely manner so that all blood donations

can be tested immediately upon licensure. Blood centers must also have equipment and must have been trained to do the testing upon licensure.

The announcement by the FDA on August 10, 1995 recommending HIV–1 antigen screening of donor blood in response to the July 12, 1995 letter of Representative Shays is the first step to initiate the process of putting HIV–1 antigen screening of donor blood in place. Hopefully, unnecessary delays will not occur. The Oklahoma Blood Institute has clearly documented the validity of HIV–1 antigen testing with the Abbott short incubation test in mass screening of donors (over 500,000 donations) prospectively since May 5, 1991.

C. Reorganization of the Blood Products Advisory Committee: The purpose of the Blood Products Advisory Committee to the FDA was originally to provide evaluation of data related to safety, effectiveness, and labeling of blood and blood products and to make appropriate recommendations to the FDA Commissioner and to other designated Health and Human Services personnel.

The purview of the FDA is to focus on product purity, safety, and efficacy. Cost is not and should not be the primary concern of either the FDA or the BPAC in evaluating blood products or testing. Unfortunately, the BPAC decided that cost was within their authority and responsibility and recommended against HIV–1 antigen screening of donor blood even though previously voting unanimously to accept the HIV–1 antigen data as valid.

With this in mind, the reorganization of the BPAC should include at least four groups of individuals: (1) physicians knowledgeable in transfusion medicine, (2) physicians outside of transfusion medicine but representing the clinical practice of medicine, (3) consumers of blood products such as blood recipients or plasma derivative recipients (hemophiliacs), (4) industry representatives who are knowledgeable of industry and technology.

In addition, the major blood banking organizations should be represented within the blood bank physician group or the industry group and should include a representative from American Association of Blood Banks, American Red Cross, Council of Community Blood Centers, and American Blood Resources Association.

Conclusions of the BPAC should be treated as advisory only, with final decisions made completely by the FDA after careful evaluation of the data and the use of privately acquired experts. The selection of BPAC members should not be by the FDA but should be independent of the FDA.

Finally, if the recommendations of the Institute of Medicine are followed the BPAC and the Blood Safety Council must be clearly differentiated as to mission and objectives. Recommendation #2 of the Institute of Medicine is to establish a Blood Safety Council to assess current and potential future threats to the blood supply as well as proposed strategies to overcome these threats, evaluate the response of the Public Health Service to these proposals and monitor implementation of these strategies.

D. Hepatitis C transmission through blood and blood products: The transmission of hepatitis C (previously non-A, non-B hepatitis) remains an important issue today even with the second generation anti-HCV test. Hepatitis C is a good example of a virus that was initially unsuspected until hepatitis A and B viruses were defined. Only then was it realized that there still existed a significant amount of transfusion associated hepatitis.

The use of the surrogate markers ALT (alanine aminotransferase) and anti-HBc (antibody to the hepatitis B core antigen) significantly reduced transmission of Hepatitis C. With the advent of anti-HCV testing and especially the second generation test, the need for these surrogate markers was eliminated for anti-HBc and dramatically reduced for ALT.

An NIH Consensus Conference in January 1995 concluded that ALT testing was unnecessary and added little value in early detection and prevention of transmission of Hepatitis C. However, it is clear that ALT elevation in acute Hepatitis C occurs before serological conversion to anti-HCV reactivity occurs. ALT elevation occurs approximately eight weeks after the primary infection, whereas seroconversion is three to four weeks later (11–12 weeks after the primary infection). Raising the ALT cutoff or eliminating ALT testing will result in a very slightly increased number of transfusion transmitted Hepatitis C cases.

The real problem with Hepatitis C transmission through blood products is the long "window" of approximately 11–12 weeks from the primary infection to seroconversion. For plasma derivatives prepared from pooled plasma sources, the use of viral inactivation technology will probably prevent HCV transmission but this is not the case for other blood components. HCV–PCR testing can detect the presence of the HCV genome approximately three weeks after the primary infection but HCV–PCR is not a technology that is currently available for mass screening.

Until such testing becomes available reduction in transfusion associated HCV transmission could best be accomplished by utilizing a higher percentage of repeat donors that have previously tested negative for anti-HCV.

SUMMARY:

(1) The benefits of doing a test or developing a new or better blood product can be unnecessarily impeded by focusing too early on the issues of cost. The result is that all progress is stopped and the end point is never achieved such as closing the HIV "window". Risk benefit analysis is a much more important focus than a cost benefit analysis in the early evaluation of a test or blood product.

The FDA and its advisory group, BPAC, must focus on their defined mission which is safety, purity, and efficacy, and not employ cost modeling as a method to impede scientific progress and discovery.

(2) Strategic planning and modeling are critical to the design in implementation of processes to assure a safer blood supply. The six point Oklahoma Blood Institute model outlined on Enclosure #1 focuses on multiple approaches aimed at a safer blood supply.

(3) Emerging transfusion associated infections in the United States are in part due to wider global travel and to new agents as well as recognizing that unidentified infectious agents may be of importance in the future. The prion diseases are an example of a group of diseases that are, as of yet, not proven to be transmitted through transfusions. However, putting in place a process to minimize the risk of transfusion transmission by decreasing pool size of plasma derivatives and emphasizing single donor products for regular blood components would be proactive instead of reactive.

(4) Hepatitis C transmission through blood product transfusions is unlikely to decrease significantly with current EIA anti-HCV testing technology because of the long interval (11–12 weeks) from infection to detectable seroconversion. New testing technologies such as HCV–PCR when automatable will narrow the infection window. Until then, processes aimed at increasing the frequency of blood donations from single individuals will help decrease transfusion associated HCV infections.

ENCLOSURE #1

OKLAHOMA BLOOD INSTITUTE'S SAFETY MODEL FOR TRANSFUSION PRACTICE AND BLOOD PRODUCT USAGE

I. Autologous Blood Products and Services:
II. Pedigreed/Frequent Repeat Blood Donors:
III. Single Donor Products:
IV. New/Improved Testing and Procedures:
V. Inactivation/Removal of Risk Agents:
VI. Substitution of Non Risk/Lower Risk Products and Procedures:

ENCLOSURE #2

OKLAHOMA BLOOD INSTITUTE'S SAFETY MODEL FOR TRANSFUSION PRACTICE AND BLOOD PRODUCT USAGE

EXPLANATION AND EXAMPLES

I. Autologous Blood Products and Services:

A. Preoperative donation of blood products
B. Intraoperative salvage of RBC's (red blood cells)
C. Postoperative salvage of blood from surgical wound drainage
D. Patients for elective surgery should be aware of the above options A, B & C

II. Pedigreed/Frequent Repeat Blood Donors:

A. Encourage donors and develop donation programs using recognition methods, special benefits such as cholesterol testing, and acceptable non-monetary incentives.

B. Frequent repeat donors generally have a greater sense of responsibility and understanding of the impact of their donation on the recipient.

C. Multiple donation screening (testing) reduces the chance that the donor is infectious.

D. Patients electively (non-emergency) should be advised that a frequent repeat donor is less likely to carry and transmit a known infectious agent.

III. Single Donor Products:

A. Platelets from a single donor obtained by an apheresis donation provides the equivalent of pooled platelets from 6–12 whole blood donations thus reducing donor exposure.

B. Fresh Frozen Plasma (FFP) from a single donor reduces donor exposures 3 x compared to FFP from whole blood.

C. These donors tend to donate regularly and are less likely to transmit known infectious agents.

D. Quality of products can be higher due to possibility of quality controlling each product for content and other factors.

IV. New/Improved Testing and Procedures:

A. Improved versions of current testing with increased sensitivity and specificity.

B. New tests designed to detect new infectious agents in blood or a new test designed to detect a different marker. For example, antibody detection tests (anti HIV–1/2) can only be reactive after the human immune system produces an antibody whereas antigen detection tests (HIV-antigen, hepatitis B surface antigen, HBV–PCR) look for the virus or viral component directly.

C. Improved computer tracking procedures, elimination of manual procedures in testing, and information tracking, blood labeling, and blood distribution from the blood center and from the hospital blood bank to the patient would significantly reduce errors that result in patient morbidity or mortality.

V. Inactivation/Removal of Risk Agents:

A. Viral inactivation technology of all blood products has areas possibilities for the future.

B. Leukocyte reduction technologoy (white blood cell removal filters) has the potential to prevent transmission of CMV, HTLV–I, HTLV–II, other intracellular viruses such as HVZ, EBV, and possibly even unknown viruses such as tumor producing viruses, as well as reducing immunologic sensitization and immunologic suppression.

C. Irradiation of blood can prevent TAGVHD

VI. Substitution of Non Risk/Lower Risk Products and Procedures:

A. Use of virally inactivated blood derived products such as albumin (decades of safety data) instead of a higher risk product such as whole blood derived fresh frozen plasma.

B. Avoidance of pooled blood products where single donor products can be used.

C. Use of growth factors (erythropoetin for red blood cells, granulocyte colony stimulating factors for certain WBC's) to replace blood products.

D. Physician education on use of autologous procedures and products vs. blood products from another person.

AABB 1990

Enclosure #3

AABB
1990

S237 *

TRANSFUSION-ASSOCIATED HIV FROM ANTI-HIV NON-REACTIVE, HIV ANTIGEN REACTIVE DONOR BLOOD.

R.O. Gilcher, J. Smith, S. Thompson, L. Chandler, J. Epstein, and F. Axelrod. Sylvan N. Goldman Center, Oklahoma Blood Institute, Oklahoma City, OK; Food & Drug Administration; and American Blood Institute, Los Angeles, CA.

A 47 year old woman with no HIV risk factors underwent mitral valve replacement and required homologous blood transfusions. All transfused units were anti-HIV non-reactive. The donor of one of the transfused units donated again exactly 56 days after the previous donation and was anti-HIV reactive by EIA and western blot positive. A repository plasma sample from the original donation was retested for HIV antibody and remained non-reactive. The repository plasma sample from the original donation in 1989 was also tested for HIV-1 antigen by the Abbott long incubation licensed reagent and was reactive. Neutralization testing confirmed the reactive HIV antigen. An aliquot of the repository plasma sample was tested by the FDA's retrovirology laboratory with 5 manufacturer's anti-HIV-1 EIA reagents and was non-reactive by all. The recipient of the anti-HIV negative HIV antigen reactive unit is now anti-HIV positive. This case documents HIV transmission by a "window" donation, demonstrating the value of a serum/plasma repository in documenting HIV "window" transmissions.

S238

HIV ANTIBODY STATUS OF SUBSEQUENT BLOOD DONATIONS FROM INDIVIDUALS FOUND TO BE HIV-AG REPEATEDLY REACTIVE/NON-NEUTRALIZABLE.

P. Ruttar, M.A. McGuire, J. Herman, E. Arnold. American Red Cross Blood Services, Penn-Jersey Region, Philadelphia, PA

From January - April 1989 our blood center screened 61,661 donors for HIV Antigen(Ag) by Abbott long incubation EIA as part of the national collaborative study to evaluate HIV-Ag screening of blood donors.

74 (0.12%) were HIV-Ag repeatedly reactive (RR); none were confirmed by neutralization. In the year following this study 45 donors(60%) have returned for blood donation with no seroconversion for anti-HIV:

Donations since study:	1X	2X	3X	4X	6X
# Donors(N=45)	27	13	2	2	1
Months between Ag(+) & next donation	8	4	4	4	2

Of 61,587 donors who were Anti-HIV negative and HIV-Ag negative, 3 were Anti-HIV RR on their next donation:

	Date Ag neg	Date HIV-ABY RR	W Blot	Risk
Donor # 1	2/9/89	8/9/89	Pos	None
Donor # 2	2/13/89	2/21/90	Pos	SP IVDA*
Donor # 3	2/22/89	2/21/90	Neg	NA

*Sexual partner of IV drug abuser.

Look-back products from the earlier donation, from donor #2, were not transfused. The platelet concentate from the 2/9/89 donation by donor # 1 was transfused and the recipient is anti-HIV negative.

These data support the recommendation that those donors found RR/unconfirmed for HIV-Ag during the study period are safe and should be eligible for future donation.

S239

PRESENCE OF IgA AND IgM HIV ANTIBODIES IN WEAK REACTIVE OR FALSE NEGATIVE BLOOD DONORS.

E.J. Weiblen, R.T. Schumacher, P.E. Garrett, and R. Hoff. Massachusetts State Laboratory, TSRI, Boston, MA and Boston Biomedica Inc. West Bridgewater, MA.

Detection of Anti-HIV in recently infected donors is crucial to prevent transmission of HIV infection via blood products. We selected 15 random donor units that were borderline reactive for anti-HIV in EIA screening tests and confirmed positive by immunoblot (CDC/ASTPHLD criteria), then did further testing for IgA and IgM HIV antibodies by immunoblot after removal of IgG with protein G. All 15 had detectable IgA HIV antibodies and 14 had IgM HIV antibodies. The 15 specimens were then tested with 9 FDA-licensed EIA tests, each by 2 independent laboratories. Two of the 9 EIA methods found all 15 units positive by both laboratories. Seven methods found 1 to 5 of the 15 units negative. In an attempt to enhance EIA sensitivity, we added enzyme-conjugated anti-IgA or anti-IgM to the kit enzyme-conjugated reagent. For 6 of 8 kits, this modification increased the O.D. values of falsely negative specimens to the positive range. We conclude that licensed EIA tests vary in ability to detect IgA and IgM antibodies and that EIA sensitivity might be improved by addition of anti-IgA or IgM.

S240

DETECTION OF HIV-1 PROVIRAL DNA AND HIV-1 RNA SEQUENCES USING POLYMERASE CHAIN REACTION METHOD.

K. Nakenaru and N. Yoshihara. National Institute of Health, Tokyo, Japan.

Polymerase chain reaction(PCR) method was applied to detect HIV-1 proviral DNA sequences(DNAPCR), and to detect HIV-1 RNA in the combination with reverse transcription method(RNAPCR).

Detection sensitivity is higher using liquid hybridization(LH) technique than southern hybridization technique. To combine with LH, the DNAPCR is enough to detect 5 copies of HIV-1 DNA by gag primer pairs as same as pol or env primer pairs. All DNA samples from 12 cases of patients and carriers' peripheral blood mononuclear cells reveal positive with at least one of the three primer pairs.

Detection sensitivity of the RNAPCR was estimated by comparison with virus infectivity. HIV-1 RNA was detected up to 10^7 dilution of the 10^{-4}TCID$_{50}$/ml virus fluid by RNAPCR using gag primer pair. With pol and env primer pairs, RNA was detected only till 10^4 and 10^5 dilution respectively. RNA is detectable in serum of patients, and also Factor VIII products since 1978.

	DNAPCR			RNAPCR		
	gag	pol	env	gag	pol	env
patient(n=9)	7/9	8/9	6/9	7/7	2/6	1/6
carrier(n=3)	3/3	2/3	0/3	0/2	0/2	0/2
Factor VIII (n=8)	not tested			4/8	0/8	0/8

TOP

Enclosure #4

Signature of Senior Author

Fold down to cover title and name(s) of author(s)

2506

CUT HERE

#154

AABB
1995

PROSPECTIVE HIV ANTIGEN (p24 ANTIGEN) TESTING: DONOR DETECTION. RO Gilcher, JW Smith, LO Belcher, and LK Chandler. Sylvan N. Goldman Center, Oklahoma Blood Institute, Oklahoma City, Oklahoma.

Background: Prospective research HIV antigen testing to determine the incidence of "window" donors (HIV-antigen positive/HIV-antibody negative) was begun May 5, 1991 under IND #3894. We previously reported the first documented "window" transmission from a repository sample that was p24 antigen positive and HIV antibody negative.

Methods: Abbott Laboratories monoclonal p24 antigen has been used to test the majority of blood donations since May 5, 1991. The remainder have been tested with Abbott's polyclonal p24 antigen test.

Results: On May 10, 1994 an HIV-antigen positive/HIV antibody negative donation was found by the monoclonal p24 antigen test and subsequently confirmed by Western Blot. This occurred on donation number 451,573 following the beginning of p24 antigen testing. From the original repository "window" case (previously reported) to the occurrence of this prospective "window" detection, there were approximately 676,000 donations.

Conclusion: This report is the first documented "window" donation in the USA detected prospectively and resulting in prevention of transmission of HIV to a blood recipient using p24 antigen testing.

Please retype title: PROSPECTIVE HIV ANTIGEN (p24 ANTIGEN) TESTING: DONOR DETECTION

If accepted this abstract will be reproduced for publication in *TRANSFUSION*. Use letter quality type and correct font to ensure 12 characters per inch and six lines per inch.

MUST BE COMPLETED BY AUTHOR

Please check the section and only one category into which you would like your paper to be scheduled.

- [x] SCIENTIFIC
  - [ ] Apheresis (Preparation, Therapy and Methods)
  - [ ] Component Preparation and Storage
  - [ ] Donor Medical and Safety Issues
  - [ ] Pediatric Transfusion Medicine
  - [ ] Plasma Components and Derivatives
  - [ ] Platelet and WBC Antigens and Antibodies
  - [ ] Platelet and WBC Biochemistry & Molecular Biology
  - [ ] RBC Antigens and Antibodies
  - [ ] RBC Biochemistry & Molecular Biology
  - [ ] Transfusion Practice/Clinical Case Studies
  - Transfusion-Related Diseases and Complications
    - [ ] Hepatitis Viruses
    - [x] HIV 1/2
    - [ ] HTLV I/II
    - [ ] Other Infectious Complications
    - [ ] Non-Infectious Complications
  - [ ] Transplantation
  - [ ] Other
- [ ] ADMINISTRATION/OPERATIONS
  - [ ] Apheresis (Recruitment and Management)
  - [ ] Donor Collection
  - [ ] Donor Recruitment
  - [ ] Financial Management/Cost Containment
  - [ ] Management
  - [ ] Management Information Systems
  - [ ] Marketing
  - [ ] Personnel/Human Resource Management
  - [ ] Product and Inventory Management
  - [ ] Public Relations
  - [ ] Quality Assurance/Risk Management
  - [ ] Training and Education
  - [ ] Regulatory Affairs
  - [ ] Other

American Association of Blood Banks
48th Annual Meeting
November 11-15, 1995
New Orleans, Louisiana

MUST BE COMPLETED BY AUTHOR:

1. Author would prefer an oral presentation Oral or a poster presentation. _____ Insofar as possible, authors' wishes will be followed. However, final program assignment rests with the respective committees.
2. The Senior Author's signature at the top of this page indicates that this material has not been accepted for publication in a peer review journal or presented at a National Meeting.
3. Full case of study was supported by an AABB Foundation grant. __ Yes X No. If yes, please specify. _____
4. Author has read the Policy on Disclosure of Faculty Relations and has filled out the enclosed form X Yes

Abstract oral presentation meeting rooms will be supplied with a 2" x 2" slide projector for your use. Video equipment is unavailable.

Mr. SOUDER. Thank you very much, and I thank the whole panel. We are going to recess for a vote and then we will ask questions. The committee stands in recess.

[Recess.]

Mr. TOWNS [presiding]. Let me begin by thanking the witnesses for their testimony and start the questioning with you, Dr. Penner.

You stated in your testimony that the restrictive and sometimes inflexible regulations implemented by the FDA have the potential to destroy the system of donating and blood banking.

What do you really mean by that?

Dr. PENNER. We have had a number of incidents. For example, one of the things listed that I did not have an opportunity to read in my testimony is an assay for syphilis, which is required for testing of all blood and blood products. The reagent at use in the test had to be employed in a certain way and there is a specific standard operating procedure for it.

The testing that was done in one of our regional Red Cross centers employed the test, but it was employed in the manner in which it was a little different from what the manufacturer had recommended or described in their package material. It differed by about five words. Those five words, fortunately, had no effect at all on the testing reagent and the conclusion of the testing itself. And this was agreed upon by the manufacturer as well as most of our medical advisory group, in fact, all of our medical advisory group; therefore, it had really no implication.

But because of it, we had to destroy about 500 units of blood and we had to recall about something of 10,000 to 20,000 units of blood because it did not meet the criteria as set up by the FDA. What we needed at that point, I think, was someone knowledgeable to be willing to accept that there was a difference but it did not affect the public and, therefore, the blood that had been donated did not have to be destroyed.

And there are other incidence that are similar to that in which the adherence to specific requirements are such that in some cases when there is a modest deviation or a meaningless deviation, it is necessary to destroy blood and to recall it. This, I think, also sets up a problem with respect to the image of the blood supply to donors who have received this notice that their blood is being recalled.

And even though we assure them that there is nothing wrong with the blood, the other side of the coin is that the recipients also get notified that they had received blood in which something had gone wrong. And, again, we have to assure them that nothing had gone wrong that would affect them; however, it was a problem related to the orientation of the blood programs.

Mr. TOWNS. What additional tests and/or safeguards do you believe should be immediately implemented to protect the blood supply?

Dr. PENNER. I believe any of the testing procedures that will reduce the incidence of these infectious agents in the product or the blood that we are obtaining should be applied.

That means, with the example we have in front of us, the HIV antigen testing, there is no doubt it will exclude some individuals in this so-called window period, as has been testified. And, there-

fore, it is important, I think, to apply it. And I don't think that we can accept cost factor as being a reason for not applying it.

Other testing procedures are perhaps a little less clear cut. A test, for example, that would exclude—and this was referred to earlier—maybe 20 percent of our donors that would come to any of our blood centers, and yet would perhaps screen out a half a percent of the population, or say 1/1000th of a percent of the population that could infect individuals with their blood, would be something that has to be looked at very carefully.

In other words, we can't eliminate the donor population blood product if we are not going to substantially improve or reduce the infectivity of the blood. So that still requires a good deal of adjudication before one comes up with a decision.

Mr. TOWNS. Why haven't these measures been implemented? Why haven't they been implemented, in your opinion?

Dr. PENNER. In my opinion, there is a lack of an advisory support from the medical community. And this, I think, harkens back to the BPAC and the advisory group and panels that have been employed to support some of the decisions made; that we need not only have industry represented.

But we need to have the users and the physicians that are providing the product or ordering the product at the present. These individuals are going to have to be able to step up and be part of this program; otherwise, one is going to end up with a very biased approach to making decisions.

And I think up till now that has been a problem. Some of the procedures have not been employed directly and we have not been able to get the educational aspects out to the public as a result of this.

Mr. TOWNS. Dr. Gilcher, you mentioned in your testimony that cost was the reason that the BPAC recommended against screening blood for HIV. To what extent have cost considerations limited the availability of new testing procedures and new technologies that would make the blood supply safer?

Dr. GILCHER. Your question is important. What happened at the BPAC committee was that cost modeling was shown to the committee members. That modeling, in my opinion, was very flawed. What it looked at was simply the cost per test and what the cost to the total system would be.

But it did not look at, for example, the credibility of our blood system in this country, because many people are absolutely afraid of receiving blood and so what they do is they go out and secure their own donors. That type of process, called a directed donation process, adds far more cost to our system.

My own estimate is—and we are the only blood center that has been doing a long-term prospective study with the HIV–I antigen test, we were not asked to present what the real costs were to us—that cost is going to be somewhere between $2 and $4 per test, probably on the lower side. But my estimate if we had to go to directed donations in our system, would be four times that.

So what I am saying to you is putting that test in place actually in the long run may turn out to be cheaper than facing this loss of credibility to our blood donation system that currently exists.

And we would be sending the wrong message to the public if we didn't put this test in place.

Now, what about other tests? What I said in my testimony, and it may have been confusing and I do want to clarify it because this is very important. There are two different ways to approach a disease process. One is to look directly for the agent that causes the infection, that is, the virus directly or whatever. The other is to look at the response of the human immune system to that. That is the antibody based tests.

By definition, it is going to take a minimum of 14 to 21 days for the human immune system to respond to any infectious agent; therefore, no matter how good an antibody based test is, we are going to have a delay.

What I am saying then is if we focus on both antibody and antigen detection systems, what we do is we narrow that window. That is exactly what we are doing here. One test does not replace the other. They are both needed. The antigen detection based test gets that early phase, that early infection; the antibody test picks it up later.

Mr. TOWNS. Thank you very much, Dr. Gilcher. Let me just ask one question to Mrs. DeFilippi. When you have used blood or blood products, have you been made aware of the risk associated with the transfused blood?

Mrs. DEFILIPPI. Generally, no. It depends on the physician that you are speaking with and the center. When we have gone to the hemophilia treatment centers, which we do when they are locally available to us, they do warn us. But we are military and we generally use the military system and we have often lived in States where the closest treatment center is hundreds of miles away and we rely on other kinds of systems.

The issue is discussed maybe once a year in a hemophilia treatment center but the rest of the time, no. So it depends. It varies from doctor to doctor and place to place.

Mr. TOWNS. Thank you very much, Mr. Chairman. I see the red light so I yield back.

Mr. SHAYS. Given the number of people here now, we should feel free to ask any question. And let me just say as an illustration of how serious this issue is and also how politics doesn't enter into it, I am totally comfortable having Mr. Towns take the chair any time on this issue.

The only reason he gave it back to me was he told me one time, he said I'm only going to be chairman for 2 years and then he gets it back, so he wants me to have some opportunity to sit in this position. But this is an issue we both feel very strongly about.

I also want to apologize. I have a budget hearing and we are reporting out legislation and I had to be there while you were speaking, Mr. Dubin. I apologize. And both doctors, I am sorry I missed your testimony here.

But what would be helpful for me to know and to have on the record is you, all four of you, were here when the Secretary testified. And that is a major announcement from the standpoint of HHS on how they intend to deal with this very serious challenge, and I would like each of your opinion about it.

And I am just going to preface this by saying, we have one issue of what we deal, how we assist, and is there any remuneration for those who have been infected by the failure to properly screen our blood supply in the past?

And then there are two elements there. There was, obviously, a time when you didn't know about HIV. That is one issue. But when you began to realize it was happening, how quickly did we respond, and how many people were infected after that, which brings it up to another level of real outrage.

That is one issue that I see. I am prefacing this because I would like your response. The other is, what is the system that we are putting in place right now as a directive, an announcement, today by the Secretary.

And the third is really kind of an appreciation of what we—and to say look forward to in the future is not the proper word, but we have a world that is constantly interacting. People can be in the heart of Africa and the heart of South America, and in 20 hours they can be right back home.

We have this tremendous interaction of travelers, particularly in the United States as opposed to other parts of the world. And what is the potential for infectious diseases in the future as a result of this kind of interaction and so on.

So my primary question though is to ask you, each of you, what you felt about the government's response: Is it a bureaucratic response, is it a substantive response, is it somewhere in between? And then the second question I will come back and ask you is, if you don't agree that it is a good process, what would you suggest in its place?

So I am going to do a little listening here, and we will start right down the row.

Mrs. DEFILIPPI. I feel kind of inadequate to answer that. I am just a teacher. But I think they seem to be moving in the right direction. But I didn't hear some of the things that I wanted to hear. And I may have misunderstood what they were saying.

Mr. SHAYS. I am going to come back to you on that. But, no, your opinion is extraordinarily valued here. You are someone who has been impacted by the failure of the government to respond properly.

And I am haunted by your son having to call up someone whom he was dating to say that she may have been infected.

Mrs. DEFILIPPI. He was so much in love with her, like you are when you are 16.

Mr. DUBIN. Mr. Chairman, when you talk about her son, I mean that is something that resonates throughout our community, talking to our mates when we begin to understand it, our wives, our girlfriends, our children. I think it is something we have all lived with.

I think the question is in terms of the process.

Mr. SHAYS. What she announced, what the Secretary announced.

Mr. DUBIN. Right, about the Council and about where they are.

Mr. SHAYS. About how it becomes the Assistant Secretary's responsibility. The Council—also the dissemination of information.

Mr. DUBIN. Right, I understand. I think there is two ways to look at it. I think the very positive side is it is clear that we have got

HHS engaged. It is clear that HHS is responding to the Institute of Medicine report at the level of the Secretary.

I think we in the community think that is a very positive step and I think for the first time in many, many years, maybe ever, for the hemophilia community, we have got high levels of the U.S. Government engaged on blood safety issues, issues, of course, that have a much wider implication than just us.

But the analogy, I think, for us is we are the canaries of the blood supply. You know, like they used to take canaries into the mines and when the canary couldn't breathe any more miners cleared out. Well, we are the canaries of the blood supply. When it is contaminated, you will see it in us.

Mr. SHAYS. Because you are the most vulnerable.

Mr. DUBIN. Right. We are at the front end where we are vulnerable. So I think for the first time we are seeing high levels of the U.S. Government engaged. I think that is very positive. I want to say that. I think this committee is very positive, its work.

I think the Secretary's work is very positive, vis a vis her announcements, the Council. We have supported and we are in an informal meeting Dr. Lee, members of industry, FDA Commissioner and others had about 10 days ago on Wednesday to discuss this.

I think we have some real concerns. I think the need for a council is a given from our perspective. It is a step this government must make because the coordination between agencies was appalling during the 1980's, and I think it goes back to this complacency about certain medically accepted risks like hepatitis. And I think the Council can really be the place.

I think our big concern is if we are going to set up a council that mimics what we have seen in the past—blood bankers, industry people, and a few others—then we have a problem. If the council is going to become a place where government, where industry, both the manufacturers of blood products and the blood banking industry—and I think it is important to see the difference between those two entities. They frequently get lopped together.

Consumers, treaters like Dr. Penner was saying, and independent scientists, which I think we sorely need in this process is some independent minds. If the Council is going to include that kind of breadth, then I think we have got something really good to work with. I think we have got an opportunity to bring all components together.

Mr. SHAYS. Dr. Penner.

Dr. PENNER. I am agreeing with the approach, and I think it is going to be very beneficial. It is the right step at the right time.

The one aspect that I am concerned about is we are dealing with two areas. We are dealing with blood banking centers, we are dealing with industry that is manufacturing a product. There is going to have to be some differentiation in the application of regulations relating to that.

I do think that industry should look very seriously, and perhaps be encouraged, to maintain a total involvement with volunteer blood only. In other words, paid blood ought to be discarded if at all possible and the resource should be volunteer blood, because there is no doubt that the volunteer blood will be safer all the way

around and that there will be less opportunity for some of these infectious agents that can get into the blood stream to appear.

Mr. SHAYS. I am going to ask you to get into that later, the paid blood versus volunteer blood.

Dr. PENNER. All right. On the blood center end of the situation, I think the concerns that I mentioned in my testimony is that one does not want to throw the baby out with the bath water. We cannot discourage the volunteers who come in and do the right thing and yet argue with us if they can't give one more unit of blood to make their 20 gallons so they can get the pin.

Those concerns are out in our communities now, and you would be just amazed at how much of a harangue we get if somebody can't come in and give one more unit of blood. These are altruistic individuals and they have to be encouraged and supported.

I have a feeling that they are going to be falling on the wayside as we go on into this venture of looking at us as an industry.

Mr. SHAYS. Thank you, Doctor. Dr. Gilcher.

Dr. GILCHER. I would really like to add to what Dr. Penner has just said. I believe that the recommendations of the Institute of Medicine are, for the most part, very appropriate, especially the Blood Safety Council.

Where I do have a concern is with the composition of that council. What we heard Secretary Shalala say was that NIH, FDA, CDC, would be on that council. That is appropriate. But if we don't have the people from the trenches—I'm talking about the Penners, the Gilchers, so to speak, who are out there at the blood center level—we need input because we know what is happening. We know what the concerns and issues are out there.

Mr. SHAYS. Does this system give you input?

Dr. GILCHER. I'm sorry?

Mr. SHAYS. Does this system give you input?

Dr. GILCHER. Only if we are allowed to be on that kind of a council so that we can put the input in. And then the process design, the plan.

If you look at my written testimony, and I showed you the plan that we have used for 10 years, that is the kind of plan that has to be designed at the very highest level at the Blood Safety Council level. It is a general plan that one could pursue or that we can pursue as a Nation to add to the safety. So the composition, I think, is critical of this council.

Mr. SHAYS. I would appreciate from all of you, in particular both of our doctors who are testifying before us, as to specific—no, actually, all of you, actually all of you, as to your written reaction to this proposal in concise form as possible, and how you would change it and where you would change it.

And the sooner you get that to us, I will go over that with Mr. Towns. Mr. Towns and I can respond together collectively, Republican and Democrat, as to how we would like to suggest changes, if any, if any changes.

If I could, had you completed your comment there?

Dr. GILCHER. Yes.

Mr. SHAYS. Let me just ask two more questions, and I'm not following the 5-minute rule right here.

Mr. DUBIN. Mr. Chairman, excuse me. Is 5 days enough time to get written testimony in?

Mr. SHAYS. Five days would be fine. Thank you for asking that. That would be helpful for us because we would like to respond timely. It has been announced and we would like to respond as timely as we can.

I want to understand the whole concept of the pool of plasma donors. And I want to understand from all of you. What do you want this committee to know about that? Where is the safety level?

I mean, I'm just stepping into this issue for the first time. What do I need to know about this issue? How large the pool is, when does it become a dangerous pool? I mean, my understanding is one individual in a very large pool can contaminate the whole mix if their plasma is infected.

Dr. GILCHER. I would like to respond to that because I think that is a very important question. When you look at pool size, that is, the number of blood donations that make up that pool, it can be as small as maybe 1,000 to 2,000, as high as 8,000 to 10,000 donors that make up the current pools.

Mr. SHAYS. Technically, it could even be larger, couldn't it?

Dr. GILCHER. They could be larger. But if we look at diseases that are emerging, and certainly the plasma manufacturers, the plasma derivative manufacturers, are looking at that right now.

The prion diseases that I spoke about earlier, Creutzfeldt-Jakob Disease is one of the prion diseases. There is no data at the current time that shows that it is transmitted through blood. On the other hand, we better be very sure that none of the prion diseases are transmitted through blood because the current viral inactivation technology will not touch that.

So one of the ways to handle it at the current time or at the present time would be to find ways to reduce pool size, reduce the size of these pools until we really have a better handle.

Mr. SHAYS. To what level?

Dr. GILCHER. That is difficult to say. Probably we are going to have to get down to pool sizes that are below 500 or 600 blood products in the pool, but that is going to add cost.

Mr. SHAYS. Thank you.

Dr. PENNER. Add a lot of cost. So maybe there is another aspect of it too.

Mr. SHAYS. Could you explain why that would add cost?

Dr. PENNER. Just on the matter of volume. Right now they have 8,000-liter vats to prepare the products from as they run through, as opposed to one getting down to, say, 1,000 liters or 500 liters.

Mr. SHAYS. So it is a volume of scale issue.

Mr. DUBIN. It's economies of scale.

Dr. GILCHER. The quality control, for example, would have to be done on the smaller lot sizes and that would add cost.

Dr. PENNER. So you are producing a lot of cost. This could be looked at a lot like the milk industry, if you will, in that you need something at the end stage to be inactivating any of the viral products that might be present there, the contaminants. And pasteurization solved a lot of that problem, although not entirely, but pasteurization is one aspect of what we are trying to do with the blood at the end stage.

The other part of the milk industry situation was you looked at the cows and the herds and, if they were infected, you would destroy the herds. But we don't suggest that you destroy the volunteers from coming in to donate the blood. However, I think there is a situation where we have been attempting to screen out as carefully as possible those donors which are relatively safe and those who are not. And that is going to have to continue to proceed.

I think the one issue that has not been looked at, or at least brought up very directly here though, is how much are we putting into developing new techniques for sterilizing this blood product. There were some initiatives about 5 or 6 years ago that have paid off. The New York Blood Center, for one, has the detergent treatment which has been very beneficial. Heat treatment commenced with the ability to find stabilizers that would allow us to treat the product and heat it without destroying the product.

But we need some new innovations in that area, and I think that can only be encouraged by providing some funding at the level of the investigative areas around the country.

Mr. DUBIN. Mr. Chairman, I think this is an area where we really need the help of Congress and the help of the committee, because I think we have experienced a great deal of frustration with the existing system at trying to raise this issue and trying to make some ground out of it.

What surprised me as I started to become educated on this was the plethora of journal articles and information beginning with World War II, when the Army began to pool plasma and send it to the Pacific theater, that the danger really began to be documented then.

The only reason we have these incredibly large pool size up to 10,000 to 20,000 donors is industrial economies of scale. And speaking to someone who is on the receiving end of that for many, many years and kind of is a hotel for virus, if you will—you know, they check into my body but they don't every check out—I think there is a sense that this has been one of the really frustrating issues that we have tried to raise.

It came up at the BPAC. BPAC decided to hold off taking any action on it. Part of the discussion focused on what the cost to industry would be. And I understand that it will cost industry. But I think this is one of those things where we need to change our perspective.

Mr. SHAYS. It will also cost consumers. I mean, I just want to put it on the record.

Mr. DUBIN. Yes, that will be passed on. But we have made it clear that that's an acceptable tradeoff for us. But that if you are talking about me paying 4 or 5 cents more a unit for a smaller pool size which will increase safety, I think we are very clear that we would like to opt for the higher safety. And I think this is where we would really ask for the help of Congress.

Mr. SHAYS. My counsel has just made the point that you could give consumers choices of larger pool sizes and smaller, and let them decide whether they wanted to pay the price.

Mr. DUBIN. I don't know if it that is feasible vis a vis industrial—their production.

Mr. SHAYS. Not everything he suggests is feasible. Isn't it wonderful? He doesn't even get to talk. I get to talk. I can misrepresent him.

Mr. DUBIN. Let me just close this. This is a critical area that has been raised for many years that we have had no action on, and I think we really need it.

Mr. SHAYS. The message is loud and clear on that. And we are going to take a good look at this, as I think both the doctors have suggested.

Mrs. DeFilippi, you had also a comment on where you would suggest a change potentially in what the Secretary said, or what made you uneasy. You weren't specific. I said I would come back to you.

Mrs. DEFILIPPI. On the issue of the blood safety pool, I am not a scientist, but one of the things that strikes me as a consumer is the difficulty in finding a location to give blood if you are a healthy donor. I know that you can give blood at hospitals, but many people are afraid of hospitals and don't like to go there.

I realize that there are Red Cross donor sites, and bloodmobiles that go around to certain large businesses and churches. On the other hand, for average folks with a very busy schedule it's not real convenient.

And I wonder why there is not a convenient donor site for volunteer donors in places like large shopping malls. I don't know about the logistics of how you would do it.

But if the people you are getting your blood pool from are primarily people who go to sell it and the blood becomes a for-profit item for the donor, then you are putting—you are adding to the risk. If you make it easier for volunteers, perhaps you can reduce the risk.

Mr. SHAYS. You know, all of you raise new questions.

Mrs. DEFILIPPI. This is a question for me. What I was uneasy about or what I didn't hear—I think I didn't hear—anything about was a necessary public information campaign.

Mr. SHAYS. Necessary or unnecessary?

Mrs. DEFILIPPI. Necessary. Surgeon General Koop is one of those people that I think is a walking hero. He stood up in front of our country and said, don't smoke; you're going to get cancer. And he stood up in front of our country and said, HIV is here, folks. Let's deal with it, and these are the things you should do.

No one has stood up and said hepatitis is here. If you had a blood transfusion, you need to get yourself tested and checked and notify your partners, your friends, and your family.

Mr. SHAYS. This is a good segue to ask both doctors, and I appreciate the patience of my colleague on this. The question I asked the Secretary at the very end about the 100,000 to 200,000 individuals who may be infected with Hepatitis C and, therefore, all who have received blood products previous to 1990, should check to see if they are infected.

Do you believe that that kind of announcement should be made to people? Why would it be any different when hepatitis is something that can be transmitted sexually? So if you could answer that, I have no more questions.

Dr. PENNER. I worry about what is right in this situation in how we provide more and more information. I think we have to be very

careful in how the information gets out there. All of the information should be given, and I am concerned primarily with how it is presented.

With Hepatitis C the public is probably ready for it, but I think it has to be phrased not as a scaring type of thing.

Mr. SHAYS. Well, couldn't it be done by just basically, a public health notification by HHS 100,000 to 200,000 sounds like a lot of individuals. Frankly, it is a lot of individuals.

Dr. PENNER. No, I don't disagree with notifying those individuals who have been subject to infection, and as a recall. Is that what you mean?

Mr. SHAYS. Well, we don't know who has and who hasn't been effected, so that is the challenge. Just like in 1985 when Dr. Koop, Surgeon General, said you need to have an HIV test if you have had a blood transfusion in the last 5 years. And I have been struck with the same reaction that what is the difference, candidly.

I understand the tradeoff. We were concerned even having this hearing because the last thing we would want is for people to think falsely that the blood supply isn't safe. It is extraordinarily safe.

But we have these challenges, and they are new challenges. But the same kind of argument that you made now could have been made to Dr. Koop in 1985.

Dr. PENNER. I would have to agree that it would be acceptable or reasonable to provide that information to the public, but there is a concern. So long as it is presented in the proper perspective.

In other words, it's like 1 out of 5,000 or 10,000 who received blood may have been infected with a hepatitis virus. Second, that if you are infected with the virus, you're not dead the next week; that this is something that many of us harbor and do not develop any major problems with. Others do and, therefore, it is worthwhile, I think, for one to get checked.

Mr. SHAYS. Let me ask you one other question. Is this a treatable virus in the sense that—it is transmittable, but is it also treatable? I mean, my logic would say if it is then, my God, the sooner they know, the better.

Dr. PENNER. No, it's not particularly treatable, unless it is very progressive. Usually, then, it is picked up by the physician that is following the individual, and then one can attempt to use things such as Interferon. But that is not that beneficial, so we don't really have any good treatment for Hepatitis C. We do have some methodologies that are worthwhile.

So if we are going to tell them that, we have to also say that many people harbor it for years without developing any serious consequences. So it isn't like an HIV infection which has a lethal quality to it. In this case, it may have but, oftentimes, it does not.

Mr. SHAYS. I understand. It is extraordinarily serious, though.

Dr. Gilcher, do you have anything to add on this?

Dr. GILCHER. Well, just a couple of comments. The rate at which we find Hepatitis C in new donors currently is about 4 to 5 per 1,000 new donors that come through our system we can actually detect through the antibody test, an antibody against Hepatitis C.

Mr. SHAYS. You said how much?

Dr. GILCHER. It's about, in other words, .4 percent.

Mr. SHAYS. That is a pretty high percent.

Dr. GILCHER. That is 4 per 1,000 new donors, not repeat donors. Now, that is important to differentiate.

Mr. SHAYS. You are saying 4 to 5 percent potentially in the United States?

Dr. GILCHER. No, .4.

Mr. SHAYS. I'm sorry.

Dr. GILCHER. Very important difference.

Mr. SHAYS. May we say that again? Point 4 percent.

Dr. GILCHER. Point 4 percent of our first time donors are found to be reactive for the antibody to Hepatitis C virus. That is important because it says that there is a lot of Hepatitis C in the population that did not get there by transfusions. It got there through another route.

One of the concerns that we have in the lookback process is, I feel, to have a compensation plan in place first. Because what will happen is anyone who has received a transfusion in the past will say that the reason that they got the Hepatitis C was from the transfusion, whereas they may have gotten it from another source. So it becomes a real quagmire to differentiate how they actually were infected. It is part of the problem. Should lookback be done? It probably should.

Mr. SHAYS. I will give you my reaction just listening to it, and no disrespect. Some of it sounds like the way someone in your position would have to think this through. But if you are saying .4 percent, that is a lot of people, 4 or 5 out of 1,000.

Dr. GILCHER. Out of 1,000.

Mr. SHAYS. And then extrapolate that to the entire population. That is a very large number. And it seems to me that that's something that needs to be shared.

Dr. GILCHER. And most of these are not ill. It also points out the fact that one can harbor this virus and not particularly suffer.

Mr. SHAYS. But is it transmittable through sex?

Dr. GILCHER. It may be. I was remarking to one of the reporters earlier that when we look at the modes of transmission of Hepatitis C, we do not know all of the modes.

Very clearly, we talk about parenteral, meaning injectable, transmission, and that is clearly a major route. People who have been transfused have been at risk in the past. People who have ever used IV drugs clearly are at risk of having been infected.

But there are other routes of infection for Hepatitis C that are not clear. When we look at the spouses of an individual infected with Hepatitis C, we do not see the same rates of transmission that we do, for example, with Hepatitis B, which is clearly sexually transmitted.

Mr. SHAYS. Mr. Towns has been very patient, and I would yield the floor to him.

Mr. TOWNS. Thank you very much, Mr. Chairman, but I think this is very, very important. So I really think that spending the time—we have the experts here and I think that we need to talk to them. So I want to let you know that I appreciate you having this hearing and, of course, I think that this is an issue that we just can't take lightly.

And on that note, let me just sort of begin with you, Dr. Gilcher. And I agree with you, incidentally, but I am not sure as to how we

get there. You mentioned that we should get to the point of no paid donors. And I agree with that. But how do we get there?

Dr. GILCHER. Well, actually, it wasn't I who said that, but one of the other members who said that. When we talk about the direct infusion of a blood product, specifically whole blood, red cells, platelets, et cetera, it is very clear that these donors should be volunteer donors and that they should not be paid in the general concept of receiving money because we get the wrong people. Now, that is not always true, but that is basically true.

On the other hand, when we look at the plasma side, that is, the commercialization to acquire plasma, the volunteer sector has not been able to supply that in the past. It is possible they could do it in the future.

So what we have is a system in this country, which is almost unique, by the way, compared to the rest of the world, where we pay donors to come in and donate plasma. That plasma is never directly transfused to a patient.

It then goes through a pooling process and then, subsequently, is made into derivatives and, now, undergoes viral inactivation technology, which it did not in the past.

And that, clearly, added to the problems. Those donors in the past were there for remuneration, not because they were wanting to do something basically good for their fellow man.

And what happened was we had a particular segment of the blood product supply that was heavily infected with Hepatitis B, Hepatitis C, and HIV and, unfortunately, with no viral inactivation technology early on we have a disaster with the hemophilia population in this country.

Mr. TOWNS. Dr. Penner.

Dr. PENNER. Maybe as an example, the Michigan Department of Public Health produced the first concentrate of anti-hemophiliac factor in the world back in the 1940's and, since then, had continued to produce the anti-hemophiliac factor with plasma that was derived from the Lansing, MI, area.

Many of my patients that I treated with the Michigan Department of Public Health product do not have Hepatitis C, do not have Hepatitis B, were not HIV positive because they were being—it was a pool of volunteer donors who were coming into the regional Red Cross at that point and then it was being manufactured in a relatively small pool by the Department of Public Health.

So that is the distinction that I think exemplifies what we are getting at here. Could you depend on volunteer resources worldwide or even nationwide? I don't know. I don't think we have—we definitely don't have enough now.

It means that there has to be some development, again, of volunteer resources. And that is publicizing it, indicating that it is, again, something that should be allotted. And the individuals who do volunteer their blood should receive some recognition, which is now not the case and perhaps we would be able to supply this plasma in that kind of volume. There is at least one manufacturer that interacts with the Red Cross and receives its plasma from the Red Cross volunteer source to make its product.

Mr. TOWNS. Thank you very much, Dr. Penner. Anybody else want to add?

Mrs. DEFILIPPI. Yes. A comment that didn't come up in my testimony is that both of my sons are HIV negative. And the reason they are HIV negative is that during the early 1980's we were patients at Bethesda Naval Hospital and our hematologist, Dr. Duvalier happened to be very current because he was working at NIH at the time as well.

And when he realized then that there was a problem even early on he said, "I don't know what it is, but there is a problem. And it's a big one."

Because of James' hepatitis he put them on products made from blood of a pool of known donors and he accepted only cryoprecipitate from people whose medical records he knew of and had reviewed. That prevented my two sons, who were being fairly heavily infused at that time, from catching HIV.

I mean, for an example, James broke his arm—or Geoffrey, rather. And Geoffrey had received factor cryoprecipitate in that case twice a day every day for 10 days to treat the break in his arm. Now, had he been using commercial product there is no doubt in my mind that Geoffrey today would have HIV. So a controlled pool of volunteer donors can make a huge difference. So that is part of it. A big part of it.

Mr. TOWNS. So, actually, it is just making the commitment to spend more. That is what you are really saying to me.

Mrs. DEFILIPPI. I don't know that. I really don't know because that's not my field. These gentlemen know more.

But certainly a commitment to try and move the blood pool, or the blood resources of this country, into public consciousness as a national resource and as an obligation. I think that people do like to help. Volunteerism is very active in this country. You see it at PTAs and you see it at Boy Scout meetings and you see it at people who volunteer at the homeless shelters. Why can't we make it that easy to donate blood?

Mr. TOWNS. Yes, thank you.

Mr. DUBIN. Well, if I heard you just ask if we are spending more money, I think it reflects back to what I tried to say in my testimony. The cost-benefit analysis that has been applied to this issue is devoid of the larger picture cost.

If we spend $2 or $3 more a unit for a P–24 test or spend some more for other tests, if you really stack that up against the cost that the taxpayers in this Nation have had to undertake with regard to treating 8,000 to 10,000 people with hemophilia for AIDS, another 20,000 transfusion-associated cases.

I mean, I keep hearing this discussion devoid of that piece of the pie. And I think we are talking about spending short term a little more money and saving the Nation hundreds of millions of health care dollars at a time when we are being told there aren't enough health care dollars to go around.

And so I think this idea of cost has to be expanded greatly. I mean, my hemophilia costs roughly $100,000, $150,000, a year. If you add AIDS care to that, it has gone through the ceiling. And I think we have yet to do that. So I think if we really want to do a cost-benefit analysis, we are going to save an awful lot of money talking about the steps that the doctors are talking about, the P–24 step.

And I think absolutely, Dr. Penner, paid donors are a major part of the problem. The European community is looking at changing that. I think it is an issue we need to get away from. And we may end up spending a little more money in infrastructure building to get the volunteerism to the table, but down the road we are going to save hundreds of millions of dollars.

Mr. TOWNS. Right. Thank you very much. Yes, Dr. Penner.

Dr. PENNER. I would just like to add one final comment. One of the problems with the Institute of Medicine report is that what it did was focus on the past. What we need to do now is to focus on the future. In a sense, what we really need is, so to speak, a report that would focus on an approach.

That is what I push so strongly. An approach that would focus on safety, not next year but well into the year 2000. And we need to do that before we spend additional moneys, Mr. Towns, and that could be done. We could put together an expert panel. It could be part of the Blood Safety Council.

That is the point that I made earlier. It is going to require the input of people outside of the FDA, NIH, and CDC. We need their input too, but we need the input from others as well to put together a plan, a proposal, for the future.

Mr. TOWNS. Thank you very much. Let me thank all of you. And just one quick question to, I guess, Dr. Penner and to you, Dr. Gilcher. The Blood Safety Council, which I think is a very important step and I think that we should move and be supportive of it.

But I must admit that I am concerned when we have independent thinkers like you and people that have had the kind of experience and expertise that you have had, that you are not being invited to serve, either you or other people that have been involved in the field like you.

Let's just switch roles for a moment. What can we do, you know, on this side to be able to make certain that you are brought into this picture? Because, if not, I think that the Blood Safety Council's name could be a misnomer.

Dr. GILCHER. Exactly. And I think that our written response back to you is going to be very critical so that you can encourage Secretary Shalala to incorporate the concepts that we are going to write to you. And, clearly, one of the things that I will write to you is how I feel the composition of that Council is going to be so critical to plan for the future so that we don't make mistakes so that we do err on the side of safety at all points.

Mr. TOWNS. Thank you.

Dr. PENNER. And I would agree with that. The make-up of the Council is going to be very important so that the voices can be heard that need to be heard.

And then, second, there has to be some clout for this Council. It has to have some impact and not be simply advisory, in which case it may again face the same problems we have had up till now that when there is a problem, a serious and significant problem, that the voices are not heard.

Mr. DUBIN. It seems to me this is where Congress can really make a difference insuring that the treaters and the clinicians and the consumers and the people that need to be a part of the future can get together on this Council and plan the future with some

cloud. And I think this is a critical step where Congress could really, really make a difference.

Mr. TOWNS. Let me thank all of you for your testimony. You have been very helpful. And thank you, Mr. Chairman, for your generosity.

Mr. SHAYS. I thank the gentleman. I thank all of you for testifying. You have been wonderful witnesses and very helpful to this committee.

Mr. DUBIN. Mr. Chairman, who do I give this horrible, long thing you didn't want to read to?

Mr. SHAYS. No, it isn't horribly long. It is wonderfully short as long as you didn't read it.

Mr. DUBIN. Thank you, Mr. Chairman.

[The panelists responses follow:]

THE NATIONAL HEMOPHILIA FOUNDATION

October 30, 1995

Representative Christopher Shays, Chairman
Subcommittee on Human Resources and Intergovernmental Relations
Room B–372 Rayburn Building
Washington, DC 20515

DEAR CHAIRMAN SHAYS,

The National Hemophilia Foundation thanks you for the opportunity to participate in the Subcommittee on Human Resources and Intergovernmental Relations hearing on protecting the nations blood supply. NHF is pleased to provide you with our response to Secretary Shalala's and the Task Force on Blood Safety's report and recommendations. Attached are two documents in response to your request. The first was prepared by Ms. Patricia DeFillippi, who ably represented NHF at the hearing. She wanted to personally respond to your request for information. The second document was prepared by the NHF Blood Products Monitoring Committee at your request.

The attached comments, like the Task Force report, follow the format of the Institute of Medicine's recommendations on HIV and the Blood Supply. Overall NHF is very supportive of the Secretary's decision to designate the Assistant Secretary of Health as the Blood Safety Director and to establish several committees to develop and oversee policy and practices related to the safety of our nation's blood supply and blood products. At a minimum this will elevate the issues of blood and blood product safety to the appropriate level in the Public Health Service and provide much needed broader based forums to discuss specific issues on both an interagency and public sector and private sector basis.

We recognize that these are merely mechanisms and first steps that will need to be fortified with clear lines of authority, responsibility, accountability and a means for consumers to provide input on both defining the issues at the front end and commenting on recommendations for implementation. For all of us this process must provide for the best scientific data available to allow for improved decision making. For the hemophilia community and all Americans, only in this way can we can we begin to repair the past, reform the process and regain public trust.

Again, thank you for this opportunity and please let me know if we can be of any further assistance to you or the Subcommittee.

Sincerely,

BEATRICE YOUNG PIERCE, MSN
Chair, Blood Safety Monitoring Committee

JONATHAN BOTELHO
President

RESPONSE OF THE NATIONAL HEMOPHILIA FOUNDATION TO TASK FORCE ON BLOOD SAFETY REPORT

While much progress has been made in identifying the many issues confronting the regulators of our nation's blood supply, the lack of accountability by a single individual or entity that resulted in the HIV epidemic in the early 1980s still plagues the hemophilia community and our nation. The hemophilia community has suffered the devastation of two generations of sons, daughters, spouses, fathers, and children

due to a flawed system of responsibility of the blood supply. The National Hemophilia Foundation (NHF) has been involved in examining blood safety issues since the first individual with hemophilia was diagnosed with chronic hepatitis. The recommendations presented in the report of the Task Force on Blood Safety and in Secretary Shalala's testimony are an excellent first step but may not go far enough in reforming the system that, if not properly monitored and regulated, can do so much harm.

The following are our comments on Secretary Shalala's testimony and the Task Force on Blood Safety's response to the 14 Institute of Medicine recommendations.

Recommendations One and Two

While NHF commends the Secretary for the appointment of a Blood Safety Director and a Blood Safety Committee, the proposed committee is composed entirely of government employees and does not offer an adequate opportunity for private sector involvement in formulating policy. The Blood Products Advisory Committee (BPAC) and the proposed Public Health Service Advisory Council on Blood Safety and Availability could fulfill this function if they have adequate representation from consumers and access to the Blood Safety Committee. The Interagency Working Group, which apparently currently meets monthly, is invisible to us and heightens our concerns that this group would be offered up as evidence of existing reform when, in fact, it remains a huge question mark in the hemophilia community. We also suggest that the representative from the Health Resources and Services Administration (HRSA) on this working group come from the hemophilia program within the Bureau of Maternal and Child Health.

BPAC has inherently been an extremely insular group. Most members have been blood bank representatives, ill-equipped to deal with the number of scientific issues intrinsic to the blood fractionation industry. The past voting record of BPAC members clearly demonstrates that they place a higher priority on the needs of blood donors than on recipients of blood and blood products. We are pleased with the recent decision recognizing the conflicts of interest of the blood banks and placing their representatives on BPAC in a non-voting role. In addition to the need for more consumer representation, individuals with backgrounds in molecular biology are needed on BPAC. Most BPAC members in the past had insufficient background in molecular biology to understand fully and vote knowledgeably on these technical issues.

The proposed function of the Advisory Council—to provide a forum in which to examine broad public health and societal implications of blood safety issues—addresses an unmet need. We would stress that the Council must have broad representation, including consumers of blood products, with adequate access to the Blood Safety Committee. This relationship, and the relationship between the Advisory Council and BPAC, is not defined in the Task Force report.

For the committees established by the Secretary to work smoothly and efficiently, clear lines of authority, responsibility, and most importantly, accountability should be established.

We believe consumer access to each of the blood safety committees as well as the blood safety director is vitally important and could be enhanced by developing mechanisms to allow for consumer input in determining issues for committee action as well as a process to comment on committee recomendations prior to implementation. This could be done formally through Federal Register notice and rulemaking or through informal channels. In addition, historically FDA has not been as open to consumer input as other agencies of the Public Health Service. As an organization NHF has always found open doors at the Ceners for Disease Control and the White House Office of National AIDS Policy allowing for consumer participation and discussion at different levels of policy development and program operation. We would like to see more open lines of communication with the FDA.

Recommendation Three

The Task Force did not take a stand on this important issue on establishment of a compensation trust fund. The impetus to move this concept forward must come from Congress itself.

The bleeding disorder community has been, and will continue to be, the nation's watchdog on the safety of the blood supply. The large presence of AIDS in this blood product-dependent group amply demonstrates the failure of blood safety regulations in the 1970s and 1980s. The continued presence of blood borne viruses (such as hepatitis C and Parvovirus B19) and on-going blood product recalls demonstrate that viral contamination of blood products remains a public health problem despite efforts to make blood collection, distribution and products safer.

Potential injury from blood, blood products, and blood derivatives continues to be a reality for all people who must use these products in the course of medical treatment. Since it is impossible to make the blood 100 percent safe, society needs to examine effective avenues for compensating those parties who will be injured as a result of the inherent imperfections in the blood supply.

The solution would be the enactment of a blood/blood products compensation trust fund that would give consumers the needed recourse now deprived of them in most legal settings. Since blood borne pathogens take years to manifest harm, not only do individuals have to over come blood shield laws, but statutes of limitation as well.

The establishment of a fund is an integral part of increasing the safety of the nation's blood supply. For individuals, it would provide protection for their families, in the event of unknown risk. The fund would provide protection for the manufacturers who are reluctant to aggressively address viral inactivation due to fear of current and future litigation. With such a fund in place, related malpractice, liability insurance, and claims would lower the overall cost of health care.

Recommendation 4

Solidifying the Centers for Disease Control and Prevention's (CDC) responsibility for public health and formalizing an interagency relationship between the CDC, the FDA, and the National Institutes of Health (NIH) on blood safety policy are, of course, excellent ideas. But this is easier said than done; we believe that FDA and NIH must come to accept the science and public health authority of CDC. Otherwise, the turf battles will continue to the detriment of blood safety. With the designation of the Assistant Secretary for Health as Blood Safety Director, someone will be responsible for assuring that these public health agencies work together as a team.

Recommendation Five

The establishment of a CDC surveillance system is long overdue. Although Secretary Shalala suggests ample surveillance is already occurring, we would dispute that claim, as it applies to chronic users of blood products. Chronic users have a higher probability of being exposed to a new agent than occasional users of blood or blood products. It is precisely this group that should be the focus of a major long-term surveillance program that is more sophisticated than the current haphazard system of voluntary reporting to a combined NHF–FDA–CDC working group. We agree with CDC's efforts to implement a nationwide surveillance system for chronic users of clotting factors next year. Adequate funding must be in place for this to occur.

We are missing a tremendous opportunity to understand the infectious risks of blood products. For instance, current surveillance does not include Parvovirus B19, an agent that is probably transmitted by all blood components and all blood-derived clotting factors, which can cause severe disease in HIV-infected individuals and miscarriages in pregnant women. Newly-identified hepatitis viruses, at least one of which is known to have been transmitted by blood products in the past, are not under surveillance presently. The recent voluntary recalls of blood products, exposed to Cruetzfeldt-Jacob disease (CJD), have not motivated the FDA, or blood bankers, to explore lookback surveillance programs for blood donors. Industry involvement in surveillance has been minimal, therefore the impetus for this must come from government.

Recommendation Six

While it is important to implement partial solutions when there is insufficient knowledge to address problems fully, it is also important to further research and gather data to make these solutions more definitive. Industry, in general, has dragged its feet in dealing with emerging infectious threats to the blood supply and has tended to respond to issues from a marketing and legal perspective, not out of primary concern for the health of their customers. The FDA must carry out its mandate to maintain a safe blood supply. There must be Federal support for epidemiology studies of transmission of agents not inactivated by current techniques, and for more global viral inactivation procedures, as well as commitments from industry for large scale funding of this work. Only by addressing potential solutions through ongoing research will the risks and benefits of partial interim solutions be understood.

Recommendation Seven

Reviewing past decisions on the basis of emerging data is obviously important, but can get lost. Secretary Shalala's example of the HIV antigen test is noteworthy since BPAC voted against implementation in 1995, yet the FDA is presently implementing it. This example serves to point out (again) that the advisory system will

work only if objective scientific expertise is available on BPAC. BPAC should not be charged with considering financial costs to society, as it did when it voted on the HIV antigen test.

Recommendation Eight

The FDA should have the ability to more easily require action by industry, especially for already-licensed products. For instance, currently licensed products transmit Parvovirus B19 and may transmit the Cruetzfeldt-Jacob agent. The FDA does not appear to be able to tell industry to initiate programs to investigate the potential for transmission of these agents, whether current viral inactivation destroys them, and what viral inactivation procedures presently in development may be effective. Critical time is being wasted by expecting voluntary implementation of these kinds of studies by industry. The FDA must issue mandates, not suggestions or guidelines.

Recommendations Nine and Ten

Having balanced composition on BPAC and defining the expectations of this committee are laudable goals; but we disagree that the FDA has been "attentive" to achieving balanced representation or defining expectations of the Committee in recent years. The assertion that "FDA restructured BPAC in 1994, by expanding consumer representation through voting consultants" is not true. One consumer, who is also a physician scientist was added to the committee in 1994. A second consumer, the first lay consumer, was added in 1995. This hardly suggests a major overhaul. Activities to reform the Committee are more substantial this year. However, the composition of BPAC has not yet been announced. Secretary Shalala stated the BPAC charter will be revised. We have never seen this charter, and frankly, did not know one existed. BPAC structure, organization, and the methods used for making decisions regarding its membership have been and continue to be shrouded in a cloak of secrecy.

We reiterate that broad perspectives and vastly improved scientific credibility are essential for the new BPAC. These critical questions must be addressed: How does the FDA manage BPAC? Who sets the agendas? Who writes the preset questions that BPAC votes upon after discussion? Wouldn't it seem more unbiased if the questions were formulated by the committee after the discussion of the data? Why can't the committee set its own agenda? Who determines what background information committee members receive, ensuring it is comprehensive and not biased toward a particular view (which has occurred this year)? Secretary Shalala states that the "FDA evaluates its committee members . . .". What criteria are used? Who are the decision makers at "FDA?" These questions have resisted straightforward answers, which contributes substantially to the cloak of secrecy surrounding BPAC and how it functions.

Recommendation Eleven

The public need for reliable sources of information on blood and blood products is critical and is absolutely dependent on the FDA mandating that industry provide this information. In many respects, the industry providing the blood for this country must be held accountable but such accountability needs a coordinated Federal oversight. There are no easy answers for this recommendation, but it is critical to the future safety of the blood supply and deserves special attention from government agencies as well as Congress.

Recommendation Twelve

If physicians and patients are going to be able to discuss options openly, they must have accurate information by which to base these conversations and decisions. Clearly some information in the early 1980s was not widely available to the public. Even government agencies with better access to information could not make clear recommendations. The emerging information must come from a partnership between FDA, CDC, NIH, industry, and consumer/physician organizations. The mandate for making the information available must come from the highest levels of government, and this is not specified by the Secretary. Fifteen years after the AIDS virus impact on the blood supply there is still no mandated system for communicating about blood product recalls or viral outbreaks to pharmacists, doctors or patients.

Recommendation Thirteen

A focused approach on how best to communicate clinically useful information to providers of care and the public from government agencies has not yet occurred. For example, neither the interim recommendations on CJD issued on August 8, 1995, nor the August 10, 1995 FDA recommendations, concerning HIV–1 antigen screening of donor blood were widely distributed to treating physicians and consumer or-

ganizations. We are concerned that no mandate exists for this to occur in the future. Emerging scientific issues are on the table now that should be distributed, and there is no mechanism for their review, study, and dissemination by the FDA. We continue to see a lack of leadership on the safety of the blood supply. It is imperative that the government establish a system to communicate information and issues to providers of care and the public quickly and in a balanced manner.

Recommendation Fourteen

The recommendation on conflict of interest in voluntary organizations is well taken and has been a central issue for the current volunteer and staff leadership of the NHF. The NHF is currently undergoing an extensive Strategic Planning Process to further address this issue.

RESPONSE TO THE TESTIMONY OF DONNA E. SHALALA, SECRETARY OF HEALTH AND HUMAN SERVICES, BY PATRICIA M. DEFILIPPI

Mr. Chairman and members of the subcommittee. I was very surprised and pleased by your request that I respond to the testimony of Secretary Shalala given at your subcommittee hearing on October 12, 1995. It seems a daunting task to respond to her thoughtful and obviously concerned speech. My remarks are primarily focused on specific problems I had with the Report of the Secretary, Task Force on Blood Safety. As you are aware, this is an area of extreme concern to my family, the hemophilia community and the general public.

This report is broken down into a series of recommendations. In the interest of brevity and clarity, I will respond to them by number without quoting each proposal.

Recommendation number 1 talks about the PHS Blood Safety Committee. I would suggest that one or more of the members of that committee be a medical doctor with experience in treating people with either bleeding disorders or with diseases resulting from those in order that the committee have a clearer understanding of the human impact of their decisions. This member could even be a person not employed by the government. In addition, this committee should be urged to keep in mind that both a considered and a timely response to a possible contamination of the blood pool are important.

On recommendation number 2, the selection of members of the Advisory Committee on Blood Safety and Availability should be carefully designed to include someone to guard the best interests of all affected consumers, in a manner so that no one group has a dominant voice. It is clear that any committee that included EACH affected group would be unwieldy, but perhaps these groups could rotate on and off the committee. Groups that might be included are: people with hemophilia A and B; women with Von Willibrands disease; affected carriers; those with other forms of clotting disorders; people with HIV or AIDS, and people without HIV/AIDS but with other blood borne illnesses; people with liver disease and/or cancer; those with sickle cell disease; and a member of the general public without any of the above who could represent those who receive transfusions. Medical members of the committee should represent providers who treat a variety of these disorders and whose patients include men as well as women. It might be advisable to include a member of the insurance industry as a consultant to reflect the effect decisions will have on the insurance coverage of individuals.

Recommendation 3 needs to address the availability of insurance or medical care to those with bleeding disorders and/or secondary infections resulting from blood transfusion. Currently, it is extremely difficult for anyone in that situation, who loses coverage to be reinsured. One group who regularly lose coverage is young adults who exit their parents insurance at the end of their schooling.

Regarding recommendation number 4, does the Public Health Service's Interagency Working Group include a seat for a hematologist with an active practice in treating bleeding disorders or diseases resulting from transfusions? If not, it should.

Recommendations 5, 6, 7, 8, 10 and 14 seem fine.

The ninth recommendation addresses the Blood Products Advisory Committee. I would recommend that the Committee include at least one consumer with a bleeding disorder and one consumer without a bleeding disorder.

Recommendation 11 addresses the manner in which the PHS could gather information to make decisions about the blood supply. Four options were discussed. Two of them seem inadvisable because of obvious conflict of interest. One is asking the blood industry to voluntarily provide the information, the other asks for "outside" organizations to provide the information. If this refers to hospitals, doctors or consumer groups, the information could be biased.

Recommendation 12 talks about doctor and patient discussing risks. I would urge that all pertinent information be made available, perhaps in summary form, to internists, and family practitioners in addition to specialists, as they treat many people who use blood products and often see those patients more frequently.

Recommendation 13 talks about a panel to decide what information the public needs to have in the event there is a potential or real threat of disease in the blood pool. I would urge the panel to be timely in its advisories to the public and to remember the lessons of 1985. As a teacher, I am obligated to assume people can learn far more than my prejudices predict, and generally people do exceed our expectations in learning and understanding. I believe almost everyone, with an adequate amount of knowledge, can make n informed decision about their risk of transmitting or receiving an infection. Whether or not you agree with me, you can be sure that without information, people have no chance of making an informed decision. Providing information needs to be the first priority of this panel.

This response is my own and does not intentionally reflect the opinions of the National Hemophilia Foundation. They are attaching a response to mine. Thank you for allowing me the honor of responding to Secretary Shalala's testimony, and for listening to my ideas.

Respectfully submitted,

PATRICIA M. DEFILIPPI

COMMITTEE OF TEN THOUSAND—WEST'S RESPONSE TO SECRETARY SHALALA

We applaud Secretary Shalala's quick response to the Institute Of Medicine Of Medicine Report. The appointment of Dr. Philip Lee to head up the effort, so far, appears to be a good choice and one that indicates the Secretary's commitment to action.

However, we take issue with some important parts of Shalala's testimony. While we agree that the safety of the blood supply has improved markedly since the 1980's, there remain serious problems that require ongoing attention and action.

At the core of our concerns is the way in which emerging threats to the blood supply are conceptualized. The AIDS/blood epidemic should teach us that the old perspective of "waiting until all the data is in" is no longer sufficient to address fatal threats such as HIV. We must cease to always be reacting to a given threat and begin developing and implementing aggressive and preemptive strategies and actions to increase the safety of blood and blood products.

The recent FDA action on CJD, Cruetzfeld-Jacob Disease, was the first example of a new approach to emerging threats. We applaud this important and ground breaking decision and strongly believe it should be a model for the future. Acting preemptively gives us the space to then rescind a given decision if the data, once complete, indicates that the decision was wrong. This is the exact opposite of what occurred during the 1980's when HIV was the emerging threat. We believe that Secretary Shalala must take a more activist stance regarding how we view emerging threats and therefore how we respond to those threats.

The Secretary also juxtaposed the issues of safety and availability in a fashion that does incorporate the whole picture. Shalala constructed this issue in terms of decisions regarding safety having a negative impact on product availability. This is an argument we have heard many times over the past ten years. However, it is an argument that fails to stand up given other mitigating factors that the Secretary and others fail to consider.

While decisions undertaken in the name of safety can have short-term impacts on product availability, if we consider the whole picture, including treatment options, those impacts can be offset. For example, in the case of hemophilia factor VIII was not the only option available for the treatment of bleeding episodes. A small number of hemophilia treaters took their patients off factor VIII during the early 1980's due to the emerging threat posed by AIDS. Cryopercipitate was an option that in instances where it was produced from a low number of donors or a single donor was, in the end, safer than factor VIII concentrates.

We have also learned that not all bleeding episodes require treatment. We do not believe that safety and availability should be juxtaposed at two ends of the spectrum. Structuring the issue in this fashion has, in reality, worked against undertaking actions that would improve the overall safety of the blood supply.

Secretary Shalala also articulated her view on the creation of the blood safety council that is at the core of the IOM recommendations. As Shalala envisions it the council would be an Inter-agency animal consisting of representatives from HHS, FDA, CDC, NIH, and the Public Health Service with an advisory committee consisting of the manufacturers of blood products, blood bankers, independent researchers

and scientists and consumers. If implemented in this format, the danger of this becoming another ineffective layer of bureaucracy is a distinct possibility. Establishing the council presents a unique opportunity to bring all of the interested parties into the decision making process.

We believe that all the above interests should sit on the council together as decision makers rather than creating a division that results in government being the only entity at the decision making level with the rest in an advisory role. The council, in our view is a real opportunity to develop and implement strategies and policies that serve the 3.5 million Americans that use blood/blood products annually.

The IOM report identified conflict of interest as a co-factor in the disaster of the 1980's. Given this it is critical that the council have strong representation from scientists and medical researchers who are not economically connected to the plasma industry; including independent experts in the areas of plasma/plasma products, and virology. Independent researches and scientists will also facilitate identifying areas where research and study are necessary to cope with future emerging threats to the blood supply.

We firmly believe that industry must also participate in the council, however that participation must occur in a fashion that does not recreate the conflict of interests that played a significant role in the disaster of the 1980's. Therefore, industry should have non-voting seats on the council, however they should be allowed to participate in all areas except voting due to their substantial economic interest.

The council should also include independent expertise in the social/public policy area as we have learned that public perceptions and educating the public are important components of the blood safety equation.

The recommendations of the IOM panel are, for the most part, sound and should be implemented. However, if they are implemented without the direct participation of the users of blood and blood products then we are right back where we started. We support the establishment of a national blood safety council at the level of the HHS Secretary but again this council must contain representation of all of the interested parties; government, industry, the Red Cross, and all of the communities that depend on blood and blood products. From our perspective this point is non-negotiable and imperative if we are to create the necessary changes in the business of blood. The council must also have the authority to ensure that federal agencies are cooperating and listening to one another when confronted with emerging threats. If the FDA had not ignored the repeated warnings of the Centers For Disease Control that the causative agent for AIDS was a blood borne pathogen, thousands in the hemophilia community would have been spared this nightmare that is HIV/AIDS.

We must create an environment within which all of the interested parties can come together to ensure that this nation has the safest blood supply that is humanly possible. Along these same lines the FDA Blood Products Advisory Committee must also contain all of the communities that use blood and blood products. We believe that both the BPAC and the new HHS council should contain one third consumers if this process of change is to be successful. Without this we will continue to barred form the forums where decisions are made that critically impact our very existence.

The IOM panel also called for the establishment of no-fault compensation funds to compensate those harmed by tainted blood and blood products; A recommendation we strongly support and are actively pursuing through the Ricky Ray Hemophilia Relief Act Of 1995, HR 1023. However that legislation, which has 146 co-sponsors in the house, is currently stalled in the House Judiciary Committee, Subcommittee On Immigration And Claims awaiting comments from Secretary Shalala. The Subcommittee has stated that no action will be taken on the legislation until comments are received from the Secretary. Those egregiously harmed by the disaster of the 1980's must be addressed if we are to move forward and prevent this from ever happening again.

October 25, 1995

Mr. Christopher Shays, Chairman
House Subcommittee on Human Resources &
Intergovernmental Relations
Room B–372 Rayburn Bldg.
Washington, D.C. 20515

Re: Protect the Blood Supply from Infectious Agents

DEAR CHAIRMAN SHAYS:

Prior to adjournment of the meeting, you requested a statement from those testifying as to recommendations for protecting the blood supply and comments on Secretary Shalala's testimony. With a few exceptions, I am in agreement with the Sec-

retary's presentation and the Institute of Medicine Report as follows: (1) Designation of the Assistant Secretary of Health, as Blood Safety Director overseeing a Blood Safety Committee consisting of FDA, CDC and NIH Directors. The latter would be served by an Advisory Council on Blood Safety and Availability. The committee, unfortunately, would lack input from physician care givers however and would not be able to offer a balanced perspective on public risk factors.

(2) Reconstitution of the Blood Advisory Committee to FDA. Hopefully, representation will be obtained from the Hemophilia Foundation, Sickle Cell Foundation, as well as the American Association of Blood Banks and Physicians with a background in patient care and hematologic disorders. There would be an advantage for investiture of some decision making power in the BPAC with capabilities of interceding with FDA in applying regulations to blood programs, blood banking centers and industry. The advantage would reside in the committee's ability to recognize that the blood donors represent a valuable resource that could be withdrawn if arbitrary regulatory powers are applied to donor participation.

(3) Implementation of new procedures to identify viral antigen or antibodies to a virus as soon as available providing the procedures can be shown to reduce or eliminate exposure of recipients to blood or blood product infective agents. Specifically, the HIV antigen test kit should be employed nationwide as soon as sufficient kits are available to apply to all donated blood, volunteer and non-volunteer sources.

The remainder of the Secretary's recommendations, I believe will be beneficial to the nation blood program, however, I would add several additional recommendations and comments that require attention.

(1) The role of the physician in blood banking programs should be reestablished to ensure that there is a medically knowledgeable individual at the helm of each center. The present lack of creditability of business type administrators must be recognized if we are to assure that the community is better served with coordination between physician, hospital, donor and recipient.

(2) An educational program also must be promulgated to enlighten physicians and community members as to risks and benefits of blood and blood products (see attached). Hospital transfusion committees are in a position to undertake such programs if provided with appropriate teaching materials and updated information from the various involved federal programs CDC, FDA, etc. Red Cross and other national organizations also are in a position to broadcast such information to their communities.

(3) New initiatives for eradicating viral contaminants from blood must be supported with funds allocated specifically for new proposals. Innovative approaches to disinfecting blood are possible and have not been encouraged sufficiently to permit development of new and more effective techniques. It is unlikely that such treatment opportunities will be created without funding.

(4) Blood products employed for non-approved use should be placed on a fast track for FDA recognition and be given suitable support to achieve standardization of dosing in relation to therapeutic effectiveness. The latter speaks particularly to several fractionated blood products that contain an unspecified amount of von Willebrand factor in addition to factor VIII, and several multi-factor products that contain vitamin K dependent factors in varying concentrations. The latter being labelled on the basis of only one of the agents present (factor IX) despite the fact that the product may be useful in deficiencies of the other vitamin K dependent factors of hereditary or acquired nature. For example, familial factor VII deficiency and acquired hepatic disorders or Warfarin overdose.

I wish the subcommittee well in its deliberations, and hope that the results of the meetings will be formulated into a new program that will transform blood banking and blood products industry into community responsive organizations that will continue to work towards totally safe blood and blood products.

Sincerely,

JOHN A. PENNER, M.D., F.A.C.P.
Professor of Medicine

RECOMMENDATIONS TO IMPROVE HEMOSTATIC PRODUCT USE BY EDUCATIONAL INTERVENTIONS

Present educational activities in this area are limited with much of the information disseminated through industry sales representatives, who interact constantly with the hemophilic population as well as physicians serving this community.

The National Hemophilia Foundation has assumed a role in patient education through regular newsletters to their members. Unfortunately, this does not reach all of the patients with hemophilia or other hemorrhagic disorders, nor does it reach

physicians managing such cases. Dr. Carol Casper at Children's Orthopedic Hospital in Los Angeles recently has been providing a quarterly newsletter to a small group of interested physicians, addressing management of hemorrhagic problems primarily in hemophilic patients. Despite these efforts, gaps in knowledge of treatment and product use persist and it is unlikely that support for non-biased informative programs will develop.

In as much as the treating centers manage the majority of hemophilic patients, the opportunity to disseminate new knowledge through this route should be recognized. The centers also allow interaction with the patients as well as with the physicians in the community and thus can provide education on a broad front.

On the larger issue of blood product use, hospitals are now required to identify a transfusion committee made up of staff physicians with the support of hospital administration services. Utilizing these operational units, it would be possible to develop an educational program that would reach physicians as well as blood recipients and the general population. A coordinated effort would require funding and could be initiated and maintained as a permanent responsibility of BPAC. Alternatively, the CDC or the FDA could undertake this commitment, however, I believe that these institutions would have less credibility than a more independent group drawn from physicians with patient care background and knowledgeable in blood related disorders.

Representative Christopher Shays
Representative Edolphus Towns
House of Representatives
Subcommittee on Human Resources
and Intergovernmental Relations
Room B372 Rayburn Building
Washington, D.C. 20515–6143

DEAR REPRESENTATIVE SHAYS AND REPRESENTATIVE TOWNS:

This letter is in response to your request for my comments regarding the recommendations made by the Secretary of Health and Human Services, Donna Shalala, On October 12, 1995 at the Congressional Hearing on "Protecting the Blood Supply From Infectious Agents: New Standards to Meet New Threats".

At the Congressional hearing, I expressed concerns about the composition of the Blood Safety Council. The composition is critical to achieve the desired goals of protecting our nation's blood supply from infectious agents as well as other threats such as non-availability of blood and blood products.

The Task Force commissioned by Secretary Shalala to study the Institute of Medicine (IOM) Recommendations agreed with the IOM recommendation #2 that the Public Health Service should establish a Blood Safety Council. The Task Force interpreted the IOM recommendation #2 that the functions outlined by the IOM for the Blood Safety Council are "governmental functions that should be performed by the Department, not by outside parties". It is this Task Force's recommendation that the Blood Council consist of only government representatives that I find unacceptable.

To create a Public Health Service Advisory Council on Blood Safety and Availability, which reports to the Blood Safety Council which is made up only of government officials, can prevent the concerns of medical practitioners from ever reaching the Blood Safety Director, who will present the recommendations of the Blood Safety Council to the Secretary of Health and Human Services. The Council must, in fact, have direct representation of leaders in transfusion medicine, as well as Public Health Service experts, in order to make scientifically sound and practical recommendations to the Secretary.

The problems of the past are due largely to a lack of effective leadership and a lack of strategic planning. The strategic planning must focus on prevention, e.g., using the safety model of the Oklahoma Blood Institute as a baseline. The Blood Safety Council must look at the global picture in dealing with future issues of blood safety and availability and should recommend approaches for the research community to pursue. Education of Public Health Service officials, clinicians, transfusion medicine specialists, and the public should also be a charge of this committee.

In summary, I strongly believe that the makeup of the Blood Safety Council should include (1) transfusion medicine experts who are not only leaders but who are also visionaries and (2) Public Health Service officials from FDA, CDC, and NIH. The charge of the Blood Safety Council should be strategic planning that encompasses all aspects of transfusion medicine and specifically focuses on prevention.

I want to thank you for allowing me the opportunity to voice my concerns. I will be pleased to serve in any way to help enhance the safety and availability of our

nation's blood supply. I can be reached through the Oklahoma Blood Institute at (405) 297–5678 (office) or (405) 297–5800 (24 hour paging).
Sincerely,

RONALD O. GILCHER, M.D., F.A.C.P.
President and Chief Executive Officer
Sylvan N. Goldman Center
Oklahoma Blood Institute

Mr. SHAYS. Thank you. Our final panel is Kathryn Zoon, Ph.D, Director, Center for Biologics, Evaluation and Research, Food and Drug Administration. Accompanied by Jay Epstein, an M.D., Acting Director, Office of Blood Research and Review, Center for Biologics, Evaluation, and Research, Food and Drug Administration.

And we sincerely thank both of you for being here. My understanding is you have been here for the whole day to hear the testimony of the others.

Ms. ZOON. We did not hear all the testimony. We came in during the second panel, Mr. Chairman.

Mr. SHAYS. Why don't I ask you if you would stand up and we will swear you in. If there is anyone else who might accompany you, please feel free to come right up front. It doesn't mean you have to answer questions but if you are, in fact, asked questions you will be under oath.

If I could, just for the record, could you state your name, sir?

Mr. SIMMONS. James Simmons.

Mr. SHAYS. And your position is at FDA?

Mr. SIMMONS. Yes.

Mr. SHAYS. And?

Ms. MALONEY. Diane Maloney.

Mr. SHAYS. Diane Maloney?

Ms. MALONEY. Maloney.

Mr. SHAYS. Thank you. It is wonderful to have all of you here.

[Witnesses sworn.]

Mr. SHAYS. We are basically, I think, having testimony from one individual; is that correct, Dr. Zoon?

Ms. ZOON. That is correct. I will be giving the testimony.

Mr. SHAYS. We welcome your testimony and appreciate you being here.

STATEMENT OF KATHRYN ZOON, Ph.D, DIRECTOR, CENTER FOR BIOLOGICS, EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY JAY EPSTEIN, AN M.D., ACTING DIRECTOR, OFFICE OF BLOOD RESEARCH AND REVIEW

Ms. ZOON. Thank you, Mr. Chairman. I would like to make a request for an indulgence for the 5-minute rule. I will try to keep my remarks very short, but I think it is important to answer the questions that you have asked us to address. So I beg your indulgence.

Mr. SHAYS. Let me just say this to you. You can give any length of testimony you want. Are you saying you want to go over the 5-minute rule?

Ms. ZOON. Yes.

Mr. SHAYS. Yes, that's fine. Your testimony is very important and we would want you to feel free to give your testimony. About how long do you think it will be?

Ms. ZOON. About 10 minutes.

Mr. SHAYS. That's fine. I don't want you to read it quickly. You give it as you feel comfortable.

Ms. ZOON. Thank you very much. Mr. Chairman and members of the subcommittee, I appreciate the opportunity to appear today to discuss progress in enhancing and insuring the safety of the Nation's blood supply. I am Dr. Kathryn Zoon, Director of the Center for Biologics, Evaluation, and Research, or CBER, at FDA, and I am accompanied today by Dr. Jay Epstein, Director of the Office of Blood Research and Review, and my colleagues who have already identified themselves.

The blood supply plays a vital role in the American health care system, and the United States has one of the safest blood supplies in the world. As Secretary Shalala noted this morning, approximately 12 million units of blood are drawn from volunteer donors every year for use in more than 3.5 million Americans. Much of this blood, and an additional 12 million units of plasma, is further processed into products, referred to as derivatives, such as immune globulin used to prevent infections, and clotting factors such as anti-hemophiliac factor used to treat hemophilia.

Because it is a human tissue, blood is by its very nature always at risk for transmitting disease. Because of this risk and because millions of Americans depend on blood products, FDA places a very high priority on blood safety.

Our goal at the Center for Biologics, Evaluation, and Research is to help insure the safety of the Nation's blood supply by minimizing the risk of infectious disease transmission and other hazards while maintaining an adequate supply.

We oversee all phases of blood preparation and manufacture from donor screening and selection and testing to product collection, processing, labelling, and storage. CBER licenses blood establishments that ship blood products in interstate commerce and inspects these establishments and more than 2,500 registered intrastate blood establishments.

We have made enormous progress in preventing the transmission of infectious agents through blood products since 1970. In fact, over the last 10 years, FDA and the blood industry have made the blood supply dramatically safer than ever before. In particular, the introduction of new screening tests for hepatitis viruses and HIV and the implementation of virus inactivation for plasma-derived products have significantly increased the safety of blood products.

In the early 1970's, the risk of contracting some form of hepatitis from a unit of blood was as high as 1 in 12. Now the risk of contracting Hepatitis B per unit of blood is approximately 1 in a quarter of a million per unit of blood. And the risk for contracting Hepatitis C is less than 1 in 3,300.

For HIV, the risk of infection has decreased from 1 in 2,500 in 1985, to approximately 1 in half a million today. For patients who need blood transfusions, the risk of transfusion-associated disease is far less than the risk of dying or become more seriously ill without a transfusion.

Blood banking has evolved in his country from a loosely organized medical service into a major manufacturing industry, an industry that must conform to high standards and quality control re-

quirements comparable to those of pharmaceutical companies or other regulated industries.

FDA can provide support and guidance, but it is fundamentally the blood banks' responsibility to comply with the rigorous standards that are necessary to protect our blood supply. We are committed to holding blood banks to those standards.

Let me say a few words about how we do that. The blood safety system established by the FDA consists of five layers, which begin at the blood collection center and encompass the manufacturers and distributors of blood product.

First, there is donor screening; second, there is blood testing; third, there is donor deferral; and, fourth, there is inventory management to insure that products have been thoroughly tested and that donation records have been verified; and, fifth, blood establishments must investigate any breaches of these safeguards and correct any system deficiencies that are found.

Earlier today, Secretary Shalala discussed the Institute of Medicine's report and the recommendations of our department's task force. As the Secretary noted, the IOM panel did not review the existing blood safety program or the current safety of the blood supply, but examined the events and public health organizational and decision structures of the early 1980's as they affected blood safety.

I just want to clarify one issue regarding this with respect to the responsibilities of the committees that the Secretary outlined. The Blood Safety Director will be the head of the Blood Safety Committee. The Blood Safety Committee's membership includes the Commissioner of the FDA, the Director of CDC, and the Director of NIH. That committee will be served by an Advisory Council on Blood Safety and Availability. That advisory group will include representatives of industry, consumers, scientific experts, and ethicists.

Let me take a moment to list some of the many significant changes FDA has made since 1986. CBER, the Center for Biologics, was reorganized in 1992 to reflect the importance of the blood supply. FDA has strengthened its internal management of blood issues. FDA has broadened the composition of its Blood Products Advisory Committee and has improved its use of the committee as an independent source of expertise.

FDA has strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products. FDA has significantly increased its oversight of the blood industry and FDA has repeatedly provided the blood industry with detailed and specific guidance about how to insure that blood and blood products are as safe as possible. Such guidance has covered deferring donors, screening blood for infectious agents, interpreting test results, reinstating previously deferred donors, and quality assurance.

Mr. Chairman, I would like to conclude my oral statement by touching on a number of issues that you have asked about. The first is the Blood Products Advisory Committee. The Blood Products Advisory Committee, or BPAC, is mainly composed of leading outside experts in the field relevant to transfusion medicines. These include hematology and infectious disease.

This committee meets regularly to review critical issues affecting the blood supply and to advise the agency on these matters. The

agency currently is in the process of reconstituting the BPAC to reduce industry membership and include broader representation from consumer advocates, care givers, and persons who frequently use blood products.

This measure is being undertaken in response to concerns about possible financial conflicts of interest and the need to increase and formalize consumer representation on the committee. The agency is committed to insuring adequate representation of scientific experts and knowledgeable consumers on this important panel.

The newly announced PHS Advisory Council on Blood Safety and Availability will provide an additional forum for consideration of the broad public health and societal implications of blood safety issues and will complement the scientific advisory role of the BPAC.

To further reduce the risk of infections blood recipients might receive through contaminated transfusions, in August 1995, FDA issued guidance to the blood industry recommending that blood establishments test donors with new HIV–I antigen test kits after they become available.

Using new antigen tests would reduce by about 1 week the window period between HIV infection and detection. Reducing the window period when a patient has been infected with HIV but does not have antibodies at a detectable level further reduces the chances that HIV contaminated blood will enter the blood supply.

Although no HIV antigen tests are currently licensed for screening, FDA's recommendations are in anticipation of products that are being developed for this use.

I know you would like to discuss Creutzfeldt-Jakob Disease as an example of FDA's response to an emerging infectious disease. CJD is a rare, fatal, degenerative disease of the central nervous system that affects approximately one person per million per year. A small number of donors of blood and plasma have been diagnosed with CJD since 1983.

Although there are no confirmed cases of CJD from transfusions and the risk of such transmission is considered extremely small, the possibility of CJD transmission through blood products cannot be ruled out at this time.

For this reason, in August 1995, the agency recommended that blood establishments withdraw and quarantine products subsequently found to have come from donations of individuals diagnosed with or at increased risk of CJD. FDA also has recommended that blood donors now be questioned to determine if they have risk factors for CJD and that at-risk individuals be permanently deferred from donating blood.

FDA's work to help insure that immunoglobulin products continue to be safe, effective, and available, also demonstrates the agency's commitment and ability to solve tough problems quickly.

In February 1994, FDA received the first ever report that implicated a U.S. licensed immunoglobulin intravenous product in the transmission of Hepatitis C. The product was quickly withdrawn from the world market. The firm reentered the market only when the manufacture process was modified to include a viral inactivation step.

As part of its ongoing research program on plasma derivatives, FDA developed methods which it used to investigate this incident.

In addition, FDA extended the investigation to intramuscular immunoglobulin products. Because viral inactivation of IGIM products was not yet in place on December 27, 1994, FDA announced that only those lots of IGIM that had been screened for Hepatitis C virus and found negative should be distributed.

In both the intravenous and intramuscular immunoglobulin episodes, FDA immediately assessed the scope of the problem, notified manufacturers and physicians, and explained what it was doing and why. FDA worked closely with the Centers for Disease Control and Prevention and manufacturers of immunoglobulin products to head off shortages of these important plasma derivatives caused by the changes in the manufacturers' criteria for product acceptance.

In conclusion, Mr. Chairman, there has been a remarkable decrease in the transmission of viral diseases through blood in recent years. Thanks to the efforts I have described, blood is safer than it has ever been, despite the threats of AIDS and hepatitis. I believe the public can and should have confidence in the safety of the blood supply.

Thank you, Mr. Chairman. We will be happy to answer any questions you or the subcommittee may have.

[The prepared statement of Dr. Zoon follows:]

PREPARED STATEMENT OF KATHRYN ZOON, PH.D., DIRECTOR, CENTER FOR BIOLOGICS, EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

Mr. Chairman and members of the Subcommittee, I appreciate the opportunity to appear today to discuss progress in enhancing and assuring the safety of the nation's blood supply. I am Dr. Kathryn Zoon, Director of the Center for Biologics Evaluation and Research (CBER) at FDA. I am accompanied today by Dr. Jay Epstein, Director of the Office of Blood Research and Review in CBER.

The blood supply plays a vital role in the American health care system and the United States has one of the safest blood supplies in the world. Each year, approximately 12 million units of blood are drawn from volunteer donors for use in more than 3.5 million Americans. Much of this blood and an additional 12 million units of plasma is further processed into products, referred to as derivatives, such as immune globulin, used to prevent infections, and clotting factors, such as antihemophilic factor, used to treat hemophilia. However, we must acknowledge that blood and blood products will never be totally risk free, which creates challenges for maximizing their safety and availability.

CHALLENGE FACING REGULATORS

Blood, because it is a human tissue, is by its nature always at risk for transmitting disease. Because of this risk, and the fact that millions of Americans depend on blood products, efforts to help ensure the greatest possible safety of this life-saving product are a high priority for the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS). Within FDA, CBER is responsible for regulating blood products.

Our goal is to help ensure the safety of the nation's blood supply by minimizing the risk of infectious disease transmission and other hazards, while maintaining an adequate supply. FDA continuously faces new challenges in meeting this goal. We must maintain a regulatory system that can respond to a changing industry as well as to any potential threats to blood safety. We must be ever diligent and attentive to the possibility that known or newly emerging infectious agents will require control measures that do not currently exist.

A close look reveals that enormous progress has been made in preventing the transmission of infectious agents through blood products since 1970. In fact, FDA and the blood industry have implemented safeguards in the last ten years that have made the blood supply dramatically safer than ever before. In particular, the introduction of new screening tests for hepatitis viruses and HIV, and the implementation of virus-inactivation[1] has significantly increased the safety of blood products.

[1] Procedures for plasma-derived products.

In the early 1970's, the risk of contracting some form of hepatitis from a unit of blood was as high as 1 in 12. Now the risk of contracting hepatitis B per unit of blood is approximately 1 in 250,000, and the risk for contracting hepatitis C is less than 1 in 3,300[2]. For HIV, the risk of infection has decreased from 1 in 2,500 in 1985 to around 1 in 500,000 today. For patients who need blood transfusions, the risk of transfusion-associated disease is far less than the risk of dying or becoming more seriously ill without a transfusion.

I would like to describe for you today the increasingly complex blood industry, FDA's role in regulating the blood supply, and significant recent developments in blood regulation.

BLOOD INDUSTRY

Blood banking is a very different industry than it was a few years ago. The use of many new donor screening procedures, including multiple laboratory tests, and an increase in the number and type of blood products being produced have made blood banking far more complex than ever before.

In general, there are three types of blood establishments: blood banks, transfusion services, and plasmapheresis centers.

- Blood banks collect whole blood for transfusion and for processing into components such as red blood cells, fresh frozen plasma and cryoprecipatated antihemophilic factor. Blood banks may be associated with hospitals or may operate as free-standing centers. The American Red Cross collects and processes approximately 50 percent of the Nation's blood supply through its regional centers.
- Transfusion services located in hospitals perform compatibility testing, store and issue blood for transfusion but do not collect and process blood. These facilities obtain blood and blood products from blood collection centers that generally service hospitals in a region.
- Plasmapheresis centers collect Source Plasma that is pooled and further manufactured into products such as immune globulin, albumin and antihemophilic factor. Some Source Plasma is used to manufacture blood testing reagents.

Blood banking has evolved from a loosely organized medical service into a major manufacturing industry—an industry that must conform to high standards and quality control requirements comparable to those of pharmaceutical companies or other regulated industries. FDA can provide support and guidance but it is fundamentally the blood bank's responsibility to comply with the rigorous standards that are necessary to protect our blood supply. We are committed to holding blood banks to those standards.

New strategies for disease control have resulted in changes in blood bank procedures, including methods for determining donor suitability, processing, testing, and labeling of blood products. The advent of new tests to detect transfusion-transmitted infectious diseases has necessitated that FDA review and approve new test kits and improvements to existing test kits. It also has resulted in the need to provide guidance to blood establishments concerning the implementation of the tests. In some cases, the increased testing has resulted in the consolidation of testing laboratories for blood establishments.

To ensure compliance with regulatory standards, FDA has implemented a vigorous inspection program for blood banks. The increased surveillance of blood establishments coupled with the enhanced training of investigators and education of the regulated industry has resulted in an increased awareness of quality assurance in product manufacturing.

FDA REGULATION OF THE BLOOD SUPPLY

The blood safety system established by FDA consists of five layers which begin at the blood collection center and encompass the manufacturers and distributors of blood products.

(1) First, donor screening is performed by asking donors questions about their health and risk factors after they receive educational material. Potential donors are interviewed by trained personnel regarding their medical history to determine whether that person is a suitable donor. Potential donors whose blood may pose a health hazard are asked to exclude themselves as donors.

(2) Second, after donation the blood is tested for blood-borne agents such as HIV, hepatitis and HTLV–I.

[2] A more current unpublished estimate places this risk around 1 in 62,500 using newer screening tests.

(3) Third, blood establishments must keep current a list of deferred donors to prevent use of units from deferred donors.

(4) Fourth, the blood products are quarantined until the products have been thoroughly tested, and the donation records have been verified.

(5) Fifth, blood establishments must investigate any breaches of these safeguards and correct any system deficiencies that are found.

CBER REORGANIZATION

In 1992, FDA's Center for Biologics Evaluation and Research (CBER) was reorganized, partly to reflect the increased visibility and importance of blood safety and product approval issues. Components of the reorganization included:

- Streamlining the review process through organizational changes, increasing automation, and increasing staffing in critical areas.
- Implementing enforcement strategies and developing quality assurance guidance to assist blood establishments in complying with FDA regulations.
- Initiating efforts to further reduce transmission of infectious diseases by blood transfusion which include product related research, initiatives related to blood donor suitability determinations and approval of new products and procedures.
- Initiating mechanisms for enhanced coordination and communication through public workshops, inter-agency communication, public education activities, and more rapid communication of guidance to the blood industry.

CBER's actions have fostered and accelerated a major change in the nation's blood industry. In expecting the same high manufacturing standards of blood establishments as we do from traditional-pharmaceutical firms, we are overseeing a sweeping transformation of the way blood and blood products are collected, processed and handled.

ADVISORY COMMITTEES

The Blood Products Advisory Committee (BPAC), mainly composed of leading outside experts in the fields of hematology and infectious disease relevant to transfusion medicine, meets regularly to review crucial issues affecting the blood supply and to advise the agency on these matters. The agency currently is in the process of reconstituting BPAC to reduce industry membership and include broader representation from consumer advocates, care givers, ethicists and persons who frequently use blood products. This measure is being taken in response to concerns about giving greater attention to the consumer's perspective. The agency is attempting to balance the membership between knowledgeable consumers and experts in the field.

In addition to BPAC, FDA furthers its commitment to broad representation in seeking outside advice on critical regulatory issues through the use of the special Ad Hoc Advisory Committees.

LICENSURE/REGISTRATION/INSPECTIONS

FDA oversees all phases of blood preparation and manufacture, from donor selection and testing to product collection, processing, labeling and storage. CBER licenses blood establishments that ship blood products in interstate commerce and inspects these establishments and the more than 2,500 registered intrastate blood establishments that collect or process blood throughout the United States. In order to obtain a license, a blood establishment must demonstrate the ability to make safe and effective products and must fully implement all safeguards over blood and blood products, including the five layers I described earlier. Collection or manufacturing establishments that are not involved in interstate commerce are not licensed, but they register with FDA and, like licensed establishments, are inspected by FDA. All blood establishments are subject to the same good manufacturing practice standards (GMPs) as licensed establishments.

FDA has significantly increased oversight of the blood industry. Inspections have allowed the agency to monitor closely the operations of blood banks and verify adherence to regulations and proper procedures. Facilities which are found to have more serious and frequent problems are inspected more frequently. Many FDA registered and licensed facilities are inspected annually and all at least biennially.

Inspections help insure that the blood establishments are adhering to current GMPs. During the inspection, investigators monitor donor screening; blood testing, labeling, storage, and handling; record keeping and other manufacturing practices. When there are violations and safety hazards, FDA can take action against the product or establishment. FDA can issue warning letters or suspend or revoke li-

censes. Legal actions can result in civil or criminal penalties, including seizure of the product or recalls.

Because of the potential risks involved, FDA regards blood or blood components as unsuitable for use if any of the safeguards is breached. Unsuitable units that are shipped are subject to recall because of the potential risk, even if tests do not show definitely that the products are contaminated.

SIGNIFICANT RECENT DEVELOPMENTS IN BLOOD REGULATION

In July 1993, at the request of three members of Congress, Secretary Shalala asked the Institutes of Medicine (IOM) to review the events between 1982 and 1986, during which HIV was transmitted through blood products to more than half of the 16,000 hemophiliacs in the U.S. The IOM released a report on July 13, 1995. Secretary Shalala appointed a task force to review HHS blood safety activities in response to the recommendations made. FDA participated on the task force. After reviewing the IOM recommendations and the existing blood safety system, the task force made additional recommendations to further enhance the blood safety system. The IOM report and the Department's response were the subject of Secretary Shalala's testimony this morning before this Subcommittee.

The IOM panel did not review the existing blood safety program or the current safety of the blood supply, but examined the events and public health organizational and decisionmaking structures of the early 1980s as they affected blood safety.

Many significant changes have been made by the FDA since 1986. These changes include:

- FDA has strengthened its internal management of blood issues.
- FDA has broadened the composition of its BPAC and has improved its use of the committee as an independent source of expertise.
- FDA has strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products, building on improvements made prior to 1986.
- FDA has significantly increased its oversight of the blood industry.
- FDA has repeatedly provided the blood industry with detailed and specific guidance about how to ensure that blood and blood products are as safe as possible.

Since 1983, before the isolation of the AIDS virus, FDA has issued over 80 memoranda containing recommendations regarding procedures to increase the safety of the blood supply. These industry on such issues as documents provide guidance to deferring donors, screening blood for infectious agents, interpreting test results, and reinstating previously deferred donors.

FDA's guidance documents provide greater flexibility than the formal rule-making process in instances where protection of the public health requires swift action. Technology advances so rapidly that many guidance documents/recommendations would be obsolete by the time notice-and-comment rulemaking was completed. Moreover, FDA has found that its recommendations quickly become the industry standard.

FDA has increased its use of Advisory Committees, public meetings and workshops as means to communicate its expectations through public discussion, and has issued increasingly specific guidance to regulated industry through Guidelines, Points to Consider and Recommendations. In addition, FDA has made increasing use of compliance policy guidance documents to clarify its positions on enforcement.

We recently issued a guideline for blood banks on development of written quality assurance programs. Carefully designed and carefully followed quality assurance programs should be at the foundation of a blood bank's program to prevent the release of unsuitable blood and blood components.

Blood donations are now tested for seven different infectious diseases—up from only two as recently as 1981. As a preventive measure, FDA instituted screening for antibodies to HIV-2 in 1992 even before the agency had any evidence that HIV-2 was being spread in the blood supply. FDA also was proactive in instituting screening for HTLV-I (the leukemia virus) in 1988. The first screening test for antibodies to hepatitis C was approved in 1990, and an improved screening test became available in 1992.

HIV-1 ANTIGEN SCREENING

In August 1995, to further reduce the risk of infecting blood recipients through contaminated transfusions, FDA issued guidance to the blood industry which recommends that blood establishments test donors with new HIV-1 antigen test kits after they become available. Using the new antigen tests would reduce by about one week the "window period" between HIV infection and detection. Reducing the win-

dow period further reduces the chances that HIV-contaminated blood will enter the blood supply and infect recipients of transfused blood or other blood products. Currently, blood donors are screened with tests that detect only HIV antibodies, normally detectable within two months after infection. The antigen screening tests detect HIV–1 antigens, which are the virus' own proteins. Although no HIV antigen tests are currently licensed for screening, FDA's recommendations are in anticipation of products that are being developed for this use.

GUIDANCE TO REDUCE THE RISK OF CREUTZFELDT-JAKOB DISEASE

Also in August 1995, FDA issued guidance to reduce the possible risk of transmitting Creutzfeldt-Jakob disease (CJD) by blood and plasma products. CJD is a rare, fatal, degenerative disease of the central nervous system that affects approximately one person per million per year. A small number of donors of blood and plasma have been diagnosed with CJD since 1983. In each established case, blood centers voluntarily withdrew all unused products derived from the infected donors. Although there are no confirmed cases of CJD from transfusion and the risk of such transmission is considered extremely small, the possibility of CJD transmission through blood products cannot be ruled out at this time. Thus, the agency has recommended that blood establishments should withdraw and quarantine products subsequently found to have come from donations of individuals diagnosed with or at increased risk of CJD. These quarantined products could be released in the case of blood product shortages if the products bear special labeling noting the CJD risk. FDA also has recommended that blood donors now be questioned to determine if they have risk factors for CJD and that at-risk individuals be permanently deferred from donating blood.

THREAT OF HEPATITIS C INFECTION IN IMMUNE GLOBULIN PRODUCTS

FDA's work to help ensure that immune globulin products continue to be safe, effective and available demonstrates the agency's commitment and ability to solve tough problems quickly. In February 1994, FDA received the first-ever reports that implicated a U.S. licensed Immune Globulin Intravenous (IGIV) in the transmission of hepatitis C. The product was quickly withdrawn from the world market; the firm re-entered the market only when the manufacturing process was modified to include a viral inactivation step.

As part of its ongoing research program on plasma derivatives, FDA developed methods which it used to investigate this incident and extended the investigation to other products. In particular, FDA tested previously released lots of immune globulins for intramuscular administration (IGIM) for HCV RNA. Some lots tested positive for HCV RNA. There has never been a documented case of HCV transmission by IGIM products; moreover, the presence of HCV RNA in the products does not mean they are infectious. Nevertheless, because viral inactivation of IGIM products was not yet in place, on December 27, 1994, FDA announced that only those lots of IGIM that had been screened for HCV and found negative should be distributed. FDA also announced that this practice would continue until viral inactivation or removal steps were in place.

In both the IGIV and IGIM episodes, FDA immediately assessed the scope of the problem, notified manufacturers and physicians and explained what it was doing and why. FDA worked closely with the Centers for Disease Control and Prevention (CDC) and manufacturers of IG products to head off shortages of these important plasma derivatives, caused by the changes in the manufacturer's criteria for product acceptance. At each step of the process, FDA has worked to update and strengthen the safeguards that protect patients from unsuitable blood products.

IDIOPATHIC CD4+ T-LYMPHOCYTOPENIA (JCL)

In 1992, there were reports of what appeared to be another AIDS-like illness. FDA and the CDC quickly studied a cohort of patients who met the criteria for this "syndrome," called "Idiopathic CD4+ T-lymphocytopenia." All results were negative, and no "clustering" of patients with this entity occurred.

FDA worked with the CDC and the blood industry and reacted in a swift fashion to assess the potential threat to the safety of the blood supply and excluded the possibility of a new transfusion transmitted disease.

CONCLUSION

FDA has made great strides that have significantly increased the safety of the blood supply. There has been a remarkable decrease in the transmission of viral diseases through blood in recent years. Blood is safer than it has ever been despite

the threats of AIDS and hepatitis and I believe the public can, and should, have confidence in the safety of the blood supply.

We continually strive to make blood safer through efforts to improve the operation of existing systems through education, regulatory controls, development of quality assurance initiatives, and development of new products. Ongoing improvements and refinements together with advances in science and technology promise more sophisticated methods of blood product manufacturing including more accurate tests to protect the blood supply.

Thank you, Mr. Chairman, we will be happy to answer any questions you: or the Subcommittee may have.

Mr. SHAYS. Thank you, Doctor, and I appreciate your statement and also agree with you that the blood supply is very safe.

Let me ask you first if you are in total agreement with the Secretary's position that blood supply should be a focus of her Assistant Secretary, and so on. Are you in total agreement with that?

Ms. ZOON. Yes.

Mr. SHAYS. Is there any part that you are not in agreement with?

Ms. ZOON. No.

Mr. SHAYS. As it relates to the Council, is there any way that you think we can involve consumers more than we are presently involving them?

Ms. ZOON. In the Advisory Council as described by the Secretary this morning?

Mr. SHAYS. Yes.

Ms. ZOON. I think the incorporation of the consumer and the user are very important. We have learned that over time with our BPAC and we do believe it is important, especially with the broad issues that the Advisory Council would deal with regarding the societal and public health impact. So I believe this is an important part.

In terms of the process to choose candidates for this process, I would leave that to the Secretary's discretion.

Mr. SHAYS. Let me understand, because you are making a strong statement that the FDA is doing its job and doing it well. How would you have evaluated what happened in the 1980's?

Ms. ZOON. I think in the 1980's, and I think from my perspective, having not been involved at that time and having experienced the issues that have been raised by the IOM report, I have to believe there were missed opportunities. I think there were times that the science was inconclusive. I think we could have potentially made some decisions at that time that we might—that we did not. So I think missed opportunities is probably a good characterization of that.

Mr. SHAYS. The Institute of Medicine's criticism was that they criticized the Federal Government and the FDA in particular. And the quote was "consistently chose the least aggressive option that was justifiable," and that the FDA "did not adequately use its regulatory authority and, therefore, missed opportunities to protect the public health."

So you agree with the second part. How about the first part, that it "consistently chose the least aggressive options that was justified"?

Ms. ZOON. Well, I think having not been there, this is conjecture, you know.

Mr. SHAYS. I tell you, that's not really acceptable. And this is why: Because you are there now to learn lessons from the past.

Ms. ZOON. That's correct.

Mr. SHAYS. And so for conjecture, no, you are not properly in that position, if that is your attitude. I am not going to try to relive what happened in the 1980's. I am not looking to condemn anyone. But I want to have a mind set that you have so thoroughly studied this issue that you could answer a question like that. So I am not viewing it as a judgment call. I am viewing it in the sense as lessons learned and what do we do differently.

Ms. ZOON. OK, thank you, Mr. Chairman. I will address it then with that in mind. I have reviewed the IOM committee report thoroughly. I believe in my review of the information, because I do consider lessons learned very important in any part of business, either science or public health decisionmaking, so that we don't repeat mistakes we have made in the past or have not judged properly in the past.

And I believe that in looking at the past and evaluating a very important area such as the emergence of a new disease, there was not scientific consensus at that time. And the lack of scientific consensus at that time led to very conservative decisionmaking. And I think people's need and want to find answers to very important scientific questions before they took action was, in my view, driving how quickly actions proceeded.

I think that perhaps looking at it retrospectively, some intermediate positions and decisions could have been made while the process was being evaluated while the science was evolving.

Mr. SHAYS. As it relates to Hepatitis C and the thought that there may be 100,000 to 200,000 who have been infected because of our not having a proper screening process, has your agency taken any position in terms of notification of these individuals or all individuals pre-1990 who might need to check to see if they have, in fact, been infected?

Ms. ZOON. I think the issue of the HCV notification, Mr. Chairman, is an evolving one. We considered this issue and we considered it with our colleagues in the Centers for Disease Control at the time when the HCV test was first approved. And there were a number of pathways that one could take at that time, but there were also a number of things that were of consideration. We did not have a confirmatory test. When the original screening test was approved, there were no known treatments for Hepatitis C at that time.

There was a discussion of how best to approach this topic and some of the approaches considered at that time, one was a lookback approach, and that was felt to be at that time not appropriate but perhaps more of an educational approach to physicians and a public health education program. And that is under the jurisdiction of the Centers for Disease Control.

I believe we constantly look at these areas. No issue is only looked at once. I think it is time to look at the Hepatitis C notification issue again, and I believe this is an issue that will be looked at by the Blood Safety Committee that has been newly formed.

Mr. SHAYS. Isn't timeliness also a factor though? I mean, pre-1990, every year you wait there is 1 year in between. And it seems to me that it becomes almost less timely, rather than more timely.

Ms. ZOON. I think our intention here is to allow individuals to get the information that they need to make decisions. As I mentioned, back in the 1990's we really didn't have a test to confirm hepatitis and the actual amount obtained from transfusions is a very low percentage.

I might ask Dr. Epstein to comment on this for us.

Dr. EPSTEIN. Thank you, Mr. Chairman. Thank you, Dr. Zoon. The amount of Hepatitis C attributable to transfusions is about 3 to 4 percent. You mentioned earlier the large number of 100,000 to 200,000, but the number of people harboring Hepatitis C is about 3.5 million in the population.

The problem with tracing the recipients from transfusions from donors found positive is severalfold.

First, when the test was implemented in 1990, most of the transmissions that would have occurred would have been in the prior decades. The donor pool was very dramatically changed in the 1980's because of all the safety precautions that were put in place and, therefore, the prospect of availability of records to identify the prior recipient was not very good. Added to that were all of the facts that Dr. Zoon mentioned about lack of knowledge of impact.

Mr. SHAYS. So your testimony would be that there may be 100,000 to 200,000 who have contracted Hepatitis C through blood transfusion, but there is a population of 3.5 million. And that would drive me to say that, obviously, anyone in that 3.5 million would want to know.

Mr. EPSTEIN. That's right.

Mr. SHAYS. So I hear your point there.

Mr. EPSTEIN. Right. And, therefore, the question as it has presented itself to the Public Health Service is, if it has become reasonable to try to identify such people because they might benefit from treatment or counseling, how do you find them and what are the effective means of reaching them and tracing them?

Mr. SHAYS. Let me yield now to my colleague, Mr. Towns. He has the floor.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me begin by asking you, Dr. Zoon, in your testimony you state that the FDA has issued guidance documents that state that blood banks should use HIV antigen tests when they become available.

Why doesn't the agency require that the blood banks use the test, period?

Ms. ZOON. Sir, currently there are no licensed HIV antigen test kits for screening. We have one HIV antigen test kit that has been approved for diagnostic use only. We are working very actively with the manufacturers to move these products along as rapidly as possible.

Mr. TOWNS. Let me go at this another way then. In your testimony you state that guidance documents are used frequently when public health requires swift action.

How responsive is the blood bank community to guidance documents?

Ms. ZOON. They are very responsive to the guidance documents.

Mr. TOWNS. If they fail to respond, what action can you take if they just ignore your guidance documents, because they are guidance documents.

Ms. ZOON. Right. We can take action based on our statutes and our regulations with respect to current good manufacturing practices in order to maintain compliance.

Mr. TOWNS. What are some of the things that you can do under guidance documents? Could you be specific in terms of what you can do?

Ms. ZOON. Yes. For instance, if someone doesn't test for HIV there is a number of actions, enforcement actions, we can take. And I will ask Mr. Simmons to outline the enforcement strategy that we could take.

Mr. TOWNS. Thank you.

Mr. SIMMONS. We would, depending on the seriousness of the violation that occurred, we would probably begin by issuing a formal warning letter requesting that they take corrective action within certain periods of time and telling us what the corrective action plan would be.

We could move progressively up from that to an injunction to prevent them from continuing to violate the recommendations, provided that the recommendations are tied to the statute. Under the Public Health Service Act, if it is a licensed firm, we could suspend the license. Finally, to revoke the license.

There are some intermediate steps that could be done in lesser significant situations, one of them being product seizures.

Mr. TOWNS. Thank you. Dr. Zoon, would you advocate requiring greater disclosure to blood users regarding the risk of blood products? And I guess would doing so have any adverse effect on blood donations?

Ms. ZOON. I think that is a very good question, Mr. Towns. I think there is a lot of emphasis placed on information currently in the labeling to physicians in the products that we regulate. And that has been—and what we have done for our biological products and for blood. I think it is an issue that we continually look at and examine in how best and who should provide information to the recipients of those products.

Part of this is the physician-patient relationship, part of it is the public health information message. But I think there are many individuals and many organizations that have a collective responsibility in dealing with that consumer information issue.

Mr. TOWNS. Thank you very much, Dr. Zoon and other members of the panel. Mr. Chairman, I yield back.

Mr. SHAYS. I thank the gentleman and appreciate you all being here. This is, obviously, something we will follow up. And we consider your testimony very helpful in that process and look forward to continuing to work with you as well.

This hearing is now adjourned.

[Whereupon, at 1:45 p.m., the hearing was adjourned, subject to the call of the Chair.]

PROTECTING THE NATION'S BLOOD SUPPLY FROM INFECTIOUS AGENTS: NEW STANDARDS TO MEET NEW THREATS

THURSDAY, NOVEMBER 2, 1995

U.S. HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RESOURCES AND
INTERGOVERNMENTAL RELATIONS,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:40 a.m., in room 2247, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Davis, Souder, Chrysler, Towns, Barrett.

Staff present: Lawrence J. Halloran, staff director and counsel; Doris F. Jacobs, associate counsel; Anne Marie Finley and Robert Newman, professional staff; Thomas M. Costa, clerk; and Cheryl Phelps, minority professional staff member.

Mr. SHAYS. I would like to call this hearing to order and to welcome our very distinguished witnesses and our guests, as well.

Three weeks ago, at our first hearing on blood safety issues, Health and Human Services (HHS) Secretary Donna Shalala announced the Department's plans to sharpen the focus and improve the coordination of Federal efforts to protect against infectious agents in the Nation's blood supply. She did so in response to the Institute of Medicine (IOM) report that critically reviewed how, in the early 1980's, new Hepatitis strains and the human immunodeficiency virus (HIV) slipped past our defense.

As a result, 10,000 hemophiliacs and 20,000 other patients were infected with AIDS through blood and blood products. More than 100,000 got Hepatitis-C, many of whom have never been told of their infection. We need to be sure the lessons of that tragedy will be used to set a higher standard for blood safety.

Our defense against nature's relentless and inventive army of pathogens relies on government leadership, corporate integrity, scientific research, and public altruism. Our witnesses today represent critical elements of that blood defense capability. We seek their assurance they are prepared to meet the challenges of both known and unknown threats to a safe blood supply.

The Centers for Disease Control and Prevention (CDC) patrol the far perimeter of the battlefield, conducting the public health surveillance essential to the early detection of new threats. Research

to characterize emerging infections and identify attack strategies is directed by the National Institutes of Health (NIH).

The blood banks guard the fortress gates, screening donors for risk factors while seeking to ensure an adequate, safe supply of blood, and the blood resources industry combats pathogens throughout the blood production process in donor screening, process design, and the application of new techniques to inactivate or separate infectious agents.

The IOM study called for a more coordinated approach to blood safety issues. Toward that goal, we invited to these hearings all those with a major role to play in the protection of the blood supply.

We are pleased that all witnesses are able to join us today and particularly welcome the representatives of the five major plasma fractionation companies. Their presence here is one clear signal that competitive pressures or other economic considerations need not mitigate against the frank, open discussion of safety issues.

Our greatest enemy is complacency. No amount of sophisticated science should be allowed to obscure the hard fact that the world today still relies on a human shield to absorb the initial impact of emerging blood-borne infections.

People with hemophilia, uniquely dependent on blood-derived therapies, stand as our sentinels. Their illness is our surest early warning that a new infection has entered the blood supply. Their plight and their courage should inspire the vigilance necessary to protect the safety of blood and blood products.

Oversight is one major weapon in our arsenal. As this subcommittee has proceeded to examine public health issues involving FDA regulation of food additives, medical devices, and blood and biologics, we have learned the benefits of challenging old assumptions and questioning longstanding procedures.

When it comes to protecting the public health, stationary defenses are no more effective than the Great Wall of China or the Maginot Line. We will continue to focus our oversight on the need for flexible, dynamic systems to meet modern health challenges.

Again, I would like to say we appreciate our witnesses' help in that effort today. With that, I would like to call on my good friend and our very distinguished and important member of this committee, my co-partner, the ranking member, Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. I'm going to be brief, because I really want to hear the witnesses, but thank you again for having this hearing.

The questions I seek answers to today are, one, whether the policies and operation of HHS agencies, with responsibilities for blood safety lend themselves to an effective, responsive, and coordinated system for protecting the blood supply. And, No. 2, what are the successful new technologies and safety measures being employed in the private sector, and how can they be supported?

I welcome not only the administration witnesses, but also the representatives from the blood collection and plasma industries. I would like to acknowledge the participation of Immuno-U.S. in today's inquiry. Although a relatively recent entry into the U.S. plasma products market, Immuno-U.S. has adopted a very aggressive

stance with respect to safety, including the use of PCR technology. However, I must admit that merits some more exploration.

I look forward to hearing the testimony of all of today's witnesses and to incorporate their views into the subcommittee's investigation. I think this is a very serious matter, and I think it should be dealt with in that fashion. I appreciate the time and energy that the witnesses are giving to this and, also, I would like to commend you again, Mr. Chairman, for making this a priority. Thank you very much.

[The prepared statements of Hon. Edolphus Towns, and Hon. Cardiss Collins follow:]

PREPARED STATEMENT OF HON. EDOLPHUS TOWNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

Mr. Chairman, thank you for convening this second hearing regarding Federal and private sector efforts to safeguard the Nation's blood supply from infectious agents; and the Institute of Medicine's recommendations for improving blood safety.

The recommendations were a part of the IOM report on the deficiencies in the Federal response to the HIV transmission to thousands of hemophiliacs in the early 1980s. As you know, last month Secretary Shalala embraced nearly all of the IOM recommendations, the majority of which are already being carried out by HHS agencies.

For both the Federal Government and the private organizations with responsibility for blood safety, the failures of the system has left us sadder and considerably wiser. We know, for example, that although the Nation's blood supply has been never been safer than it is today, it is still vulnerable to a host of life-threatening infectious agents.

Millions of people who depend on blood products rely on HHS agencies to promulgate effective measures that minimize the risk of transmission of infectious agents—measures that are responsive to the emergence of new pathogens, but also to innovations in blood collection and plasma industries.

Mr. Chairman, the questions I seek answers to today are: one—whether the policies and operations of HHS agencies with responsibility for blood safety lend themselves to a effective, responsive, and coordinated system for protecting the blood supply; and two—what are the successful new technologies and safety measures being employed in the private sector, and how can they be supported?

I welcome not only our administration witnesses, but also our representatives from the blood collection and plasma industries. I would like to acknowledge the participation of immuno-U.S. in today's inquiry. Although a relatively recent entry into the U.S. plasma products market, immuno-U.S. has adopted a very aggressive stance with respect to safety, including the use of PCR technology. That merits some exploration.

I look forward to testimony of all of today's witnesses and to incorporating their views into the subcommittee's investigation.

PREPARED STATEMENT OF HON. CARDISS COLLINS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Chairman Shays, I am pleased to join you and Subcommittee Ranking Member Towns to continue the Subcommittee's consideration of this important issue: protecting the blood supply from debilitating and life-threatening infectious agents.

Our vulnerability to emerging infections was never more tragically demonstrated than during the early 1980s and the advent of HIV. The slow, uninformed, and largely ineffective Federal response to the viral contamination of the blood supply contributed to the transmission of HIV to thousands of people with hemophilia, as well as to thousands of other blood recipients.

Our goal here today is to learn what Federal efforts have been, and are projected to be, put in place to guard against a recurrence of this tragedy and to minimize the exposure of the U.S. blood supply to viral and bacterial contamination.

Mr. Chairman, the Federal government and the blood collection and plasma industries have made great strides toward improving the safety of the blood supply over the past decade.

As you know, the Health and Human Services Secretary has embraced the recommendations of the Institute of Medicine report on the Federal response to the

HIV contamination of the blood supply. Many of these recommendations have already been implemented by HHS agencies and have been in place for several years, making the U.S. blood supply among the safest in the world.

The Administration witnesses are joined by representatives of the blood collection and plasma industries, who share some responsibility for the blood safety. A number of innovative approaches to donor screening, plasma pool size, and viral inactivation and plasma sterilization have arisen from this community. I look forward to hearing both the encouraging news as well as the concerns that these witnesses bring us.

I thank all of our witnesses for their participation in this important oversight inquiry, and look forward to a productive discussion.

Mr. SHAYS. I thank the gentleman. Mr. Davis.

Mr. DAVIS. No, sir.

Mr. SHAYS. Mr. Chrysler. Thank you.

At this time, I would like to welcome our four witnesses, David Satcher, Director, Centers for Disease Control and Prevention, accompanied by Rima Khabbaz, Associate Director of Medical Science, and Bruce Evatt. Are the two individuals accompanying you presenting testimony as well, or just accompanying you?

Dr. SATCHER. No, they're just accompanying.

Mr. SHAYS. Thank you. And then we have testimony, as well, from Paul McCurdy. If you would rise, It's our practice with all our witnesses, we swear in our witnesses. Anyone who might be testifying or adding, that would be helpful. Thank you.

[Witnesses sworn.]

Mr. SHAYS. For the record, I note that all the witnesses have answered in the affirmative. If we could, the two individuals who were standing in the back, if you would identify for the record who you are.

Dr. GANGULY. I am Dr. Pan Ganguly from the National Institutes of Health.

Mr. SHAYS. Thank you.

Dr. GROFT. Dr. Stephen Groft from the National Institutes of Health.

Mr. SHAYS. Thank you very much. At this time, just to get some housekeeping out of the way here, I ask unanimous consent that all members of the subcommittee be permitted to place any opening statements in the record and that the record remain open for 3 days for that purpose. Without objection, so ordered.

I also ask unanimous consent that our witnesses be permitted to include their written statements in the record and be able to summarize and so on. Without objection, so ordered.

Dr. Satcher, very nice to have you here. It's a privilege to have you here, and I welcome your testimony.

STATEMENT OF DAVID SATCHER, DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION; AND PAUL McCURDY, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NATIONAL INSTITUTES OF HEALTH

Dr. SATCHER. Thank you, Congressman Shays, Congressman Towns, and other members of the subcommittee. As you pointed out, I am Dr. David Satcher, Director of the Centers for Disease Control and Prevention, and I have with me Dr. Rima Khabbaz, who is Associate Medical Director for Medical Science at the National Center for Infectious Diseases and represents the CDC on the Interagency Working Committee. Dr. Bruce Evatt is the branch

Chief for hematological diseases in the National Center for Infectious Diseases.

We're very pleased to have this opportunity to testify on this very critical subject. I will summarize my statement, but will submit for the record a full statement.

First, I would like to say that, in follow-up to Secretary Shalala's and Assistant Secretary Lee's presentation, we feel at CDC that the new strategy within the Department of having a blood safety director and a Blood Safety Committee reporting to that director significantly improves communication and coordination of our efforts in this very important area.

So we're very pleased with the new developments and look forward to working with the new Advisory Council on Blood Safety and Availability in continuing our work with the FDA Advisory Council.

Let me say that I think you realize that this issue, I think, suffered from the same overconfidence that we experienced coming out of the 1940's and 50's with infectious diseases in general. There was a feeling that we had conquered infectious diseases, and I think that feeling of security carried over to this very important problem of the safety of our blood supply.

CDC's role in protecting the blood supply is one that we carry out in partnership not only with the FDA, that's responsible for regulations, and NIH, with basic research, but also with the State and local health departments throughout this country. Without strong State health departments, we would not be able to carry out our functions of surveillance.

By the same token, we work very closely with industry, and that working relationship has been very important in some of the new developments in terms of strategies and new discoveries in terms of threats to the blood supply. So all of those partnerships are very important.

We agree that the blood supply in this country is safer than ever, but we also agree that there is need for increased vigilance. I think if we just think back to the problems of the early 1980's with HIV/AIDS and, later in 1990, with the transmission of Hepatitis C in blood transfusions, then it's very clear that we have to continue to be quite vigilant.

In response, specifically, to Congressman Towns' question about our strategies, let me just summarize three very important strategies which we use to try to protect the blood supply.

One is the strategy of surveillance. CDC is responsible for conducting surveillance of donors who contribute blood throughout the year, and also surveillance of the hemophilia population that receives so many of the transfusions and blood products.

What we do that's very important is serological screening of a large segment of blood donors every year. We defer blood donors when that is appropriate, and we watch very closely the hemophilia population for any signs of new illnesses or new challenges that might be derived from the blood supply.

That surveillance is very important. I believe that two-thirds of the hemophilia centers throughout the country are part of our surveillance system now, so we watch very closely what's going on. That surveillance is really critical. It is the basis of public health,

and when it works well, then I think the chances of protecting our blood supply are very good.

The second strategy that we use that's equally important is the issue of epidemiological investigation. If you think back to the early 1980's, it was in fact CDC's response to the reports of new illnesses starting in California that led to our discovery that there was something being transmitted through the blood supply.

We estimate that even before the HIV virus was discovered in 1983–84, over 700,000 lives were saved because of the epidemiological investigations that were able to show that there was something being transmitted through the blood supply and other means.

We continue to investigate new problems in this country and throughout the world as they come up, and those investigations are very important. There are also a lot of special studies that we engage in. I won't go into a lot of detail, but I will say that it was, in fact, Dr. Evatt's involvement with special studies that led to the treatment of blood to reduce the transmission of viruses in the blood supply.

Also, special studies between CDC and industry led to the discovery of Hepatitis C and, more recently, Hepatitis G. So, in addition to surveillance and epidemiological investigations, we continue to do research at the laboratory level, but also population-based research that results in our discovering new challenges to the blood supply and new strategies for protecting it.

I think the biggest concern that we have would be with these new challenges, things that we are not now aware of. What are we doing to make sure that, as new things develop, we detect them as early as possible, new uncharacterized threats?

There are several things that we are doing to try to stay on top of those kinds of challenges. I think the sentinel surveillance networks that we have developed throughout the country, where we monitor very closely all of the recipients of blood in that network and respond to any challenges, help us to stay on top of these kinds of threats.

I could mention in some detail issues like Chagas' disease, that is transmitted through a parasite, Trypanosoma cruzi, and we monitor very closely the challenge that this provides to the blood supply. There have been only three or four transmissions of Chagas in the blood, and yet we think it's very important that we stay on top of that.

Another issue, though, that represents a different challenge, is the whole issue of CJD disease, where we don't have any evidence to date that there has been transmission in the blood, but there is a lot of concern that there could be, and we have major studies going to try to monitor very closely the possibility that that could occur.

Those are examples where we have more questions than answers, but we think we have strategies for making sure that, as new challenges develop in the blood supply, we're in a position to get on top of them.

Let me close by pointing out that, in 1994, CDC developed this approach to addressing the threats of emerging infection. This was in direct response to a 1992 Institute of Medicine report on emerg-

ing infections. This report includes four strategies for addressing emerging infections.

In addition to surveillance and response, integrated research represents another strategy—integrating basic research, epidemiological research, behavioral research. A third approach is communication, improving our communication with physicians, other health care providers, but also with patients.

Finally—and I'll submit this report for the record—part of this strategy is to continue to strengthen the public health infrastructure. A good example of that would be the studies that we have going in the States of Connecticut, California, Minnesota, and Oregon, where we are trying to develop the kind of surveillance systems, in conjunction with State health departments and universities, where we are detecting new threats to the blood supply as early as possible.

Thank you, Mr. Chairman, for the opportunity, and we would be very happy to respond to any questions.

[The prepared statement of Dr. Satcher follows:]

PREPARED STATEMENT OF DAVID SATCHER, DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION

Good morning I am Dr. David Satcher, Director of the Centers for Disease Control and Prevention (CDC) I am accompanied by Dr. Rima Khabbaz and Dr. Bruce Evatt, both with CDC's National Center for Infectious Diseases. We are pleased to be here this morning to discuss with you CDC's role in protecting our Nation's blood supply.

In the past few decades, many of the best scientific minds in the country expected infectious diseases to be eliminated as a public health problem in the United States. As recent events have shown, these pronouncements were premature. Infectious diseases remain the leading cause of death worldwide and among the most important causes of death in the United States.

In addition, we are faced increasingly with new and re-emerging infectious disease challenges. At home, we have seen the reemergence of a public health scourge, tuberculosis; recent outbreaks of food and waterborne illnesses, such as those caused by *E. coli 0157.H7* and cryptosporidiosis; and the emergence of a new hantavirus. On a global front, the worldwide HIV/AIDS epidemic is now in its fifteenth year. We recently witnessed an epidemic of plague in India; diphtheria outbreaks in the New Independent States of the former Soviet Union; and the frightening reemergence of the Ebola virus in Zaire.

To meet the challenges posed by infectious diseases and to reduce their potential threat to safety of the blood supply, a strong public health capacity is needed at both the federal and state levels. At the federal level, CDC, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) provide our first-line of defense in ensuring that the Nation's blood supply and products made from blood are free of infectious agents.

The U.S. blood supply is currently safer than it has ever been, but the HIV experience in the early 1980's and the more recent experience with hepatitis C virus (HCV) transmission from intravenous immunoglobulin illustrate the need for continued vigilance regarding unrecognized, uncharacterized, and new threats to the blood supply.

The safety of the blood supply is a shared responsibility of many organizations. While CDC has no regulatory responsibility for blood safety, as the Nation's Prevention Agency, it has the expertise and responsibility for surveillance, detection, and warning of potential public health risks associated with blood and blood products. CDC is an active member of the Public Health Service (PHS) Blood Safety Working Group, and CDC has nominated a voting member to serve on FDA's Blood Products Advisory Committee. CDC shares the Secretary's commitment to enhance the Department's blood safety operations through implementation of the Institute of Medicine's recommendations for blood safety. To monitor and improve the safety of the blood supply, CDC has developed and used a number of strategies. These strategies fall into three general categories: 1) maintaining and enhancing public health surveillance systems; 2) conducting epidemic investigations of outbreaks due to blood and blood products and special studies to assess the risk of specific infectious

agents; and 3) developing preventive strategies to address new and uncharacterized threats to the blood supply. In addition, throughout all of these activities, CDC develops and implements laboratory techniques and conducts applied research for the diagnosis and characterization of infectious agents. I would like to review, in some detail, each of these components of CDC's contribution to ensuring the safety of the Nation's blood supply.

PUBLIC HEALTH SURVEILLANCE SYSTEMS

CDC has a number of public health surveillance systems for the detection of bloodborne diseases, including systems to detect specific diseases such as HIV, and hepatitis B and C viruses (HBV, HCV) among recipients of blood and blood products.

In 1981, CDC initiated a surveillance system for AIDS. Through this system, together with detailed follow-up investigations of reported cases, CDC gathered the epidemiologic data that established that HIV infection could be transmitted by blood and blood products. Currently, CDC utilizes multiple systems to monitor the present risk of HIV transmission in the nation's blood supply. CDC's national AIDS surveillance system monitors transfusion-associated AIDS cases, particularly those with a history of receipt of screened blood products.

CDC, in collaboration with the American Red Cross, also has ongoing HIV surveillance of blood donors. This surveillance system collects information from about 2 million donors a year. Through this system, CDC has documented the decreasing risk of transmitting HIV through the blood supply; the current risk is estimated to be about 2 per million donations. CDC's surveillance of blood donors also includes evaluation of donors found to be seropositive for HIV to determine their risk behavior and reasons for donating blood. This information is used to improve deferral strategies for donors with risks for HIV infection, which are essential components of efforts to enhance blood safety. In addition, once p24 antigen tests are licensed for use in blood screening, CDC will establish a surveillance system for donors whose blood tests positive for p24 antigen to evaluate the benefits of the new recommendations.

Historically, viral hepatitis has been the major infectious disease hazard associated with transfusion of blood and blood products. These viral infections can lead to severe illness, liver damage, and in some cases, death. Donor screening has reduced the risk of transfusion-associated HBV infection to 0.001%, and transfusion-associated HCV infection to less than 0.1% per recipient of screened blood products. Inactivation procedures have virtually eliminated transmission of HBV and HCV from clotting factor products. CDC has two disease-specific surveillance systems for hepatitis. Both systems involve evaluating cases of hepatitis for history of receipt of blood or blood products. Through these surveillance systems, CDC has documented the dramatic decline of posttransfusion hepatitis in the United States. Although other hepatitis viruses transmitted by blood are now being characterized, no cases of transfusion-associated hepatitis due to known or unknown agents have been identified through CDC's sentinel surveillance system. However, rare cases may occur, and CDC is currently seeking to expand its surveillance to enhance the ability to detect new hepatitis infections associated with transfusion.

In addition to these disease-based systems, CDC has a Hemophilia Surveillance System. Persons with hemophilia receive large quantities of blood and blood products and therefore are at increased risk for transfusion-related diseases. Fifty-nine hemophilia treatment centers currently participate with CDC, FDA, and the National Hemophilia Foundation, in a surveillance system for HIV and hepatitis viruses. Currently, 15–20% of patients seen in hemophilia treatment centers are seropositive for HIV; more than half are seropositive for HBV. In September 1995, 17% of persons with hemophilia tested for hepatitis A virus were seropositive; 64% of those tested for HCV were seropositive.

In addition to established surveillance systems, CDC uses other mechanisms, such as its Drug Service, to identify and monitor unrecognized threats to the blood supply. For instance, in 1981, CDC's drug service activity was the only available source of pentamidine, a drug used in the treatment of *Pneumocystis carinii* pneumonia. CDC staff nosed an increase in the number of requests for this drug among persons not known to be immunocompromised, contributing to the recognition of an illness later known as AIDS.

EPIDEMIOLOGIC INVESTIGATIONS AND SPECIAL STUDIES

CDC's longstanding epidemic assistance ("epi-aid") mechanism also allows us to respond rapidly to requests from public health officials and healthcare providers to investigate unusual occurrences of disease or clusters in special populations. This

approach was used in the investigation of hepatitis C virus transmission by intravenous immunoglobulin last year. In collaboration with FDA, the CDC investigation implicated lots of one immunoglobulin product from a single manufacturer, which was withdrawn from the market, and demonstrated the safety of other commercially available products. This investigation resulted in PHS recommendations for screening and counseling of patients who received the implicated product. The recommendations were published in CDC's Morbidity and Mortality Weekly Report. This investigation also contributed to FDA's efforts to require inactivation of all immune globulin products.

Another instance in which the epi-aid mechanism has been used by CDC to address blood safety issues was the investigation of transfusion-associated sepsis (bacterial bloodstream infections). In response to requests from either FDA or state health officials, CDC has investigated several of these episodes and traced these infectious episodes to mild or asymptomatic infection with Yersinia enterocolitica in the donor at the time of blood donation. Prolonged storage of the packed red blood cell units resulted in high bacterial and endotoxin concentrations in the transfused unit. Results of these investigations have been shared with FDA and others. CDC is working with these organizations to develop prevention strategies for transfusion-associated sepsis. In September 1995, CDC participated in an NIH workshop on transfusion-associated sepsis.

CDC also conducts special studies and other applied research to characterize transfusion-associated infectious agents and to address their risks to the blood supply.

In 1984, CDC conducted studies that demonstrated the effectiveness of heat treatment on HIV inactivation in clotting factor concentrates. These data led to the worldwide change in the use of heat treatment for viral inactivation of clotting factor and dramatically reduced the risk of transfusion-associated HIV infection among persons with hemophilia. With further NIH-led viral inactivation technology, CDC continued to monitor these improvements and worked with NIH and FDA to ensure improved safety of clotting concentrates.

More recently, CDC scientists evaluated the FDA-licensed HIV antibody screening tests in response to reports from Africa and Europe that one variant of HIV–1, known as subtype 0, may not be readily detected by some commercially available screening tests. These investigations determined that several of the most widely used assays failed to detect the subtype O variant of HIV–1; however, this variant is rare. To determine the prevalence of this HIV variant in the United States, CDC has collaborated with FDA and the blood industry in studies of high-risk populations, namely those with HIV or from geographic areas where this variant has been detected. To date, no subtype O infections have been detected in this country.

CDC scientists also collaborated with industry to identify and characterize new transfusion-transmitted hepatitis agents. CDC codiscovered the hepatitis C virus (with Chiron Corporation), which resulted in the development of serologic tests to screen donors for HCV infection. CDC's early evaluation of the performance of these screening tests allowed CDC to determine the burden of transfusion-transmitted disease due to HCV.

CDC has played a major role in assessing the risk of HTLV–I and HTLV–II in the blood supply. Since 1988, the blood supply has been screened for HTLV–I and screening tests have been improved for detection of both HTLV–I and HTLV–II. CDC scientists collaborated in NIH's Retrovirus Epidemiology Donor Study (REDS), to characterize the epidemiology and clinical spectrum of disease associated with these viruses in blood donors.

NEW/UNCHARACTERIZED THREATS TO THE BLOOD SUPPLY

CDC recognizes that there may be new and uncharacterized threats to the blood supply. One such agent is the very recently described hepatitis G virus (HGV), which was codiscovered by CDC, NIH, and industry (Genelabs, Inc.). HGV is a newly characterized virus cloned from the serum of a patient with posttransfusion non-A, non-B hepatitis, who was identified through CDC's Sentinel Counties surveillance system. Preliminary studies suggest that HGV accounts for 0.3% of all acute viral hepatitis in the United States.

Retrospective studies have shown that transmission of HGV has been associated with blood transfusion, but no cases of hepatitis G with a transfusion history have been detected in our Sentinel Counties surveillance system during the past 4 years. Although HGV can be detected by research-based polymerase chain reaction assays, no serologic test has yet been developed. Thus, it is not feasible to screen donors for HGV at this time.

Another potential threat to the blood supply is Chagas' disease, a parasitic disease caused by *Trypanosoma cruzi*, which is endemic in Latin America. Four transfusion-transmitted cases in North America (three in the United States, one in Canada) have been reported. However, these cases were recognized because they occurred in immunosuppressed persons who developed symptomatic, acute Chagas' disease. Presumably, other cases, particularly ones in immunocompetent persons, have occurred but have not been recognized during the acute stage. Persons whose infections are unrecognized may develop life-threatening cardiac or gastrointestinal sequelae of chronic Chagas' disease, years to decades after they become infected.

If cases of transfusion-transmitted Chagas' disease would occur in the United States, CDC is likely to be the first agency notified. Nifurtimox, the only drug available in the United States for treating acute Chagas' disease is available only through CDC's Drug Service. CDC was contacted about all three U.S. cases that have been published to date. They all occurred in the mid to late 1980s.

Various studies have been or are being conducted to determine the prevalence of *T. cruzi* antibodies among blood donors. By far, the largest of these is a study being conducted by the American Red Cross in its Los Angeles and Miami blood centers. Although serologic tests for *T. cruzi* antibodies have recently been licensed for diagnostic purposes, no such test has been approved for screening of blood donors.

CDC plans to assess the prevalence of *T. cruzi* antibodies in persons who have hemophilia and have received whole blood products. We will also work with the blood industry to better assess the risk for *T. cruzi* infection in blood donors and to evaluate strategies for their deferral.

Recently, concerns have been raised that Creutzfeldt-Jakob disease (CJD) may pose a risk to blood safety. CJD is a rapidly progressive cementing disease that is endemic throughout the world. CJD has been transmitted by injections of pituitary-derived growth hormones, corneal and aura mater transplantation, eardrum repair, and by contaminated surgical instruments. CDC's national mortality surveillance data since 1979 show that the rates of CJD in the United States have been reasonably stable at about 1 case per million population per year. Further, through this system, no cases of CJD have been reported among persons in the United States with hemophilia, thalassemia or sickle cell disease.

There are no confirmed cases of CJD from transfusion. Nevertheless, a theoretical, extremely small, risk of CJD transmission from blood may exist. Currently, there is no available screening test for the detection of CJD. FDA has recommended deferral of donors with risk factors for, or with known, CJD and withdrawal of residual blood products from donors who are later diagnosed with CJD.

To assess the risk of CJD transmission through the blood supply, CDC is working with hemophilia treatment centers to obtain clinical histories and neuropathologic examinations. These will be looked at for evidence, prospectively and retrospectively, of CJD in persons with hemophilia who die or have died with dementia. If CJD is indeed transmissible by blood products, its incidence in this population of heavily transfused patients is likely to be higher than the age-adjusted incidence of CJD in the United States. CDC has also initiated a collaborative long-term study with the American Red Cross to monitor recipients of components derived from CJD donors for this disease.

To address new and uncharacterized threats to the blood supply and detect unexpected clusters of known diseases, CDC is expanding its surveillance system in hemophilic persons to include nearly 2/3 of all hemophilic persons in the United States. This surveillance system will obtain data on all health outcomes in hemophilic patients receiving care in federally funded treatment centers. In addition, population-based emerging infections programs have been established in four state health departments (California, Connecticut, Minnesota, and Oregon), in partnership with universities and other organizations and agencies. In these programs a pilot surveillance system for monitoring unexplained severe illnesses and deaths has been initiated. Because this system collects information on receipt of blood transfusion it may assist in the identification of unrecognized transfusion-associated infections.

Education remains an important component of CDC's prevention activities. As new threats are characterized and further defined CDC will develop educational materials and provide information to the lay public, public health community and health-care providers about the risks of and preventive and therapeutic measures for these agents as it has done for other transfusion-associated diseases, such as HCV and HIV.

CONCLUSIONS

History tells us that infectious diseases will remain important, evolving and complex public health problems. To meet these challenges, we must strengthen our capacity to address the threat of emerging infectious diseases. In 1994, after extensive consultation and input from numerous outside organizations and experts, CDC released a plan, "Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States." This plan addresses necessary action for revitalizing our nation's ability to identify, contain, and prevent illness from emerging infectious diseases. Particularly critical to meeting the challenge are CDC's partnerships with both domestic and international organizations. Each of these partners will play an integral role in the cooperative efforts required to safeguard the public's health from emerging infectious disease threats. I would like to submit a copy of the full report for the record.

Investments in surveillance and response, laboratory research and training, and epidemiologic investigations cannot guarantee that an infectious agent will not emerge. However, such measures will ensure that we are better prepared to respond and to lessen the impact of infectious disease threats. In addition, they can guarantee that CDC will be able to identify which pathogens may be potentially hazardous to the blood supply. As the Nation's Prevention Agency, we will continue to be in the forefront of blood safety and will work in collaboration with other public health agencies, industry, private organizations, and health-care providers to refine our systems for monitoring the safety of the Nation's blood supply.

Thank you for the opportunity to testify before the Subcommittee. I will be happy to answer any questions you may have.

Mr. SHAYS. Thank you. We'll definitely have some questions. We appreciate your testimony.

Dr. McCurdy, we welcome your testimony at this time.

Dr. MCCURDY. Mr. Shays, Mr. Towns, members of the subcommittee, I'm Dr. Paul R. McCurdy, Director of the Blood Resources Program, Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute, one of the National Institutes of Health.

With me today and introduced previously are Dr. Pan Ganguly, who is the leader of our Thrombosis and Hemostasis Scientific Research Group in the Heart, Lung, and Blood Institute, and Dr. Stephen Groft, Director of the Office of Rare Diseases Research in the Office of the Director at NIH.

Mr. SHAYS. You know, I would welcome both gentlemen to come up to the panel. I'm sorry, I should have done that.

Dr. MCCURDY. I'm here to discuss the activities of the NIH in the field of transfusion safety, mostly by the NHLBI and the Transfusion Medicine Department of the NIH Clinical Center. I might add that we also, at the NIH, support the report of the Secretary, the report of the task force, and the response to the Institute of Medicine report.

The greatest public concern in transfusion safety is the potential for transmitting HIV, human immunodeficiency virus, by blood components and blood plasma protein derivatives. However, in the past decade, better blood donor screening, along with utilization and improvement of HIV antibody tests, has reduced the risk that an infectious unit of blood would escape the screen and be transfused from as high as 1 in 100 in the early 80's to now about 1 in 500,000.

Nevertheless, the NHLBI continues to seek even better detection systems by supporting research to develop tests for HIV RNA directly, using amplification techniques such as the polymerase chain reaction or PCR, as mentioned by Mr. Towns. The first priority of

two recent NHLBI research initiatives is to adopt this technology for blood bank use and for testing of solid organ donors.

Another serious infection agent transmitted by blood is Hepatitis C, of which you've heard a little bit this morning. Ten to 15 years ago, the risk of Hepatitis C infection from fresh blood products was about 5 to 10 percent per unit. That was extremely frequent. Now, recent unpublished data from the Institute's Retrovirus Epidemiology Study, or REDS study, have shown that the current likelihood of HCV infection after blood transfusion is about 1 in 100,000.

Because we believe this is not low enough, we have made detection of HCV RNA with amplification technology the second priority of the research initiatives noted above. Multiplexing these and other tests may permit the detection of more than one virus per test, thus increasing through-put without sacrificing sensitivity.

When considering new or emerging diseases, it is important to note, I think, that any infectious agent that has a blood phase before clinical symptoms appear potentially can be transmitted by blood transfusion. One such disease, Chagas' disease, has been discussed a few minutes ago.

Also brought up is Creutzfeldt-Jakob disease, or CJ Disease, a neurologic disorder that can be infectious or inherited, although most cases—perhaps 90 percent—are from an unknown cause. It may decrease muscle coordination and produce dementia, and, most troublesome, it is always fatal. Related animal disorders can be transmitted by blood, although there is no evidence, epidemiological or other, that the CJD agent is transmitted by blood transfusion.

The National Heart, Lung, and Blood Institute convened a small workshop of experts in CJD in April 1995, and we are now working with other NIH institutes and other public health agencies to carry out the recommendations of that workshop.

It has long been hoped that infectious agents and cellular blood components could be inactivated, but it seemed that anything that would destroy a virus would also destroy blood cells, making them lose efficacy or actually be dangerous for transfusion.

Nevertheless, hoping for new technology, the Institute in October 1993, sought research proposals to study the elimination of viruses in donated blood. The six grants in this program are now ending their first year of research, and we have scheduled a meeting with them to discuss progress with us and others for December 1995. We are also considering a workshop jointly with the FDA on this very important topic.

With the frequency of infectious agent transmission decreasing, other threats to transfusion safety, such as human error, have assumed increasing importance. One of our grantees is searching for ways to reduce human error in transfusion medicine practice by examining the efforts of other industries where zero tolerance for error is the norm, such as commercial aviation and nuclear power.

Although we have learned much about reducing the risk of transmitting infectious diseases through blood and blood products, many questions still remain. The NHLBI and other appropriate NIH components will continue to support research that addresses these questions in order to ensure the safety of the blood supply through

improved detection and inactivation technology. I would be pleased to answer any questions you or the committee may have.

[The prepared statement of Dr. McCurdy follows:]

PREPARED STATEMENT OF PAUL MCCURDY, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NATIONAL INSTITUTES OF HEALTH

Mr. Chairman and Members of the Subcommittee, I am Dr. Paul R. McCurdy, Director of the Blood Resources Program, Division of Blood Diseases and Resources, of the National Heart, Lung, and Blood Institute (NHLBI). The NIH has designated the NHLBI as the lead institute in transfusion-related research, including transfusion safety. The Department of Transfusion Medicine of the National Institutes of Health (NIH) Clinical Center also has been very active in research to improve the safety of blood transfusion, notably with respect to transfusion-transmitted hepatitis. I am pleased to provide you with an overview of NIH research activities in the field of transfusion safety.

TRANSMISSION OF INFECTIOUS AGENTS

Human Immunodeficiency Virus (HIV)

In considering blood transfusion safety, people are concerned about transmission of human immunodeficiency virus (HIV) by blood, blood components, and blood plasma protein derivatives. Prior to changes in donor acceptability criteria and the introduction of universal donor screening for HIV antibody in 1985, risk of contracting the virus from transfusion in high risk areas of the country was 1 per 100 to 1 per 1,000 units of blood. By 1989, NHLBI-supported research in Baltimore, Houston, and San Francisco demonstrated that utilization and improvement of HIV antibody tests had reduced the risk that an infectious unit of blood would escape the screen to about 1 per 33,000 to 1 in 100,000 units transfused. Data from the Centers for Disease Control and Prevention (CDC) and from another NHLBI-supported study, the Retrovirus Epidemiology in Donors Study (REDS), have led to the present estimate that approximately 1 in 500,000 HIV-infectious donations escape the screen.

Nevertheless, the NHLBI continues to seek even better detection systems by supporting research to develop tests for HIV ribonucleic acid (RNA) itself, using amplification techniques such as the polymerase chain reaction (PCR). The first priority of two recent research initiatives is to adapt this technology for blood bank use and for testing of solid organ donors. Blood banks perform large numbers of tests daily, and thus require highly automated techniques that will control costs and improve accuracy. Solid organ donors usually are tested singly, at odd hours of the day or night, by trained, but less practiced technical staff. The NHLBI expects that these tests will further reduce the time period between infectivity of blood or tissue and detection of the donor's antibody response to that infection.

Hepatitis C

Another serious infectious agent transmitted by blood is hepatitis C. After tedious and meticulous use of new biochemical tools, intense cooperative research by CDC and industry successfully isolated the hepatitis C virus and developed a specific antibody test for it. Although NHLBI-supported research was not involved directly in these breakthroughs, specimens collected as part of the NHLBI Transfusion-Transmitted Viruses (TTV) study to investigate surrogate or indirect tests for post-transfusion hepatitis (then called "non-A, non-B," now known as hepatitis C, or HCV) were used to help validate the role of HCV as a cause of disease and the value of an antibody test to detect donors most likely to transmit it. Ongoing studies of post-transfusion hepatitis, by the Transfusion Medicine Department of the NIH Clinical Center, begun in the 1960s, also demonstrated the value of surrogate tests in decreasing transfusion-associated disease. When NHLBI and NIH Clinical Center studies proved that hepatitis C was a serious disease and not, as some originally thought, a biochemical, or testing, phenomenon without clinical significance, blood banks universally adopted surrogate tests to test donated blood. NHLBI-supported research demonstrated the value of the surrogate tests, but later showed that the "second generation" hepatitis C antibody test provided all the benefits of the surrogate tests and more. These findings were corroborated by work in the NIH Clinical Center.

In the last 10 to 15 years, the risk of posttransfusion hepatitis C has dropped from as high as 1 per 30 units of blood to the most recent, as yet unpublished, estimate from REDS of about 1 in 100,000. This is partly the result of better donor screening practices, but primarily from universal use of second-generation tests for hepatitis C antibodies.

Risk of hepatitis C from blood transfusion is still of concern because of the relatively long "window" period between infection and development of detectable antibodies. Further, if an HCV vaccine is developed in the future, it may be difficult to interpret today's antibody tests, that is, distinguish true infection from a vaccine protection response. Therefore, the second priority of the research initiatives noted above is detection of HCV RNA using amplification technology such as PCR. An additional goal of this research is to develop "multiplexing" tests that will permit detection of more than one virus per test. Multiplexing should reduce costs without adversely affecting the sensitivity of the test procedure. When a multiplexed test is positive, the specimen can be retested for individual viruses so that the test implications for the donor's health can be assessed.

Our information indicates that the detection technology for virus nucleic acid (DNA and RNA) now has progressed to where it is feasible to test donated blood for portions of viruses themselves. Further, it is probably feasible to detect more than one virus per test. As noted above, and because we believe that this technology should be utilized, the NHLBI has a new research initiative to study such testing procedures and bring them to the point of approval for blood bank use. The top priority viruses are first, HIV, and second, hepatitis C. We believe that the technology will be readily extendable to other viruses, such as hepatitis G and hepatitis B.

EMERGING INFECTIOUS DISEASES

Any infectious agent that has a blood phase before clinical symptoms appear potentially can be transmitted by blood transfusion.

Chagas' Disease

In January 1995, the NHLBI, in conjunction with the NIH Office of Medical Applications of Research, the Clinical Center Transfusion Medicine Department, and the National Institute of Allergy and Infectious Diseases (NIAID), sponsored a Consensus Development Conference on Infectious Disease Testing for Blood Transfusions. The panel considered approaches to discontinuing tests that had outlived their value, and managing potential threats to transfusion safety from emerging diseases. They used Chagas' disease, caused by a protozoan parasite, as an example. This disorder is known to be transmitted by blood transfusion in Latin American countries where it is endemic. In some of these countries, blood banks are testing donated blood for antibodies to the Chagas' organism but, until recently, the available tests were rudimentary and crude.

Improved tests are being investigated in the United States, and considerable information is being gathered regarding protection of recipients of blood transfusions from Chagas' disease. The American Red Cross is studying these tests by selectively screening donated blood in parts of the United States with large numbers of people who have spent considerable time in endemic areas. Its goal is to determine if testing blood only from at-risk donors would suffice for eliminating blood-borne transmission, or if all blood donations should be tested. Positive antibody tests have been found in some numbers among donors at risk; all tests of blood from donors without risk factors have thus far been negative. These studies are continuing: more information may be provided later by the American Red Cross. As yet, Chagas' disease is relatively uncommon in the United States. Only a few cases of blood-borne transmission have been reported. Nevertheless, with increasing travel and immigration, this could change.

The NHLBI currently is supporting a study to determine the prevalence of antibodies to the Chagas organism in serum specimens from blood donors collected and stored in the REDS serum repository. Several thousand specimens are being tested.

Creutzfeldt-Jakob Disease (CJD)

Another disease that has caught the attention of those concerned about blood transfusion safety is CJD, a neurological disorder that can be infectious or transmitted genetically, although most cases are of unknown source. CJD may cause varying degrees of unsteadiness or difficulties of movement and dementia, and is always fatal. Similar animal disorders can be transmitted by blood, although there is no evidence, epidemiological or other, that the CJD agent is transmitted in blood transfusions.

In the past, a number of CJD cases have resulted from injections of human pituitary-derived growth hormone. However, human-derived materials have long since been replaced by hormone made as a result of genetic engineering, and therefore CJD is no longer a health risk from this treatment. Recently, however, several manufacturers withdrew from the market blood components and plasma protein derivatives that contained starting material-plasma from a donor who, months after donation, was diagnosed with CJD.

Some concern remains that the risk that CJD is transmitted by blood, currently theoretical, will be found to be real with further study. The NHLBI, therefore, convened a small workshop of experts in April 1995. The Institute is working with the extramural and intramural programs of the National Institute of Neurological Disorders and Stroke (NINDS) to follow through with the workshop recommendation that new assay systems for CJD be developed and applied to blood, blood components and blood plasma derivatives. Most current experimental animal assay systems require years to obtain an answer. The NHLBI is participating with the CDC in planning and designing some of the epidemiological studies that will be necessary to determine if CJD is transmitted by blood. NINDS and NHLBI staff also participated in an FDA meeting on June 22 on this topic.

VIRUS INACTIVATION

In the 1980s, the NHLBI supported research at the New York Blood Center to develop a solvent-detergent technique for inactivating viruses in blood plasma protein derivatives. This procedure is very effective against viruses with fatty envelopes, such as HIV, HCV, and hepatitis B virus (HBV), and it should work well against the newly discovered hepatitis G virus. Although an attempt was made, at the time, to apply virus inactivation technology to fresh blood and blood components, it seemed that anything that would destroy a virus would also destroy blood cells, making them lose efficacy or actually be dangerous for transfusion. With improving technology, in October 1993 the NHLBI again sought research ideas to eliminate viruses in donated blood. The six grants awarded as part of this program are now ending their first year of research. A closed meeting for the grantees to discuss progress with us and each other is scheduled for December 1995. One grantee is just beginning clinical trials of platelets treated with a process that, in test tube studies, inactivated infectious agents without damaging the platelets. Proof that this new technique is safe and effective in clinical situations will be necessary before it can be put into general use.

OTHER TRANSFUSION SAFETY RESEARCH

Blood Transfusion Substitutes

Substitutes for blood transfusion that will transport oxygen to the tissues, as do red blood cells, have long been sought. This is particularly so in the private sector since it is likely that a successful product will be used widely and be very profitable. In the past, most hemoglobin-based products have been found by their developers to have unacceptable toxicity; however, the information obtained in the research studies has been proprietary and has not been made public. The NHLBI is now supporting research to determine why hemoglobin-based products are toxic so that the problem can be corrected if possible.

Another NHLBI grantee is searching for ways to reduce human error in the practice of transfusion medicine by studying the procedures used by other industries where there is zero tolerance for risk, such as commercial aviation and nuclear power.

Transfusion in AIDS Patients

The NHLBI Virus Activation by Transfusion (VAT) trial will use sensitive techniques to study AIDS patients who need blood transfusions, to determine if one of the immunological consequences of allogeneic (from another person) transfusion is activation of viruses by those very transfusions. Viral activation could make the AIDS syndrome progress more rapidly and might actually shorten life. Other parts of the VAT trial will examine the potential for transfusion-induced graft-versus-host disease in these immunologically depressed patients. Transfusion-related graft-versus-host disease is serious, often fatal, and poorly understood. Its apparent rarity in transfused patients with AIDS is contrary to expectation. These studies may improve transfusion safety by increasing our knowledge of the immune consequences of blood transfusion.

INTRAAGENCY COORDINATION

Throughout the development and conduct of these studies, the NHLBI has kept CDC and Food and Drug Administration (FDA) representatives informed and often involved directly. For example, the CDC is represented on the REDS Steering Committee and both the FDA and the CDC participated in the CJD workshop noted above. The FDA and the NIAID were well represented on the Planning Committee for the Consensus Conference on Infectious Disease Testing for Blood Transfusions. CDC representatives made presentations of major import to panel members, who depended heavily on their data in developing the panel statement. The FDA co-spon-

sored the recent NHLBI workshop on "Microbial Contamination of Blood Components," and FDA data were used to help identify the issues.

In addition to these activities, representatives from the CDC, the NIH Department of Transfusion Medicine, the Armed Forces Blood Program and Blood Resources Program, and the NHLBI participate in monthly conference calls chaired by Dr. Epstein, FDA. The monthly conference call provides a forum for exchange of information on emerging or continuing problems in transfusion medicine, and allows the NHLBI to inform the other groups about Institute activities. Follow-up calls further enhance these communication efforts.

Although we have learned much about reducing the risk of transmission of infectious agents through blood and blood products, many questions still remain. The NHLBI and other appropriate NIH components will continue to support research that addresses these questions in order to assure the safety of the blood supply through improved detection and inactivation technology.

I would be pleased to answer any questions you or the Committee may have.

Mr. DAVIS [presiding]. Thank you. We'll start the questions now. Mr. Towns, let me start the questioning with you.

Mr. TOWNS. Thank you very much. Let me begin with you, I guess, Dr. McCurdy. You described current research initiatives to develop amplification techniques, such as the PCR. Are you aware that this is a technology that is also being pursued in the private sector with some positive results?

Dr. MCCURDY. Yes. We are well aware of many of the efforts. Until fairly recently, there have been very few of these efforts directed toward blood transfusion and screening blood donors, based on concern that the technology was too difficult and too sensitive for that purpose. We have reasons to believe this is not the case, which is why we're pushing forward for its use in transfusion medicine.

Mr. TOWNS. Right. Well, even with the progress that they've made, how can the government benefit from this private sector progress? How can we?

Dr. MCCURDY. I think that what our initiatives were seeking were members of the private sector to proceed more rapidly than they might on their own, than we perceive them to do on their own, to bring such testing to market.

If there are private sector organizations that are willing or able to do it on their own—and we have some information that that may be the case—then we won't interfere, certainly. But our approach is to try and stimulate this so that it comes to market as soon as possible.

Mr. TOWNS. All right. Thank you very much. What additional steps do you suggest that the blood banks and transfusion services take to improve safety?

Dr. MCCURDY. Well, I think that what we have been doing is emphasizing these improved tests. I think the PCR technology that we were talking about a minute ago was focused on HIV. I think it's equally important to focus on Hepatitis C virus since there's a longer window, and there may be developed in the future a vaccine that would confound the antibody tests that are now being used.

So I think improving these tests, multiplexing these tests so that more than one test can be done at a time, thus improving efficiency, are the ways to go.

I mentioned the REDS study of the Institute. This study has been looking very carefully at donor infectious disease markers, seroconversions, and particularly looking at how donors respond to

the questions that are posed to them as part of their pre-donation process.

We hope and expect to refine the questions that are asked so that we'll get the answers that are important and will jig the memory of people who may have forgotten some at-risk behavior that they had in the past.

Mr. TOWNS. Also, you state that the NIH is considering approaches to discontinue tests that have outlived their value. Could you provide some examples of these outdated tests?

Dr. MCCURDY. We held a consensus development conference in conjunction with other NIH components last January, and the two issues were, one, are there any tests that no longer serve their purpose, and two, how do you determine how to institute new tests? How do you approach emerging infections?

The panel came up with the recommendation that the ALT test, which had been put in as a surrogate test to test for non-A, non-B Hepatitis—non-A, non-B Hepatitis is now known mostly to be Hepatitis C—and they came up with a recommendation that that test be discontinued as having outlived its usefulness.

I believe that the blood banking community has generally accepted that recommendation. I don't know how far they are in discontinuing that test. The Hepatitis C test, the antibody test, provided much better safety than the ALT test did, and the ALT test was found not to give any added improvement.

Mr. TOWNS. All right. On that note, do you think that the—and I'm always concerned about communication, in terms of how information gets around. Will the advisory board help in that regard? How can we improve, what can we do here in the Congress?

Dr. MCCURDY. The Blood Safety Committee that you're talking about?

Mr. TOWNS. Yes.

Dr. MCCURDY. I think that certainly will help with communication and provide a focus to deal with many of the issues that have been brought up today and will be brought up later today.

Mr. TOWNS. Let me just ask Dr. Satcher one question.

Mr. DAVIS. If there is no objection, sure.

Mr. TOWNS. Yes. Dr. Satcher, does CDC control the distribution of certain drugs in order to attract blood-borne diseases? Is that correct?

Dr. SATCHER. Yes. An example of that is pentamidine for treating Pneumocystis carinii. The increased request for this drug in the early 1980's was one of the indications that something was going on in terms of the incidence of this unusual infection.

So this is one example of where CDC controls the distribution of a drug that is so rarely used that it's not approved for general distribution, but it also allows us to monitor diseases that are treated with this drug. There are other examples, but when you go back and look at the history of the HIV infection, AIDS, I think the control of pentamidine is a good example of that strategy.

Mr. TOWNS. Thank you very much. I yield.

Mr. DAVIS. Thank you very much. I recognize the gentleman from Indiana, Mr. Souder.

Mr. SOUDER. Thank you, Mr. Chairman. In our earlier hearing, we heard some concerns about warning and how, in the past, a

number of things have been missed. How does the CDC plan to implement recommendation 5 of the Institute of Medicine report, which recommends that the Public Health Service establish a surveillance system lodged in the CDC that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products?

Dr. SATCHER. I think—and I'll ask Dr. Khabbaz to also comment on that—but let me say that I think we have developed surveillance systems, especially utilizing the hemophilia population. We monitor very closely the health of this population, the response of this population which receives an excess of blood products.

And, therefore, any change in terms of new threats, new diseases, in this population, we monitor very closely. We try to trace back to the donor and to try to discover what the problem is and whether or not it relates to a donor in the blood supply. So I think that's probably our best surveillance technique right now, because there are so many people in this surveillance system.

There are other examples. Do you want to add some examples to that?

Dr. KHABBAZ. Yes, sure. I think Dr. Satcher has already alluded to our existing surveillance system. We have a number of disease-specific surveillance systems, and we plan to enhance them.

For instance, I'll give you an example. For Hepatitis viruses, we have two systems, a national system, and we have one based on four sentinel counties, if you may, that allows us to get more specific serologic test results, and we can look at newer Hepatitis viruses, and we plan to expand the system so that we can get the numbers to better assess transfusion transmission.

With regard to the hemophilia surveillance system, we are in the process of expanding it to look for other health outcomes, as well, and monitor for clusters of diseases or other markers to be able to detect newer, unknown threats.

As part of our emerging infection programs—and Dr. Satcher alluded to—we have four emerging infection programs, and in those we are piloting a surveillance system to look for unexplained illnesses and deaths that may be infectious, and we do ask about a history of transfusion.

So that's another system that we think will help us look for unknown threats. We continue to work with other agencies and other groups and will explore other ways to improve and address threats as they arise.

Mr. SOUDER. Nothing is much more touching than to talk with somebody who is dying because of their blood transfusion, particularly hemophiliacs. I met with one young father who no longer can hold a job, and he has—he's only in his 30's.

What warning system is there going to be? You're doing the checking. How soon can you catch that? Are you getting out quickly to the people who would be most affected? How long do you wait in some of the research to check it and try to find a person before you give a warning?

Dr. KHABBAZ. I think, in general, we are in the process, as soon as we gather enough information to establish a threat, then we go out with information. And within the hemophilia community, we

have a number of information systems developed to quickly allow that to happen.

Dr. SATCHER. That also, I think, indicates, though, the importance of this partnership. Some States are better prepared to report new illnesses than other States are, and that's why we're concerned about the strength of the public health laboratories in all of the States throughout the country.

Right now, of course, we're developing some special projects. We mention four States; there are 10 other States that are involved in the sentinel system. But, ultimately, we need to have strong State public health laboratories and a very strong reporting relationship in order to detect things as early as possible, and we need to respond as rapidly as possible.

Mr. SOUDER. Another thing that's very difficult and controversial, and I would appreciate your comments on, does payment for plasma donation reduce the safety of the product, as opposed to volunteers? Does it stimulate some people who maybe shouldn't be giving blood to give blood? Could you give your comments on that?

Dr. SATCHER. I would be interested in Dr. Evatt's responding to that, because I think there are two perspectives on that. It depends. I know that we generally say that, because of the people who appear to give blood for money, that generally it's high risk. And that's probably generally true, but I think there's another angle.

Dr. EVATT. Yes, and there's two different ways of looking at it, one from the point of view of the individual transfusion recipient. The second is from a pool of plasma-derived product.

In general, volunteer donations comprise recovered plasma, which comes from—and so it usually goes into a pool of multiple individual donors. Plasmapheresis is—it's usually the material that's collected by plasmapheresis goes into a pool of products and is comprised, usually, of repeat donors, and so there's fewer donors in the pool.

Depending on the type of disease, volunteer donors are considered to be a safer donor pool, primarily because there's no incentive for them to donate, for example, from the lower socioeconomic levels, where they may be associated with certain blood born diseases, such as Hepatitis.

On the other hand, the fewer donors that go into a plasma pool from repeat donors, where the donors are clearly identified and monitored very closely, may be safer in some instances.

Also, not all infectious diseases that are transmitted in blood are not necessarily associated with lower socioeconomic groups. For instance, in the early days of HIV/AIDS, AIDS was not necessarily a lower socioeconomic level infection. It was frequently associated with the higher socioeconomic groups, which were volunteer donors, in the beginning stages of AIDS. And so I think that it depends on the disease, and it depends on the balance.

I think there's no good answer to that question currently. In reality, there's not enough recovered plasma that comes from volunteer donation that is sufficient to supply the needs of industry for plasma products that are made from those donations, so that plasmapheresis is the only way to obtain that.

In countries where there are rules that suggest that only volunteer donors can go into pools, those countries are extremely rare, and almost no country is able to obtain enough self-sufficiency with plasma to meet the needs of the plasma-derived products.

Mr. SOUDER. Thank you.

Mr. DAVIS. Thank you very much. The gentleman's time has expired.

Let me start with a question, Dr. Satcher. I noted in your testimony, you noted that one variant of HIV–1 known as subtype O may not be readily detected by some commercially available screening tests. What strategies does the CDC have in place to confront HIV?

Dr. SATCHER. Well, it's a very important observation because, again, it points out that the biggest risk that we face, I think, is the risk of these new and emerging infections. This variant of HIV–1 is an example, subtype O.

Among the strategies that we have in place, and of course, is the surveillance system to detect it, not only in this country. I was recently in Uganda, where I visited the Uganda Viral Research Center, where we have a laboratory.

In that laboratory, one of the things that we're doing is monitoring the incidence of HIV–1 subtype O. We know that in that area of the world, subtype O is more common, so we're trying to learn as much as we can about it, wherever it occurs in the world.

And I wanted to point out, I think that's one of the responsibilities that we, the CDC, as the prevention agency of this country, has, and that is to monitor the emergence of new diseases, wherever they occur in the world. We cannot protect the health of the people in this country unless we know as much as we can know about new diseases, wherever and whenever they occur.

So we do have field laboratories throughout the world. Not just CDC—the Department of Defense has field laboratories; NIH has laboratories; and we're trying now to better network those laboratories than we have in the past. But subtype O is an example where the surveillance system cannot be limited to this country and answer the questions that we need to answer about this new variant.

Mr. DAVIS. OK. But your comments said that some of the commercially available screening tests didn't do it. Is there a screening test that works?

Dr. SATCHER. We think now—do you want to comment more about that? We think now that there is, but at the beginning, I think it's true that we were not detecting all of the subtypes.

Mr. DAVIS. Sure. This is one of the success stories, as we've tracked it down.

Dr. SATCHER. Right.

Dr. KHABBAZ. Some of the tests were not able to detect. I think we've been working with FDA and industry, and we've looked at a number of modified tests that have been developed that are better able to detect these variant strains. And, like Dr. Satcher noted, HIV type O may be just one spectrum of variants, and we continue to work on detecting new variants and go back and assess existing tests and work with industry and others to make sure that the tests improve.

Mr. DAVIS. Let me follow up on a question Mr. Souder raised and the answer, and see if either one of you would like to amplify. Do you think that a reduction in plasma pool size would provide greater safety for hemophiliacs and other patients dependent on treatment derived from pool plasma?

Dr. EVATT. Reduction in pool size carries with it, of course, a smaller risk, because anytime you reduce the number of donors' exposure for any given dose of medication, it does reduce the risk. So donor pool size is equivalent to risk.

On the other hand, there are certain other factors which go into this, including the ability to manufacture smaller pools in a way that will allow a cost-effective provision of medication. I think the most effective people to speak to this is probably industry, who have the information that can tell you whether or not a donor pool size is practical from their point of view. But clearly, reducing the donor size does reduce risk.

Mr. DAVIS. OK. Anyone else want to add anything to that? Let me ask, also, how is the NIH addressing the need for research into other treatments, and particularly non-blood-based treatments for hemophilia?

Dr. MCCURDY. We have had in the past a considerable research effort in the molecular aspects of hemophilia, the molecular genetics of it, and, as a result of those and other studies, recombinant Factor VIII is now available. Recombinant Factor IX will be available sometime in the near future. It's under test. These are genetically engineered and not from human sources.

We also have a sizable program in genetic treatment of hemophilia, which is a ways away, probably, but is another approach to this. If you would like more information on the genetic area, Dr. Ganguly can elaborate.

Mr. DAVIS. I would like some follow-up on the genetic area.

Dr. MCCURDY. Follow-up in writing? Fine.

Mr. DAVIS. We thank the panel. Mr. Towns? Sure, I would be happy to yield.

Mr. TOWNS. BPAC, the Blood Product Advisory Committee, has recommended against antigen screening despite a unanimous finding that the tests were very effective. Ostensibly, this recommendation was made because of concerns over the cost of the tests. That's the information that's out there. How do cost considerations influence the development of testing procedures that would improve blood safety? What role does cost play in this?

Dr. SATCHER. Let me say two things. I think—and Dr. Khabbaz is our appointment. I think you know that CDC now has a representative on the BPAC.

Mr. TOWNS. Yes.

Dr. SATCHER. And Dr. Khabbaz is our representative. I want to make one comment, though.

Mr. TOWNS. Congratulations.

Dr. SATCHER. It's a very important question. According to the guidelines of BPAC, as I understand them, cost is not supposed to be one of the things that BPAC considers in making recommendations.

Mr. TOWNS. Right.

Dr. SATCHER. However, I think, realistically, cost certainly affects availability. But I don't believe the issue in terms of the p24 antigen was limited to cost. And I say that—you know, I'm not on BPAC, but my impression was that it was sort of a judgment as to the efficacy of this particular screen in terms of the risk of attracting more people as blood donors, as opposed to, I guess you would detect about six more cases of HIV than you would if you did not include the antigen screening.

But, as you know, Commissioner Kessler did not agree with BPAC's advice, and he has the final say in terms of that. Do you want to comment further?

So I think, in answer to your question, theoretically, cost is not supposed to be a factor in the considerations of the advice of this scientific advisory committee. And yet we are continuing to question the availability and the ability to provide. Some of the industry people would probably want to comment on that further.

Mr. TOWNS. Right. Well, I raise this for several reasons, in terms of, as we do the budget and as we talk about dollars, and we also have to think about in terms of savings lives.

Dr. SATCHER. Sure.

Mr. TOWNS. I just don't want this get lost in terms of our activities around here. I know it's also difficult sometimes to openly discuss these matters, because the point is that we don't want to scare people, either.

Dr. SATCHER. Exactly.

Mr. TOWNS. And I understand that. So it's a very delicate, kind of situation that we now find ourselves in. But I think that those folks who insist upon just cutting everything, I think we need to sort of look at what we're doing, because if we sometimes spend money, on the front burner, we don't have to spend it on the back burner.

And I think that, somewhere along the line, we have to help to make this case, and it's not being made too well around here today, and I think that somewhere along the line, it's going to require further discussion.

Dr. SATCHER. I think you're absolutely right. I think one of the real challenges that we face is improving communication. We haven't talked about the new Advisory Council on Blood Safety and Availability that will report to the Blood Safety Committee, which reports to the Blood Safety director.

But the idea there is to have the kind of people on that Advisory Council who can look at social, ethical, legal, and business considerations in looking at these issues. I think that's going to help. They have a major responsibility, representing more of the general population's concerns about the blood supply, but also helping to communicate to the general population issues related to the blood supply.

I think you're right. I think one of the major challenges we face is improving communication among ourselves, among the agencies, with industry, but also making sure that providers out there on the front line and the patients with whom they interact have as much information as they can get about these issues.

Mr. TOWNS. All right. Thank you very, very much. I would like to thank all of you for your testimony. I yield back, Mr. Chairman.

[Additional information on research follows:]

ADDITIONAL INFORMATION FROM DR. MCCURDY AND DR. GANGULY ON RESEARCH SUPPORTED BY THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Question. What research does the National Heart, Lung, and Blood Institute (NHLBI) support to improve the safety of treatment for hemophilia?

Answer. Hemophilia is a hereditary bleeding disorder that is characterized by a deficiency of blood proteins called clotting factors. Hemophilia A is caused by a deficiency of Factor VIII and hemophilia B is related to Factor IX. Hemophilia treatment usually entails a risk of infection because it requires transfusion of purified quantities of the missing factor isolated from donated human blood. Obtaining therapeutic quantities of these factors requires pooling plasma from a number of donors, a process that necessarily increases the risk of transfusion-related infections. The NHLBI is seeking to eliminate the risk by supporting research to produce the clotting factors without use of human blood.

The NHLBI hemophilia research program has provided the foundation for advances in hemophilia diagnosis and treatment. Basic research on hemophilia led to the isolation and characterization of the deficient clotting factors and their genes. A genetic defect that affects about half the families with severe hemophilia A was identified by a NHLBI grantee and an assay to detect it has been developed that can be performed with only a small blood sample. This information on the protein and gene structure was essential to the development of recombinant Factor VIII, which is produced without the use of human blood. Recombinant Factor VIII effectively stops bleeding in severe hemophiliacs and is now commercially available. Recombinant Factor IX has also been produced; the results of its effectiveness trials are expected in a few months.

Gene therapy to insert the missing clotting factor gene into cells of hemophilia patients could lead to continuous production of the deficient clotting factor and may be the next major advance in hemophilia treatment. The NHLBI has provided leadership in this area. For example, in 1994, the Institute implemented a major initiative on gene therapy in hemophilia. Significant progress has been made in obtaining, modifying, and inserting hemophilia genes in animals. Although initial results appear promising, longterm expression at a therapeutic level of genes inserted into cells of large animals has been difficult to obtain. Additional studies are needed on the level and duration of gene expression before these procedures can be used in human trials.

The results of gene therapy studies for hemophilia are likely to provide information that will also be useful in the development of gene therapy procedures for other genetic disorders. The recent development of a transgenic mouse model of human hemophilia by an NHLBI grantee should expedite studies of gene therapy protocols. These developments hold promise for ultimately developing a cure for hemophilia without running the risk of a transfusion-associated infection.

In addition to the answer provided by Dr. McCurdy, the National Institutes of Health (NIH) provided an itemized report of all intramural and extramural research on hemophilia and other coagulation disorders funded by the NIH in FY1994 and FY1995. These documents are in Subcommittee files.

Mr. DAVIS. Thank you. And I thank you all, as well. Thank you very much.

We call now our second panel. The second panel will be Karen Shoos Lipton of the American Association of Blood Banks, Dr. Toby Simon of the Council of Community Blood Centers, and Dr. Richard Davey from the American Red Cross.

As you come forward, if you could get behind your seat and just remain standing, I'll swear you in.

[Witnesses sworn.]

Mr. DAVIS. Thank you. Thank you very much. Why don't we start with Ms. Lipton.

STATEMENT OF KAREN SHOOS LIPTON, CHIEF EXECUTIVE OFFICER, AMERICAN ASSOCIATION OF BLOOD BANKS; TOBY SIMON, PRESIDENT, COUNCIL OF COMMUNITY BLOOD CENTERS; AND RICHARD J. DAVEY, CHIEF MEDICAL OFFICER, AMERICAN RED CROSS BIOMEDICAL SERVICES

Ms. LIPTON. Thank you. Mr. Davis, Mr. Towns, and members of the subcommittee, I am Karen Shoos Lipton, chief executive officer of the American Association of Blood Banks. Thank you very much for this opportunity to discuss the role of our association in ensuring the safest possible blood supply. Most of our comments are contained in our rather lengthy written statement, and I would like simply to highlight a few of the items in there.

Since we began in 1947, the AABB has promoted quality assurance through the adoption and publication of standards for blood banking, through the AABB Technical Manual and its other publications, through our educational programs, and through our inspection and accreditation program.

Beginning in the early 90's, the AABB began transitioning our traditional error detection systems to systems that emphasize error prevention, and in 1994, we introduced the AABB quality program that offers an error prevention system for use in individual blood collection and transfusion facilities.

We have worked closely with the Council of Community Blood Centers and Orthodiagnostics on the development of a separate quality engineering training program that's currently being offered around the country to our members. This year, the Health Care Financing Administration granted the AABB inspection and accreditation program "deemed status" to inspect laboratories for compliance with the Clinical Laboratory Improvement Amendments of 1988.

But most important to us this year is the restructuring of our inspection and accreditation program. Our 800 volunteer inspectors will now receive additional and advance mandatory training, and, in addition, we're in the process of developing separate specialized programs for our blood collection facilities and our hospital transfusion facilities.

With regard to the emerging infectious agents and the effects of technology on the blood banking community, AABB's written statement noted the following: First, bacterial contamination is a top priority for us right now. Our volunteer committees, which include some of the best experts in the world in blood banking, are now evaluating technology that, at least on an interim basis, will hopefully reduce bacterial transmission by identifying the contamination prior to transfusion.

With respect to Creutzfeldt-Jakob Disease, AABB has added two questions to the Uniform Donor Health History questionnaire, in spite of the fact that, as Dr. Satcher stated, there is no evidence of the transmissibility of CJD through blood transfusion.

Chagas' disease is rare in the United States, but fairly endemic in Latin America, and with increasingly mobile populations, Chagas' disease is a potential threat to our blood supply. A diagnostic test is currently available, but the practical application and success of its use in the blood donor setting are still being evaluated. The AABB is working toward identifying what we hope will

be an optimal mix of donor questioning and serological testing to ensure the maximum prevention of Chagas' transmission.

HCV look-back is another issue currently under debate. Although the Association has periodically reviewed this issue, we have not supported the concept in the past for several reasons.

First, the disease is prevalent in the population from other sources; second, the earlier test, with less specificity, simply could not distinguish between those carrying the infection and those who had recovered from infection but retained residual antibodies; and third, there were no successful intervention therapies available.

With the advances in testing now and the availability of interferon as a possible treatment for HCV, the AABB is currently reconsidering its position. The AABB also strongly agrees that Hepatitis C look-back is an appropriate issue for the Blood Safety Committee. We emphasize, however, the need to address look-back for all potentially transfusion-transmitted diseases as a public health issue.

Our actions, we believe, speak for themselves. As an independent professional association representing the blood community, we have been seeking safety improvement since our inception in 1947. That's our business. Transfusion medicine is a balance of science, societal, and ethical issues that must be judged when considering the impact on both safety and adequacy of the blood supply.

Over the years, we have worked with other blood organizations, with the National Institutes of Health, the FDA, and the Centers for Disease Control, through consensus conferences, the IOM forums, and other joint programs. We're continually seeking new avenues to identify issues and achieve solutions and interim improvements.

We were pleased with the IOM recommendations and impressed with the quick action of HHS to elevate the decisionmaking authority with regard to blood safety and adequacy to the highest levels within that department.

We plan to work with Dr. Lee and others in any way we can, and, in fact, we have invited Dr. Lee to address the 6,000 attendees at our annual meeting next week in New Orleans. He would have there a unique opportunity to address the entire blood banking and transfusion medicine community.

Finally, from our perspective, scientific research is at the heart of all solutions in any emerging disease. Equally important, blood is only as safe as the donor. Education of donors is absolutely critical to increasing the safety and availability of blood. We need more research and more education, and we need both quickly.

At the bottom line, that means more resources for our community, already stretched thin with the very significant pressures imposed by enhanced regulatory attention and cost control and for agencies currently pressured to do more with less. We encourage you to encourage your colleagues to support the Public Health Service agencies, specifically the FDA, the Centers for Disease Control, and the National Institutes of Health. Thank you.

[The prepared statement of Ms. Lipton follows:]

PREPARED STATEMENT OF KAREN SHOOS LIPTON, CHIEF EXECUTIVE OFFICER, AMERICAN ASSOCIATION OF BLOOD BANKS

Mr. Chairman and members of the Subcommittee, I appreciate the opportunity to appear before you today to discuss the role of the American Association of Blood Banks (AABB) in ensuring that the safest possible blood is provided for the health care needs of the American people.

In your invitation to testify you asked that witnesses focus their testimony on the recent Institute of Medicine report HIV and the Blood Supply: An Analysis of Crisis Decision Making (IOM REPORT), emerging infectious agents in the blood supply, quality practice standards and application of new technology to improve blood safety.

Before responding to your questions, I first want to lay some groundwork that I believe is crucial to understanding the AABB's positions on these issues, as well as the AABB's overriding concerns for safety of the blood supply.

I. THE AMERICAN ASSOCIATION OF BLOOD BANKS

I am Karen Shoos Lipton, Chief Executive Officer of the AABB. The AABB is a not-for-profit professional, educational, scientific and administrative association established in 1947. Our mission statement today—adopted in 1990 as part of our continuing effort to support the blood banking community in its quest for the safest possible blood supply—is to establish and promote the highest standards of care for patients and donors through leadership in all aspects of blood banking and transfusion medicine.

Specifically, the AABB:

i) sets standards in blood banking and transfusion medicine for voluntary compliance by association members,

ii) operates a voluntary inspection and accreditation program for member facilities that is specially designed as an educational program to measure performance against AABB standards and

iii) provides continuing education in blood banking and transfusion medicine on topics related to compliance with AABB standards, FDA regulations, and emerging science and medical technology in the fields of blood banking and transfusion medicine through periodic news publications, seminars and teleconferences and our premier educational program which takes place each year at an annual association meeting.

The AABB institutional membership includes more than 2,500 community and Red Cross blood collection centers, hospital based blood banks and transfusion services. These facilities collect, process and distribute virtually all of the nation's blood supply and transfuse more than 80 percent. Almost 9,000 physicians, scientists, medical technologists, administrators, blood donor recruiters and nurses involved in all aspects of blood banking and transfusion medicine are also individual members of the AABB.

A. AABB Standards and Guidelines

AABB standards are published periodically in Standards for Blood Banks and Transfusion Services (AABB Standards). AABB Standards are developed through a careful and thorough process that elicits the consensus of the leading authorities in transfusion medicine. The Technical Manual of the American Association of Blood Banks (AABB Technical Manual) is a supplementary textbook publication to AABB Standards that outlines blood banking and transfusion medicine techniques.

Experts representing all aspects of blood banking, transfusion medicine and related science and medical technology are asked to serve on standing volunteer committees. The AABB Committee on Standards is charged with reviewing specific issues and developing proposed standards. Proposed standards are provided to the AABB membership for comment. The Board of Directors, which is composed of individuals with blood banking and transfusion medicine expertise in their own right, has the ultimate responsibility to collect all information and recommendations and adopt the standards for voluntary compliance by the members.

Issues raised between revisions of Standards are addressed in a similar fashion, but on an expedited basis with publication of interim policy statements and/or standards through Association Bulletins issued to members. Emerging issues are traditionally reviewed by the standing committee with the best expertise applicable to those issues. Issues concerning HIV antigen testing and implementation, for example, are referred to the AABB Committee on Transfusion Transmitted Diseases (TTD Committee) for the purpose of considering scientific and medical issues associated with antigen testing. The Board of Directors takes the committee recommendations and incorporates them into interim policy statements, and where appropriate,

the Standards Committee formulates for member consideration and Board approval interim standards.

B. Education

As part of our mission, the AABB strives to educate its members and the public about emerging science and technology in transfusion medicine and to analyze blood policy issues. Vehicles for education include publishing monthly and weekly newsletters and the peer reviewed medical journal, Transfusion; operating a voluntary educational biannual inspection and accreditation program; and producing state-of-the-art educational programs utilizing the latest communications technology.

The Annual Meeting is the AABB's premier educational event and has proven to be one of the most effective methods of communicating with professionals in the fields of blood banking and transfusion medicine. Next week the 1995 meeting will take place in New Orleans. Almost 4,000 people are registered with an anticipated attendance of over 6,000. Topics covered in seminars and workshops range from assessment of the latest science and technology to administrative forums. Although I was only able to do so on short notice, I have invited Blood Safety Director, Philip Lee, MD to speak at the meeting's National Affairs Symposium. The meeting offers a unique opportunity for Dr. Lee to begin his tenure by describing the HHS agenda under their new structure for the entire regulated community. We are eager to work with both Dr. Lee and the new Blood Safety Committee.

C. AABB Inspection and Accreditation and Quality Programs

The AABB's Inspection and Accreditation Program (I&A Program) is administered by an oversight committee composed of volunteers and supported by over 800 volunteer inspectors. Since compliance with state and federal regulations is required for AABB accreditation, AABB inspectors must be especially knowledgeable about the blood regulations and the Good Manufacturing Practices promulgated in Title 21 of the Code of Federal Regulations, as well as FDA's blood establishment related memoranda and other guidance documents. This year, the Health Care Financing Administration granted the AABB I&A Program "deemed status" to inspect laboratories for compliance with the Clinical Laboratory Improvement Amendments of 1988.

In August 1994, the association introduced the AABB Quality Program to provide blood banks and transfusion services with the tools needed to develop a specific, detailed, and formal quality assurance program that will generate self-assessment data through a system of checks. By assessing the root causes of deficiencies themselves, institutions are able to develop and implement improvements to their standard operating procedures and systems. This program supports FDA initiatives in quality assurance.

As AABB members implement quality assurance plans, the I&A Program will transition away from current spot reviews for deficiencies to quality audits that focus on a blood bank's mechanisms for ensuring that its products and services meet all requirements. The AABB inspector will concentrate on verifying that staff consistently evaluate the success of the blood bank's quality plan.

To meet these new challenges, the AABB is devoting significant resources this year to a major restructuring of the I&A Program. Inspectors will receive mandatory training. Specially designed separate programs are being developed for blood collection facilities and hospital transfusion facilities.

II. AABB'S RESPONSE TO THE INSTITUTE OF MEDICINE'S BLOOD SAFETY RECOMMENDATIONS

With that groundwork in mind, I report that the AABB supports the recommendations in the IOM Report. We submitted for the record of this Subcommittee's October 12 Oversight Hearing on HHS Management of Possible Threats to the Nation's Blood Supply the attached October 3 letter to HHS Blood Safety Director Philip Lee, MD. We were pleased to learn from Secretary Shalala's recent testimony to this Subcommittee that the Department has restructured the blood programs of the Public Health Service (PHS) to promote high level coordination between the blood programs of the PHS agencies so that optimal blood safety policy is quickly and efficiently developed. We have already initiated communications with Dr. Lee and the new Blood Safety Committee.

As noted in the letter, the IOM Report raised some significant limitations in the way that the federal government developed blood safety policy in the early 1980s. However, the report did not reflect the progress that has been made in blood safety in the intervening years.

Since 1984, six new infectious disease tests have been incorporated into the FDA required practices of blood collection establishments. Among these tests is the HIV

antibody test designed to reduce the risk of HIV transmission through blood transfusion, and tests to detect hepatitis viruses. Increasingly sensitive HIV antibody tests have been adopted as the technology has improved. The risk of acquiring HIV from a unit of donated blood has been reduced to about 1 in 420,000. Implementation of a screening test for the antibody test to the Hepatitis C virus has reduced the risk of transfusion associated Hepatitis C to 1 in 4,000 or less.

Prospective blood donor screening procedures have been continually revised to reflect the better understanding that we now have from additional research that there is a need for clearer and more direct questioning. The AABB, in fact, has developed a Uniform Donor History Questionnaire that has been reviewed by the FDA and is used by members as a basis for developing their own SOPs. The questionnaire is revised as necessary and has recently been revised to address concerns regarding Creutzfeldt-Jakob Disease. Building on this progress, the AABB supports additional measures to enhance blood safety.

III. HIV ANTIGEN TESTING

Consistent with the IOM recommendation that interim actions be taken where complete answers are not available, the AABB spoke in favor of FDA licensure of HIV antigen test kits for screening volunteer blood donors for HIV. In fact, it was largely an AABB initiative that prompted FDA action. As has become clear in recent studies, a short incubation monoclonal HIV-1 antigen test reduces the "window period," the time immediately after HIV infection when licensed tests are unable to detect an HIV infected blood donor, from 22 to 16 days. Since current licensed HIV blood screening tests in use in blood collection facilities only test for the HIV antibody, blood donated after donors are infected with HIV but before their bodies produce antibodies to the virus are not detected as HIV positive. Transfusion medicine scientists estimate that HIV antigen testing would additionally identify approximately 10 donations capable of transmitting HIV through blood transfusion each year, with minimal loss of units suitable for transfusion.

Continued study of the epidemiology of HIV today suggests that transmission of the HIV virus is occurring most rapidly from those individuals who are least likely to recognize, or be aware of, their own risk—and therefore to self-defer on the basis of questions asked of donors—such as partners of intravenous drug users. This shift underscores the significance of testing as a means of identifying those individuals at risk of transmitting HIV.

The AABB believes that all efforts to increase safety must be taken to ensure that the public's confidence in the safety of the blood supply is restored. The Association applauds the FDA's decision to move forward on HIV antigen testing by releasing the August 8 memorandum entitled Recommendations for Donor Screening with a Licensed Test for HIV-1 Antigen. Although a test is not yet licensed, the AABB is helping blood collection facilities to prepare for immediate action as soon as a test is licensed.

The AABB has already taken a number of steps to assure smooth adoption of HIV antigen testing by blood collection facilities:

1. We just published an article in the AABB Weekly Report providing information on implementation of HIV-1 antibody testing.
2. We are cosponsoring a public workshop featuring speakers from the pharmaceutical companies with applications for antigen test kits pending next Tuesday, November 7. They will discuss implementation issues with blood bankers to better enable them to plan for implementation.
3. At a recent meeting with the FDA to clarify issues raised by our members, we were able to obtain clearance, for the first time, for blood collection personnel to train with sample test kits in advance of license approval.
4. AABB committees have been specifically charged with developing standards and guidelines for HIV antigen testing. Recommendations are anticipated in time for licensure.

IV. EMERGING INFECTIOUS DISEASES AND NEW SCIENCE AND TECHNOLOGY

In response to your request for comment on emerging infectious diseases and new technology, I'd like to report to you on the AABB's response to the recently highlighted challenges presented by bacterial contamination of blood for transfusion, Chagas Disease, Creutzfeldt-Jakob Disease (CJD), and issues surrounding HCV look-back.

In fact, although you have referred to these diseases as "emerging," they have been studied by the transfusion medicine researchers for a number of years. Researchers are working to develop scientific consensus on the risks presented to the blood supply and potential strategies for reducing these risks. However, as the IOM

Report points out, until scientific consensus is developed and practical preventative medical technology is available, implementation of interim measures must be considered.

A. Bacterial Infection

Utilizing data released by the Centers for Disease Control and Prevention (CDC) and data collected by AABB member institutions, the AABB Transfusion Transmitted Diseases Committee (TTD Committee) recently identified bacterial contamination of blood components as a leading cause of transfusion associated mortality. The Association has maintained standards on blood collection processes designed to avoid bacterial contamination, but no procedure is fail-safe in this area. The AABB views this as a critical issue and assigns it the highest priority.

The AABB TTD Committee reviewed reports that bacterial contamination of blood components accounted for 29 (16%) of the 182 transfusion-associated fatalities reported to the FDA between 1986–1991. Of these fatalities, 21 (72%) were associated with transfusion of platelets, while 8 (28%) were associated with transfusion of red cells. The latest data from the CDC for 1987 to 1994, indicate a bacterial contamination rate of less than one per million red cell units (22 cases per 28 million units of red cells transfused). The bacterial contamination rate for platelets, based on culture studies, varies between 1/900 and 1/2000 random donor units. However, prospective studies suggest that the risk of symptomatic sepsis due to bacterial contamination of platelets is between 1/2000 and 1/12000 random donor units.

Strategies for Preventing Bacterial Infection

At the present time, there are no definitive solutions to identify bacterially contaminated blood products. Potential interim solutions are being evaluated; and the AABB Board of Directors will consider recommendations to test units prior to transfusion. Possible solutions for the short-term include use of dip-stick and/or staining technology that indicate the presence of bacteria.

In the long term, refined donor screening, improved arm preparation procedures, and the development of new blood collection technology capable of diverting the first 10 milliliters of donated blood show promise to reduce this threat. The ultimate solution may be to test blood for bacterial contamination immediately prior to transfusion. Unfortunately, there are currently no known tests with the acceptable combination of sensitivity, specificity and practicality for screening blood for bacterial infections. Such a test is needed.

While these short-term and long-term solutions are developed, the AABB continues to encourage strict adherence to AABB Standards to prevent bacterial transmission. As effective techniques for reducing microbial contamination of blood components are identified and proven to be effective, the AABB will, of course, actively review these processes for inclusion in AABB Standards.

B. Chagas Disease

Chagas disease is rare in the United States, but endemic to Latin America. With increased mobility of world populations and the ability of pathogens to travel with people, the American transfusion medicine community has identified this disease as a potential threat to U.S. blood supply safety.

The disease is caused by a parasite called *Trypanosoma Cruzi* (*T. Cruzi*). The most common mode of *T. Cruzi* transmission is through insect bites. However, in Latin American urban areas, the most common mode of transmission is blood transfusion.

An insect known as the "assassin bug" serves as a vector for the disease between infected wild animals and people. Individuals living in close proximity to wild animals in substandard housing are at risk for infection.

Data show that 30 to 40 percent of those infected with the parasite develop chronic long term infections. Of this number, 20 to 30 percent may eventually succumb to unexpected heart disease or disturbances of the gastrointestinal tract.

Transfusion medicine investigators are conducting a number of studies to determine the seroprevalence of *T. Cruzi* in U.S. blood donors. In a Red Cross study conducted in metropolitan Miami and Los Angeles, potential blood donors are asked if they were born in South America, Central American, or Mexico, or if they had spent more than four weeks in one of those areas. In Los Angeles seven to eight percent answered yes. In Miami 12 percent responded affirmatively.

Donors who responded "yes" and a cohort of controls were tested for *T. Cruzi*-antibodies by Abbott Laboratories' Chagas enzyme immunoassay. Repeatedly reactive (RR) samples were confirmed by radioimmunoprecipitation. Testing was performed under a research protocol, since the tests are not FDA-approved for screening blood donors.

Of the donors who answered the screening question affirmatively, 1 in 800 to 1 in 1000 were confirmed positive for the *T. Cruzi* antibody. From these data, researchers extrapolate that the upper limit of *T. Cruzi* infection in the Los Angeles donor base is .012 percent and .010 percent for the Miami donor base.

Look-back investigations of units previously donated by donors testing positive for the *T. Cruzi* antibody identified six or seven recipients. None of these recipients tested positive for the antibody.

Preliminary data indicate that questionnaires designed to detect risk for *T. Cruzi* infection may have limited usefulness for donor deferral. However, researchers are gathering additional data and are estimating *T. Cruzi* antibody prevalence in other parts of the nation. By analyzing the risk factors experienced by *T. Cruzi* antibody positive donors, investigators hope to develop an optimal mix of donor screening questions and clinical laboratory tests to effectively reduce the transfusion risk of this pathogen.

C. Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob Disease (CJD) is a rare, usually fatal degenerative disease of the brain that typically strikes in middle life. Scientists theorize that CJD is transmitted by an unusual protein or virus. Each year, CJD occurs in about one in a million individuals in the U.S.

In later stages of the disease, the cerebral cortexes of CJD patients are riddled with abnormal cavities. The disease is accompanied by progressive dementia and occasionally wasting of the muscles and tremors.

Although transmission of the disease has occurred through transplantations of the aura mater tissue that covers the brain and spinal cord, it is not clear if the disease is transmissible through blood transfusions. Nevertheless, on August 8, the FDA issued a memorandum entitled Precautionary Measures to Further Reduce the Possible Transmission of Creutzfeldt-Jakob Disease by Blood and Blood Products. The memorandum recommends permanently deferring from blood donation the following people:

i. individuals who have received injections of growth hormones derived from human sources,

ii. individuals who have received transplants of aura mater, and

iii. individuals with a family history of CJD.

In support of the FDA action, the AABB Donor History Committee developed additional questions for the AABB Uniform Donor History Questionnaire which are designed to elicit this information. These questions have been approved by the FDA and we are providing these questions to all AABB Institutional Members.

D. Hepatitis C Look-Back

Look-back refers to the process of notifying recipients of prior donations from a donor subsequently identified as seropositive for a transfusion transmissible infectious agent. Notified recipients may then elect to undergo diagnostic testing to determine whether they are infected. If so, appropriate treatment may be initiated and the patient may take appropriate precautions to prevent transmission to others.

The PHS recommended against Hepatitis C virus (HCV) look-back when the HCV antibody test was first licensed for screening blood donations in 1990. The AABB Board of Directors recommended against HCV look-back in 1991 and 1993. Until recently, it was not clear what a positive test result meant for the patient, little was known about how HCV was transmitted, and treatment options for those infected with HCV were limited.

HCV testing technology has advanced. It is now possible to more accurately identify those individuals who are positive for HCV. Additionally, interferon therapy has been identified as beneficial for some HCV infected patients.

On the other hand, there is still insufficient information about HCV look-back to determine the frequency with which transfusion recipients identified through look-back would actually be infected with transfusion associated HCV. There is also no information to indicate how often secondary infections might be prevented.

The ethical and public policy issues that relate to look-back are similar for all infectious agents and must be accorded proper weight when look-back policy is developed. At the same time it is appropriate to consider the public health benefits and scientific basis for a look-back policy.

In response to these new considerations, in 1994 the AABB Board of Directors asked the AABB TTD Committee to again review the scientific data pertaining to HCV look-back. The Board has also assembled a special work-group to address the related ethical and public policy issues. We recommend that HCV look-back should be a primary focus of the new HHS Blood Safety Committee.

CONCLUSION

In conclusion, I think it is particularly important to note that both our association and the blood banking community, in general, have come a long way in our continuing efforts to improve blood safety. The AABB welcomes the changes that are anticipated from the HHS restructuring and will work as closely as possible with both HHS and FDA to enhance and support these initiatives.

The Safety of the blood supply, and ultimately the donors and patients we all seek to serve, rests on science and medical technology developed through scientific research. In everything we do at the AABB, we seek to identify and educate our members with respect to the latest scientific knowledge and medical technology that will produce the safest possible blood supply. We also do this also in the context of the adequacy of the blood supply. As I am reminded by blood bankers and regulators, the most unsafe unit of blood is the one that is not there when it's needed.

To make advances in safety without sacrificing adequacy, we need the successes achieved through advances in scientific research and the development of new medical technologies that can be used in blood collection and transfusion facility environments.

The long-term solutions to blood safety questions clearly depend on scientific advances translated into practical applications for use in blood banking and transfusion medicine. For our part, the AABB and it's members support research initiatives in every way that we can. The AABB has just developed an ambitious program to raise $10,000,000 over the next five years through our National Blood Foundation (NBF). The funds will be used to expand an existing $2,000,000 endowment that funds blood and transfusion medicine research. The NBF is the only private national funding source exclusively devoted to the advancement of research in transfusion medicine. Even with achievement of our initial goal, however, the results will be inadequate to cover the need.

The AABB has also worked closely with the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) to assist in identifying research initiatives in transfusion medicine that merit government funding. We strongly support continued and increased federal support for medical research at the NIH. All of this research is needed to solve, in the long-term, the threats to blood safety. In the short term, interim solutions must be developed to reduce the risks presented by potential blood born pathogens. The AABB will be in the forefront of this effort.

In the short-term, we all should recognize the IOM's recommendation to implement partial solutions where long-term solutions are not available. As an organization representing a community based largely on science and medical technology, the AABB has been careful to ensure the widest possible scientific debate and has worked carefully to develop a full consensus of recognized experts before acting. As we move forward, the AABB will continue to seek that scientific knowledge. However, as reflected in our actions on HIV antigen testing, we are moving to implement internal reviews that will provide for development of short-term/interim recommendations in response to emerging threats to the blood supply.

Thank you again for the opportunity to speak to you today. I hope that my testimony and these hearings, in general, will assist in focusing the energy and resources still needed to make our blood supply as safe as humanly possible and available to any who need it.

October 3, 1995

Philip R. Lee, MD
Assistant Secretary for Health
Department of Health and Human Services
Washington, DC 20201

RE: Task Force to Review Current Blood Safety Program

DEAR DR. LEE:

The American Association of Blood Banks (AABB) appreciated the opportunity to participate in the HHS Task Force meeting on September 27 regarding the IOM report, "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking," and would like to provide, through this letter, its thoughts on the IOM's recommendations.

The AABB is the professional medical society for over 9,000 persons engaged in blood banking and transfusion medicine and approximately 2,400 community, regional and American Red Cross blood centers, hospital-based blood banks and transfusion services. Our member facilities are responsible for collecting virtually all of the nation's blood supply and for transfusing more than 80 percent of the blood used for patient care in the United States. Many of our individual members and member facilities engage in the collection and transplantation of hematopoietic stem cells.

In general, we support the recommendations noted in the report and the Red Cross joins us in expressing its support. Specific comments and a brief analysis of the recommendations follow:

Recommendation 1: The Secretary of Health and Human Services should designate a Blood Safety Director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.

Recommendation 2: The Public Health Service (PHS) should establish a Blood Safety Council to assess current and potential future threats to the blood supply, to propose strategies for overcoming these threats, to evaluate the response of the Public Health Service to these proposals, and to monitor the implementation of these strategies. The Council should report to the Blood Safety Director. The Council should also serve to alert scientists about the needs and opportunities for research to maximize the safety of blood and blood products. The Blood Safety Council should take the lead to ensure the education of public health officials, clinicians, and the public about the nature of threats to our nation's blood supply and the public health strategies for dealing with these threats.

We support both of these recommendations in concept. The AABB, the Red Cross and other blood service organizations have clearly demonstrated a desire to cooperate together and with government agencies in efforts to coordinate prompt and clear responses to public health concerns. The AABB Ad Hoc FDA Advisory Committee, the Coalition for Regulatory Reform (a coalition of the AABB, the Council of Community Blood Centers, and the American Blood Resources Association) and the IOM Forum on Blood Safety and Availability are several examples of recent efforts to address critical issues facing blood banking to identify leadership and increase coordination within the blood community.

The AABB concurs with statements made at the September 27 meeting regarding the limitations of the IOM report, particularly the failure to address the processes now in place to improve decision making with respect to blood safety issues. Prior to the implementation of any additional structures, the AABB recommends that the Task Force fully consider and incorporate into its recommendations the strengths of current processes.

If the Task Force determines that a new structure is necessary, a Blood Safety Director at a senior level should coordinate, manage and provide leadership in the development of critical responses affecting the safety and adequacy of the blood supply.

Currently, each relevant agency of the Public Health Service (PHS) has a narrow area of responsibility for blood safety. None of the key players, National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC) or the Food and Drug Administration (FDA), has been charged with leadership in critical issues affecting blood safety and adequacy. Fundamentally, issues relating to blood safety and adequacy, as well as the costs of the blood delivery system, are public health issues that require coordination. As we have seen in many instances, including the initial 1983 PHS recommendations regarding AIDS and the blood supply, NIH research, CDC surveillance of transfusion transmitted diseases, and ongoing FDA regulatory activities, all benefit from effective coordination. The development of a PHS Blood Safety Council to expand that coordination has the potential to increase benefits.

The AABB supports the development of a system that increases data exchange between involved organizations. Steps must be taken to ensure that good communication exists among the Blood Safety Director, the Blood Safety Council, the expert panel (Recommendation 13), the Blood Products Advisory Committee (BPAC) and the FDA. These additional structures should not impede or delay the development and implementation of actions that will further increase blood safety or adequacy. Moreover, the specific role of the Blood Safety Council must be evaluated against the role of the newly reconstituted BPAC to confirm that their efforts are not duplicated.

Finally, discussion during the September 27 meeting focused on the need for an efficient decision-making process, open communication and, in particular, the need for participation and, where possible, consensus by all stakeholders. While the AABB agrees with all of these points, without appropriate direction, defined authority and strong leadership by the individuals holding the authority, the proposed structure will not meet its charge.

Recommendation 3: The federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood components.

The AABB supports initiatives to consider and develop options for prospective no-fault compensation systems. As noted, for several years, the AABB, the CCBC, the

Red Cross, and other blood service organizations, have been exploring the feasibility of using alternative dispute mechanisms and no-fault compensation programs as a means to achieve better and more efficient resolutions for claims resulting from transfusion-related injuries. The AABB, the CCBC, and the Red Cross are currently working with the Arizona Hospital Association to develop a pilot no-fault compensation program for Arizona hospitals and blood centers that would offer persons with designated transfusion-associated injuries a package of compensation elements, including actual medical costs, disability wage losses, and/or death benefits. If successful, the program will offer eligible persons compensation with no requirement that they establish fault.

Experience to date suggests that development of such a program involves resolution of many complex issues, including development of sufficient funding mechanisms and obtaining the cooperation of both government and private insurers to support an alternative to the traditional tort system with which they are familiar. The program is still in its developmental stages and is expected to undergo considerable refinement before being enacted later this year or early next year. The participants, however, are committed to establishing a pilot program. A brief description of the program is provided in an attachment to this letter.

Recommendation 4: Other federal agencies must understand, support, and respond to the CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.

Recommendation 5: The PHS should establish a systematic, ongoing surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products.

The AABB supports the role of the CDC in maintaining the primary responsibility for monitoring threats to public health and warning other agencies of threats to the public health. The AABB, together with the Red Cross and other blood banking organizations, relies on the CDC to detect, monitor, and warn of adverse outcomes in the transfusion of blood and blood products. Early warning indicators of potential transfusion transmitted diseases including both recent infections and emerging threats in the general population, are processed through AABB expert committees.

Committee recommendations are communicated to the AABB Board of Directors for final review and consideration. Established positions are then communicated to AABB members and, if appropriate, incorporated into the AABB's voluntary standards for blood banks.

As part of its professional and educational mission, the AABB utilizes its various publications, AABB Weekly Report (formerly Blood Bank Week), Newsbriefs, and Transfusion, to notify its membership of relevant information provided in the CDC's Morbidity and Mortality Weekly Report (MMWR).

The Code of Federal Regulations currently requires that blood banks maintain records and report to the FDA adverse outcomes that result from transfusions. Accurate reporting from blood centers, hospitals and transfusion services is critical to the success of the early warning system.

Several AABB members are currently studying the effect of the punitive actions imposed for failure to report errors and accidents on the premise that the potential for punishment actually operates as a deterrent to full disclosure—the key to use of error and accident reporting as a mechanism to fix systemic problems in the blood collection and processing. As a model, the FAA has supported the Aviation Safety Reporting Program system, which does not impose punitive action for failure to report in an effort to encourage full voluntary reporting.

The AABB recommends that, to encourage and facilitate more complete and timely reporting, requirements be centralized and separated from FDA's compliance. In the event that reporting requirements are transferred to the CDC or another centralized authority, present reporting requirements would need to be revised to avoid unnecessary duplication.

Recommendation 6. Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

The AABB, the Red Cross and other blood banking organizations have consistently supported the use of partial solutions that will provide incremental improvements in the safety of the blood supply. Screening measures adopted in early 1983, following the first reported cases of transfusion-associated AIDS, were later determined to have been largely effective. As recently as February 1995, the AABB Board of Directors issued a written statement supporting the licensure of a monoclonal antibody-based HIV p24 antigen test for screening blood donations. The AABB and Red Cross issued written statements and later spoke in support of HIV antigen testing before the BPAC. This test would not close the HIV window but would shorten

it by several days. Estimates suggested that 5–10 cases per year could be eliminated. The AABB Board reached its decision after reviewing recent data, which indicated that the PCR testing would close the HIV window to an even greater extent, but determined that a routine PCR screening test would not be available for several years.

In 1986, the AABB, the Red Cross and other blood banking organizations also supported the implementation of both ALT and anti core testing to reduce post-transfusion hepatitis before a specific test for non-A, non-B hepatitis was available. While implementation of a partial solution works until a better solution is available, continued use of the partial solution must be reconsidered in the event of the better solution.

Moreover, the AABB Standards Committee continuously reviews donor deferral criteria set forth in AABB Standards with the goal of improving the safety of the blood supply and proposes modifications to the Standards when appropriate.

Recommendation 7: The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

The AABB strongly supports this recommendation. In fact, the AABB's support for reevaluation of the HIV antigen issue recently prompted the BPAC to readdress the issue. This item, which had not been addressed by BPAC since 1989, appeared on the agenda as a result of a letter written to the FDA by the AABB requesting that the committee revisit this issue.

Recommendation 8: Because regulators must rely heavily on the performance of the industry to accomplish blood safety goals, the FDA must articulate its requests or requirement in forms that are understandable and implementable by regulated entities. In particular, when issuing instruction to regulated entities, the FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.

The AABB agrees that many recommendations or guidance memoranda sent to blood establishments often do not clearly identify the required actions. Requirements for blood establishments can be found in the Code of Federal Regulations (21 CFR Part 211 and Parts 600–680), FDA memoranda, letters to blood establishments, the Compliance Program Guidance Manual, Compliance Policy Guides and the FDA Guide to Inspections of Blood Bank Establishments. The AABB, the CCBC, the Red Cross, and other blood banking organizations have consistently requested that requirements be clarified, coordinated, and codified in an organized and usable manner. In fact, the AABB and others submitted comments to the FDA in May 1992 and again in January 1995 in response to a request from the agency for views on how to clarify and better organize the FDA regulations and requirements (Copies of our comments can be provided if necessary.)

The AABB supports the position enunciated at the September meeting to employ the rule-making process where possible. While the rule-making process offers all stakeholders the opportunity to comment and the certainty of a final rule against which to evaluate alternative options for performance, scheduled steps often make the process cumbersome and time consuming. Therefore, the AABB believes it is essential that, regardless of how FDA guidance is communicated, the process must provide for input from individuals regarding valid operational concerns.

Recommendation 9: The FDA should ensure that the composition of the Blood Products Advisory Committee reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.

The BPAC must include a balance of members connected to blood banking and transfusion medicine and members who are independent of the blood banking community to properly advise the FDA. The BPAC is responsible for providing guidance to the FDA on scientific and technical issues. A blend of individuals active in the blood banking community and those independent of blood banking is important for discussion and well-balanced recommendations. Without this balance, the FDA will lack input from members who play key roles in delivering blood and blood-related services to the public at a time when the FDA should be seeking more, rather than less, input from all individuals with the knowledge, skills, and expertise to contribute to the safest possible blood supply.

We recognize the concern for avoiding the potential for conflict of interest, financial or other. However, individuals selected for their scientific expertise do not necessarily reflect the views of their respective institutions with respect to cost and analysis. To the extent that selected individuals do have a conflict of interest, they can be asked to recuse themselves from a particular issue rather than loosing the benefit of their expertise entirely. Indeed, under federal conflict of interest laws, for individuals with the necessary expertise who may have a conflict, the Code of Fed-

eral Regulations provides a mechanism for declaration of a conflict of interest and recusal (5 CFR 2635.501).

In light of the IOM recommendation to establish a Blood Safety Council, the role of the BPAC will need to be clarified to eliminate duplication of effort by other groups.

Recommendation 10: The FDA should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.

The AABB fully agrees with the recommendation to delineate clearly what is expected from the advisory committee and to evaluate agendas and performance independently. To a large extent, FDA staff has provided the committee with thorough information on the complex issues presented to it. However, certain steps could be taken to allow the BPAC to function more effectively. Background materials provided to the BPAC should be in-depth and should be provided sufficiently in advance of the meeting to allow for thorough review and analysis. The FDA should prepare the committee by presenting, or having invited speakers present, the scientific data as well as a variety of views related to the specific topics. This process can include recognized experts and selected regulated parties, and should provide committee members adequate time for comment and debate prior to a vote. Moreover, defining the basis for which a decision is made (i.e., cost analysis v. technical/scientific data) will make the process more consistent, and will allow those providing comment a baseline for input. Questions posed to the committee should be worded succinctly and should contain instructions to respond based on uniform criteria. Failure to clearly identify issues for consideration and to develop uniform criteria for decision making have, in the past, resulted in inconsistent decisions.

The FDA must routinely develop guidance in a timely manner following issuance of the BPAC recommendations.

Recommendation 11: The PHS should develop reliable sources of the information that it needs to make decisions about the blood supply. The PHS should have its own capacity to analyze this information and to predict the effects of regulatory decisions.

The AABB fully supports the development of independent scientific expertise, and of PHS' capacity to analyze and predict effects of regulatory actions.

To facilitate the collection of reliable information, the AABB has defined as one of its top priorities the development of an independent Blood Data and Collection Center that will periodically survey the blood banking community for aggregate data on blood safety, adequacy, and usage. Efforts are currently underway to define the structure of the Center and the scope of the data to be collected.

Recommendation 12: When faced with a decision in which the options carry risk, especially if the amount of the risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.

The AABB, together with the Red Cross and other blood banking organizations, firmly believes in strong communication between physicians and their patients. In 1986, the AABB recommended that patients who receive non-emergency transfusions be informed of the risks and benefits of blood and blood products and consent to their use. Over the years, the AABB has routinely offered educational programs and publications to encourage physician-patient communications by providing physicians with information concerning blood and blood component transfusions, including risks and benefits, options and how to obtain informed consent. In the early 1980s, the AABB worked with the National Autologous Blood Research Center to identify blood usage needs. Later, this effort was transferred to the National Heart, Lung and Blood Institute (NHLBI), and the task expanded to include patient and donor needs.

Recommendation 13: An expert panel should be created to inform the providers of care and the public about the risks associated with blood and blood products, about the alternatives to using them, and about treatments that have the support of the scientific record.

The AABB supports creation of an expert panel charged with disseminating information and education to health-care providers and the public with respect to transfusion-associated risks and alternatives to allogeneic transfusions. The work of such a panel would dove-tail with the efforts of the AABB and other blood banking organizations. For example, the AABB and other blood organizations produce and distribute a Circular of Information for the Use of Human Blood and Blood Components that is distributed to health care professionals who order and transfuse blood. AABB also publishes information about transfusion medicine through books, journals, newsletters, faxes, and electronic media.

The AABB also supports providing the public with complete and easy to understand information about the risks and benefits of blood transfusion and the transfusion alternatives that are available to patients. Working with the NHLBI's Na-

tional Blood Resources Education Program, the AABB and other national blood organizations developed and distributed brochures, posters and other materials intended to explain to the layman the various aspects of blood donation and transfusion.

Recommendation 14: Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgement and otherwise act so as to earn the confidence of the public and patients.

The AABB agrees with this recommendation. As a professional, voluntary organization, the AABB requires, as a matter of course, that every participating volunteer and staff member identify and clear all potential conflicts of interest with the Board of Directors. The ability to render impartial judgements is crucial in the development of consensus on scientific issues.

Again, we appreciate the opportunity to provide our thoughts on the IOM recommendations as the Task Force is developing its report for Secretary Shalala. The volunteer membership of the AABB stands ready to further assist the PHS and its Blood Safety Task Force in developing plans to implement the proposals discussed above. Please call me (301–907–6977) if you have questions or need more information.

Sincerely,

KAREN SHOOS LIPTON, JD
Chief Executive Officer

PILOT PROGRAM FOR THE MANAGEMENT AND COMPENSATION OF TRANSFUSION-RELATED INJURIES AND CLAIMS

The blood centers serving Arizona, together with several of the State's principal hospitals and health care providers, and in collaboration with medical societies and liability insurance companies, will soon implement, on a pilot basis, a program for compensating persons who have incurred transfusion-related injuries; and for managing such claims through alternatives to the public litigation system. Compensation for covered events will be available to patients who elect to participate, after the injury or event has occurred. The process will be an administrative, nonfault, and wholly voluntary option. The program is also entirely private: no enabling legislation is either sought or required.

I. PREMISES AND OBJECTIVES

The program is built on several assumptions. Among them is the suspicion that the tort-litigation system, which governs much of the policy and shape of present medical-injury compensation, is imperfect. There is reason to believe that as a compensation system it is inefficient; that as a system for assuring patient safety it is neither optimal nor uniquely able; and that as a method for linking economic compensation with instances of medical negligence, it is frequently inaccurate, causing both overcompensation in some cases and under compensation in others. These flaws may result in instances of injustice and in excess costs ultimately included in the costs of medical care.

Under present law, health care providers and blood centers may be liable for injuries caused by transfusion or the use of blood products only if they were negligent, or in a legal sense at fault, with respect to that product or service. A substantial part of the costs of the legal process are devoted to determining, case by case, whether the provider was at fault or not. Resources spent on that determination are not available for compensating injured patients. Another substantial part of the costs of the legal process are attributable to the adversary system by which claims are advanced and defended. The resources devoted to bringing legal claims and to defending legal claims are likewise not available for compensation. In addition, the adversary system may be inconsistent with the purposes and relationships that are vital to effective medical care.

The purposes of the pilot program are:

(1) to implement a cost-effective alternative to the legal process, where doing so appears to be feasible and in the best interests of all the participants:

(2) to monitor the financial and administrative results and the patient-safety implications of such a system; and

(3) to employ the transfusion-injury pilot program as a field test of compensation principles that my be applicable to medical injury in general.

II. BACKGROUND

The pilot program has been investigated since 1991, when it was recommended to the national bloodbanking organizations by the Center for Public Resources. It draws on a substantial body of literature and experience, including the concepts of "neo-contractual" liability, "designated compensable events," and the nofault paradigm of the 1991 Harvard malpractice compensation study. The Arizona pilot has since 1993 been investigated and developed by a working group organized through the Arizona Hospital and Healthcare Association (AzHHA), including experts in law, medical economics, hospital management, medicine and blood banking. In 1995 the program was endorsed by the AzHHA Board of Trustees.

III. THE PROGRAM IN OUTLINE

The program will be a pilot, with no certain termination date, subscribed to by blood centers, participating hospitals and physicians and their insurers,

that offers to persons with designated transfusion-associated injuries, after the injury occurred,

a package of compensation for attributable economic losses, including actual medical costs if and when incurred and (subject to some limits) actual disability wage losses, and a death benefit when appropriate,

on a non-fault basis, but only for injuries actually caused by the activities or products of a member of the group.

The injured person will release all participating individuals and organizations from other liability,

and agree to resolve all future disputes by arbitration or other ADR.

The events to be included will be all blood-borne pathogens, transfusion errors, and (for blood centers) donor injuries. [This would typically include, in Arizona each year, one case of HIV; four HBV (of which one or two would be likely to have a compensable claim); 80 +/- HCV (of which 8–10 would recognize compensable claims); 4 HTLV–I and II (one or two compensable); and one or two others.]

The offer will be made once there is a recognition that an infection or injury has occurred, for example through the process of "lookback;" or when a claim is brought against a participant by an injured person.

Causation will be assumed for the designated injuries, subject to the broad center's or hospital's ability to disprove it (e.g. a known pre-transfusion infection, or a donor who tests negative at a later time, or an implicated unit of blood not handled by any of the participants.)

Compensation funding will be on a "pay-as-you-go" basis, with each, participant contributing to the pool necessary for a compensation package for its patients.

There will be agreements in advance to participate, from which a participating organization may withdraw prospectively as to any claim not then known.

Allocations of the costs among the hospital, the blood center and, where appropriate, the physician will be negotiated, with some form of ADR agreed to in advance to resolve disputes. Some hospitals may participate on a case-by-case basis, though doing so will not be encouraged.

Claims management—including both contact with the injured person and management of the claim thereafter—will be done centrally, on behalf of all participants.

Mr. SOUDER. Thank you. Dr. Simon, go ahead.

Dr. SIMON. Good morning, Mr. Chairman, Mr. Souder, Mr. Towns, and members. I am Dr. Toby Simon, president of the Council of Community Blood Centers and of Blood Systems in Scottsdale, AZ, and it is my privilege today to represent the 67 independent not-for-profit community blood centers that are our members. They account for approximately 40 percent of the blood collected in the United States.

We want to emphasize three facts initially. First, that blood is life-giving. It must be available when patients need it. Second, the only reason there is blood available is because millions of volunteers are willing to roll up their sleeves and give the gift of life. Third, while blood is safer than ever before and we must strive to continually make it safer, we must use it with minimal manipula-

tion from the body—this very valuable human tissue—and thus absolute safety would currently mean no blood available at all.

We have over 5 million annual volunteer blood donors to thank for the safety of our blood supply, and their altruism, studies show, has been the single biggest factor in blood safety. The volunteer community has made great strides in implementing the kinds of quality assurance standards that we owe to these donors and to the greater community and patients.

We have launched many quality initiatives for our members so that they will have these higher standards, including the quality engineering training program to which Ms. Lipton referred. Today, donor screening procedures and public education programs eliminate over 99 percent of carriers of either HIV or Hepatitis before the blood is even collected or tested.

To increase this safety even further, we feel that the focus should be on improved donor screening technologies, strategies to reduce the need for transfusion, and viral inactivation of blood components.

First, we would like to emphasize in these steps to improve blood safety that repeat blood donors are the safest donors. Recruiting a low-risk group of volunteer donors, using screening questions, and encouraging repeat donations has led to this safety.

We are concerned about the continued loss of many safe donors due to the sensitivity of the test procedures and regulatory requirements which could jeopardize both safety and adequacy. We therefore recommend more research into the effectiveness of the donor screening process and methods of increasing donor retention.

Our Donor Resources Committee is currently identifying the best practices in donor retention so that they can be more widely used. To further increase patient safety, CCBC members are also working hard to ensure that blood is used only when medically necessary.

We believe that greater centralization of the total transfusion services now being developed by many of our members will help assure appropriate utilization and also allow more effective continued surveillance for emerging infections. Our members are doing this through centralized transfusion services.

Of course, we realize that new technologies can help, as well, and we have recommended that the Public Health Service Advisory Council on Blood Safety and Availability examine viral inactivation as one of its first priorities. Plasma derivatives are safe today because of viral inactivation.

One of our members, the New York Blood Center, has developed a solvent detergent method for fresh frozen plasma that is currently under review by the Food and Drug Administration. Many studies indicate that some of these technologies can be applied to cellular blood components, as well, and clinical trials will soon begin for solvent detergent treated platelets.

We are pleased that the Department of Health and Human Services is taking steps to improve government coordination and responsiveness in these areas. We hope to have a parallel effort in the private sector that will allow us to work effectively with the government using a neutral forum, and hopefully we'll work closely with CDC, FDA, NIH, and the Secretary's office. Similar to AABB,

we believe that continued support by Congress is important in ensuring safety.

Decision-making plays a critical role in ensuring blood safety. It is our hope that this subcommittee will assist the FDA and the blood community in examining the decisionmaking process and recommending how it can be improved.

On behalf of the 67 members of the Council of Community Blood Centers, I thank the Chair, the members of the subcommittee, and the staff for giving us this opportunity to present our views.

[The prepared statement of Dr. Simon follows:]

PREPARED STATEMENT OF TOBY SIMON, PRESIDENT, COUNCIL OF COMMUNITY BLOOD CENTERS

Mr. Chairman and members of the Subcommittee:

I am Dr. Toby Simon, president of the Council of Community Blood Centers (CCBC) and of Blood Systems Foundation, a Scottsdale, Arizona nonprofit organization dedicated to promoting excellence in transfusion medicine. I appreciate the opportunity to appear today on behalf of CCBC to discuss the volunteer blood community's efforts to ensure the safety of the nation's blood supply.

CCBC is an association of 67 independent, not-for-profit community blood centers nationwide. CCBC's members are not part of the American Red Cross network. Our members collect approximately 40 percent of the total volunteer blood supply in the US, and provide various therapeutic, tissue banking, stem cell, and laboratory services. All of the blood our members provide comes from unpaid, volunteer donors.

Blood safety is of utmost importance to CCBC's members, who are licensed and regulated by the Food and Drug Administration (FDA).

There are two important facts that we all must remember when considering blood safety in the U.S.: First, blood is life-giving. Millions of lives are saved each year because blood is there when people need it. Second, the only reason that there is blood available for emergencies and patient needs is that millions of Americans continue to be willing to roll up their sleeves and give the gift of life.

I. BLOOD SAFETY TODAY

The volunteer blood supply is safer today than ever before. Many steps have been taken since the early, confusing days of the AIDS crisis more than 13 years ago. Blood centers have worked with government agencies and other entities to implement intense blood donor screening, increased disease testing, improved computer tracking systems, and good manufacturing practices.

However, we also know that given the nature of blood and current technology, absolutely safe blood means absolutely no blood will be available. Blood is a human tissue, it must remain largely intact as it comes from donors, and it has a limited "shelf life." As long as these facts remain true, there will be possible risks for known and unknown disease transmission. We simply cannot guarantee that blood will be totally safe. But we can continually strive through research and practice to find ways to improve safety further.

The volunteer blood community and the federal government have come a long way from the early days of the AIDS epidemic. Today there is not a crisis in the safety of the blood supply. But there is a lingering public concern about the safety of the volunteer blood system.

Because of joint efforts by community blood centers and other professional groups, utilization of some blood components has fallen over the last few years. Yet volunteer blood shortages occur with greater frequency. There is a direct link between the public's confidence in its blood system and their willingness to donate blood. It is our hope that this hearing and the work of the Subcommittee will help reenforce that confidence.

ICL RESPONSE MODEL FOR POTENTIAL THREATS

AIDS was the volunteer blood community's first experience with a deadly epidemiological crisis. That unavoidably tragic experience became a galvanizing force for change in blood services. Blood providers learned lessons from AIDS and have put mechanisms in place to ensure that it will not happen again. These mechanisms were tested and proven successful in the case of the blood community's response to a potential disease threat not long ago.

In July 1992, reports of a handful of people with AIDS-like symptoms but no evidence of HIV infection came from an international AIDS meeting in Europe. The Centers for Disease Control (CDC) called this syndrome idiopathic CD4-positive lymphocytopenia, or ICL. Fearing that this could be a revisitation of the early days of AIDS, CCBC and the rest of the blood banking community responded rapidly by convening a workgroup with public health officials to assess the potential threat to the blood supply and examine the possibility of a new transfusion-transmitted disease. In fact, the blood organizations planned a meeting on ICL even before CDC had a chance to convene its own viral disease experts.

Fortunately, no evidence linking ICL to transfusions was found. But this experience continues to function as a model for the private sector in responding quickly to potential new threats to the blood supply.

Blood safety also depends upon the CDC and other public health surveillance programs. We urge Congress to continue to provide funding and support for the CDC, the National Institutes of Health, and the FDA so that critical mechanisms such as the Retroviral Epidemiology in Donors Study—which is used to develop more effective blood donor screening—remain in place.

ROLE OF VOLUNTEER DONORS IN ENSURING SAFETY

We also have over five million annual volunteer blood donors to thank for the safety of our blood supply. Each day, thousands of faithful donors subject themselves to a rigorous and sometimes embarrassing screening process because they understand their critical public health contribution. Studies have shown that the rate of HIV in the volunteer blood donor population is one-one hundredth of that in the general U.S. population.

Volunteer donors must not be forgotten in the race to improve testing technology, add more screening questions, and otherwise pursue the elusive goal of absolutely safe blood. We must remember that not only are blood centers the guardians of donors' blood, but also of their trust and support. Our nation is dependent upon the continued relationship between blood centers, their communities, and their donors. Without donors, we would not have any blood at all, and vital health-care services would grind to a halt.

COMMUNITY BLOOD CENTER QUALITY STANDARDS

The volunteer blood community has made great strides in implementing quality assurance programs and standards. CCBC in particular has played a pivotal role in initiating quality training for blood center employees. In 1992, CCBC and Ortho Diagnostic Systems developed a comprehensive good manufacturing practice (GMP) training program. The focus of this program was to train blood center staff to implement and comply with sweeping FDA manufacturing regulations. That same year, CCBC initiated a program called CITINGS, which continues to serve as an early warning system for compliance problems in blood establishments. The CITINGS program maintains a database of specific information on citations issued to blood establishments during FDA inspections. Blood centers can access this information—through a publication and on-line—to monitor their own quality programs and performance.

In addition, from 1993 to 1995, CCBC has published the first volume (and subsequent update) of over 100 quality operating procedures for blood establishments; initiated a Continuous Quality Improvement (CQI) program to train blood establishments in applied quality management and problem solving techniques; launched a comprehensive computer validation training program (together with AABB and the Red Cross): and launched the second phase of our GMP quality engineering program.

The second phase of our GMP quality engineering program provides more extensive training in auditing, error management, and process control to quality assurance specialists in our members' blood centers. Ortho Diagnostic Systems and FDA participated in the development of this program. CCBC also has made the program available to the American Association of Blood Banks (AABB). We now are working with Abbott Laboratories to explore whether ISO 9000 standards can help raise and standardize quality systems for blood establishments.

CCBC has identified an area for improvement in blood banking quality standards. Several studies have shown that there continue to be compliance and quality problems among some unlicensed blood establishments and transfusion services. FDA already has demonstrated strong regulatory enforcement toward licensed blood establishments. We recommend that the agency take the same approach with unlicensed establishments and transfusion services to assure greater consistency in blood banking quality.

Quality standards have been a top priority for CCBC and our members. Coupled with the extensive testing, screening and record-keeping mechanisms in place, these programs have helped us maintain the safest blood supply this country has ever known—and will continue to assure the safest blood possible in the face of any future threats.

II. STEPS TO IMPROVE BLOOD SAFETY

Blood safety is an ongoing process. We have been fighting infectious diseases in the blood supply for over 25 years. We have gone from two tests for infectious diseases 10 years ago to eight tests today. But we do not simply rely on blood testing. We also educate donors about who can and cannot donate. Then we ask donors a litany of questions about their medical history and personal behavior. Those questions are tough—in fact, 90 percent of the people we defer from donating are identified during the medical history portion of their interviews.

These donor screening procedures, combined with blood centers' public education programs, now eliminate over 99 percent of carriers of HIV or hepatitis before the blood is even collected and tested. This number shows that all of our efforts to keep people with risky behavior out of the donor population are working. And we're constantly striving to improve that process.

CCBC believes the public and private sectors should work together to develop near- and long-term strategies for protecting the blood supply from transfusion-transmitted diseases. While there is substantial public interest in the area of red blood cell substitutes, it is unlikely that such substitutes will be a reality any time soon. Even if enough research funds were expended to develop a blood substitute, it is unlikely that it would be able to replace most of the 12 million red blood cell transfusions. Furthermore, there is little substantial research into developing a substitute for the eight million human platelet transfusions used each year to support cancer and bone marrow transplant patients.

CCBC believes that the most practical research investment is to increase the safety of blood donated by volunteers through a multifaceted approach. This approach should include improved donor screening technologies, the development of strategies to reduce the need for transfusions, and viral inactivation of blood components.

DONOR RETENTION

Repeat blood donors are the safest donors; therefore, donor retention is a major goal for our members. Recruiting a low-risk group of volunteer donors, using screening questions, and encouraging repeat donations have led to greater increases in safety than has blood testing.

CCBC believes that further study of the effectiveness of the donor screening process is needed. For example, studies should be done to determine whether the screening process should be streamlined to focus on the most important questions. We also will continue to work with FDA on plans to re-enter donors who are not infectious but who have been knocked out of the system because of oversensitive tests or overly-broad donor behavior questions.

The continued loss of many safe donors because of new test procedures and regulatory requirements jeopardizes the safety and adequacy of the blood supply. Because repeat donation is critical to safety and supply, CCBC recommends further research into methods of increasing donor retention. Currently, CCBC's Donor Resources Committee is working to identify and make available blood center "best practices" to help our members improve donor retention.

SAFETY THROUGH BLOOD TESTING

Specific tests help increase the safety of each unit of blood by identifying those units with increased likelihood of viral disease transmission. CCBC helps its members utilize the best testing technology through our group purchasing program, which includes a vendor qualification component.

CCBC also has taken a leadership role in the implementation of p24 HIV antigen testing by arranging an implementation workshop with test kit manufacturers, FDA and public health officials, and members of the regulated community. The workshop will be held next week and is being co-sponsored by CCBC, the American Association of Blood Banks, the American Blood Resources Association, and the American Red Cross. Participants will discuss issues such as antigen test sensitivity and specificity and a variety of outstanding operational implementation details.

SAFETY THROUGH APPROPRIATE BLOOD USE

CCBC members, as stewards of the community's blood supply, also have sought to ensure appropriate therapeutic use of blood and blood components. That is, we are committed to helping ensure that blood is transfused only when medically necessary. We do so by providing continuing education to health-care providers on transfusion indicators and alternatives, and by working with hospitals to monitor for inappropriate use and follow up with any necessary corrective action.

A growing number of our members also are providing blood compatibility testing—previously done by hospital laboratories—through centralized transfusion services. This movement has strengthened blood centers' ability to help decrease blood utilization while holding down costs. It also has allowed those blood centers to apply good manufacturing practices to transfusion services as well as blood collection services. In addition, the expertise of blood center technologists and physicians as specialists in transfusion medicine enhances the quality of patient care. The centralized transfusion service experiences of community blood centers in Seattle and Pittsburgh (two of our members) are increasingly being implemented in other areas of the country because of the clear benefits to patients and providers.

NEW TECHNOLOGIES

CCBC has recommended that the new Public Health Service Advisory Council on Blood Safety and Availability examine viral inactivation as one of its first issues. As part of a long-term strategy, the Advisory Council should determine how the PHS can best facilitate implementation of technologies already under investigation that reduce or inactivate viruses in cellular blood components.

Plasma derivatives are safe today because of the application of viral inactivation techniques. One of our members, the New York Blood Center, has recently developed a solvent detergent treatment for fresh frozen plasma that currently is under review by FDA. Many studies indicate that similar technology can be applied to cellular components as well. In fact, clinical trials for virally-inactivated platelet concentrates are expected to begin next year. But because many of these techniques are without proprietary incentive, there is little venture capital to facilitate their development and evaluation.

In addition to recommending this topic to HHS Assistant Secretary for Health Dr. Philip Lee, CCBC has asked FDA Commissioner David Kessler to commission a high-level study—which would include members from all relevant public and private health-care organizations—to determine whether viral inactivation is practical for cellular blood components. We continue to hope that FDA and HHS will pursue a potential solution in this area.

III. BLOOD POLICY DECISIONMAKING

INSTITUTE OF MEDICINE (IOM) REPORT RECOMMENDATIONS

The Institute of Medicine's report presents valuable, although not entirely new, insights in to the very confusing and volatile early days of the AIDS crisis more than 13 years ago. Much has changed since that time. Many steps have already been taken, and they have given us the safest blood supply in our country's history. We agree with the IOM Committee's statement that "hindsight offers an opportunity to do better the next time."

Some of the recommendations in the IOM's report have been implemented previously. CCBC is pleased to see that many of those recommendations which have not already been implemented are being executed by the Department of Health and Human Services. We look forward to working with the Department to help carry out those new steps.

CCBC recently wrote to Dr. Philip Lee, the newly-designated national Blood Safety Director, to express our support for the October report of the Secretary's Task Force on Blood Safety. In particular, we are hopeful that a new Public Health Service Advisory Council on Blood Safety and Availability—which will be made up of representatives of a range of interests, including the regulated blood community—will help address the often complex and difficult societal, legal and ethical issues surrounding the safety and availability of the blood supply.

The Institute of Medicine report also recommended that the federal government consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products. CCBC supports the concept of a prospective, no-fault compensation program for transfusion injuries. In fact, we are co-sponsoring a private pilot project which is expected to be implemented later this year.

STRATEGIES FOR ENSURING FUTURE SAFETY

For the future, no single issue is more important than assuring the quality and credibility of decisions made to protect blood safety. For this reason, CCBC has urged HHS and the FDA to focus on proven, inclusive methods for consensus development on major controversial issues.

In the wake of the AIDS tragedy, decisions on blood safety have become highly controversial and politicized. FDA is increasingly caught between the patient groups most dependent on blood products, who want "absolute safety," and those in the regulated community, who, under increasing pressure from managed health-care forces, attempt to assure the availability of a safe, adequate and affordable blood supply. This situation is only likely to intensify as shrinking health-care resources force the public and private sectors to make difficult risk-benefit choices.

Within the past few months, FDA has held advisory panel meetings to develop recommendations for blood safety involving Creutzfeldt-Jakob Disease (CJD) and HIV antigen testing. These meetings revealed the inadequacies of the current mechanisms used by FDA to obtain consensus on controversial issues of major public policy.

In each case, FDA's advisory committees reached majority votes, but yet left many, if not most, of those involved with a certain dissatisfaction and uncertainty with the outcome. For example, during the CJD meeting, a special advisory committee vote conflicted with recent FDA Blood Products Advisory Committee votes. Additionally, during the antigen testing meeting, the consumer advisory committee members generally were lined up against those in the blood community. In CCBC's view, these results are inconclusive and unsatisfactory outcomes for such important issues. If possible, these issues should be resolved with all parties participating, supporting, and holding a stake in the outcome.

CCBC RECOMMENDATIONS

CCBC believes that FDA's advisory committees—as they currently are being utilized—have limited effectiveness in dealing with important public policy issues where consensus does not already exist. Recent changes to make the FDA's Blood Products Advisory Committee (BPAC) more "neutral" by removing blood banking expertise only heighten the need to have a deliberative consensus development process. CCBC believes that by reducing the so-called "industry" influence on the Committee, the FDA may actually have increased the likelihood of policy deadlock because there will be less expertise available for decisionmaking. There also is an increased possibility that blood safety decisions will not be made on the basis of sound science and medicine.

We therefore recommend that FDA incorporate decisionmaking mechanisms that are specifically designed to achieve consensus. These mechanisms could be reserved for urgent issues that involve substantial controversy. There are two potential working models already in existence: the National Institutes of Health consensus development conference process and negotiated rulemaking. While neither method is perfect, we believe both are superior to the current use of the BPAC. CDC and the NIH should be included in this process, along with patient representatives, the regulated community, and neutral experts.

CCBC also is working with the American Association of Blood Banks to seek a neutral, private-sector public policy forum that can be used for consensus development when needed. We are exploring the possibility of using an academic institution for this purpose, rather than the Institute of Medicine (which previously had sponsored a Blood Forum that was not authorized to make policy recommendations or seek consensus).

IV. CONCLUSION

Decisionmaking plays a critical role in ensuring blood safety. Because we know we can not yet guarantee absolute blood safety, the government and the private sector constantly must decide how to make tradeoffs of safety and supply, and risks and benefits. While each new decision may bring improvements in safety, someone still may be injured by a transfusion.

Most of the fourteen recommendations issued recently by the Institute of Medicine pertain to decisionmaking in blood policy. Great strides have been made to improve the quality of blood regulatory decisions. However, the regulatory decisionmaking process is not always inclusive, nor does it always seek to achieve consensus among public health, blood community, and consumer groups.

It is our hope that this Subcommittee will assist the FDA and the blood community in examining the decisionmaking processes in place and recommending how

they might be improved. In doing so we should keep in mind our important, common goal—to make sure that blood is there when patients need it and that it continues to be as safe as possible.

CCBC thanks the Chair and members of the Subcommittee for the opportunity to present our views.

Mr. DAVIS. Thank you very much for your testimony. Dr. Davey.

Dr. DAVEY. Thank you, Mr. Chairman, Congressman Towns, Congressman Davis. We appreciate also the opportunity to speak before this subcommittee on this important matter.

I am Dr. Richard Davey, chief medical officer of the American Red Cross. Before joining the Red Cross, I was with the National Institutes of Health for 19 years, where I conducted research in transfusion medicine and cared for patients requiring transfusion support. I have also been a medical officer with the World Health Organization, where I assisted developing African countries organizing national blood transfusion systems.

The American Red Cross, which collects 45 percent of the Nation's blood supply, has experienced tremendous change in the past few years. We have undertaken a $162 million transformation of our blood services program into a state-of-the-art system that can quickly incorporate new medical information and evolving technology.

We are transforming 50 largely autonomous blood regions into a unified system, a process that is now nearing completion. By the end of this year, for example, we will have consolidated our regional testing laboratories into nine advanced national testing facilities. In January, we will begin implementation of a national computer system, linking all of our facilities nationwide.

In the interests of time, I refer you to my written statement, which provides further information on transformation and also addresses an issue of special importance to me, and that is the changing role of the blood center physician in this new environment.

The American Red Cross welcomes the appointment of Dr. Philip Lee to the newly created position of Blood Safety director and supports the creation of the Blood Safety Committee and the Advisory Council on Blood Safety and Availability.

In its first hearing on blood safety, this subcommittee discussed the issue of Hepatitis C look-back and notification of those individuals who may have been exposed to that virus through transfused blood. While substantial progress has been made in reducing the risk of contracting Hepatitis C through transfusion, Hepatitis C look-back is an area that warrants a thorough review.

To that end, the Red Cross is pleased that the Blood Safety Committee will address that issue as a first order of business, and we look forward to participating in a much needed discussion of that multi-faceted issue.

Now, looking to the future, as you have asked us to do, I would like to discuss measures to further improve blood safety. Careful vigilance and cooperation are required to detect and evaluate emerging threats to the blood supply.

Blood banking organizations, the scientific community, the CDC, the FDA, and patient advocacy groups such as the National Hemophilia Foundation already work very closely together. The newly created Advisory Committee and the Blood Safety director will further enhance this cooperative effort.

The Red Cross is involved in a range of epidemiologic and clinical studies of potential threats to the blood supply. I chair the Red Cross Research and Development Committee, responsible for establishing our priorities in those areas.

Many of these studies are conducted by our nationally recognized Jerome Holland Laboratory for Biomedical Research. Other studies are collaborative efforts with academic institutions or with biotechnology firms. For example, Red Cross centers in Atlanta, Baltimore, and Detroit collaborate with two other blood centers in a surveillance effort, funded by the National Heart, Lung, and Blood Institute, that Dr. McCurdy referred to.

This study, called the REDS study, evaluates a range of blood donor characteristics that may influence donor safety, such as the prevalence of disease markers, donor motivation, and donor demographics. Importantly, when NIH funding for the REDS study ceases in 1998, the Red Cross will continue and expand our own surveillance system.

I would now like to give three specific examples of how the Red Cross evaluates and responds to potential threats to the blood supply. The first is Chagas' disease, caused by a parasite passed to humans by the bite of infected insects.

As you've heard, this disease is endemic in Latin America and can be transmitted by blood transfusion. Most people with Chagas' disease develop no ill effects. However, a minority can develop severe heart and gastrointestinal disease many years after the exposure or the transfusion. As migration from Latin America to the United States increases, the blood banking community has become concerned about a possible threat to the Nation's blood supply.

To study this question, the Red Cross initiated a specialized screening study of donors at our Los Angeles and our Miami blood centers in 1993. Questions were developed and subsequently refined to identify potentially high-risk donors. These donors are then tested with a research blood test by Abbott Laboratory.

Data from the Los Angeles study indicates that less than 15 thousandths of 1 percent, or 0.015 percent of these donors have tested positive for Chagas' disease, and these data are consistent with data collected from our Miami Center. Reassuringly, none of the recipients of blood from earlier donations from these donors has tested positive for Chagas' disease.

This study is being expanded to other Red Cross centers under an FDA-approved protocol, and its results will permit informed decisionmaking about the management of Chagas' disease in the blood supply.

The second example is our approach to further reduce the already minimal risk of HIV transmission. The Red Cross joined the AABB in supporting the licensure and implementation of the HIV antigen test, and we recommended to BPAC that it be licensed for blood donor screening.

We plan to participate in studies evaluating this test after its implementation. For example, we will study its "magnet effect." That is the potential to draw high-risk individuals to a blood bank solely to be tested. This will provide additional data which we hope will assess the effectiveness of the test.

Finally, we are concerned about the infrequent but potentially serious problem of bacterial contamination in the blood supply. Data from a recent survey by Holland Laboratory scientists suggests that 1 in 2,000 to 1 in 6,000 units may contain harmful bacteria.

Although most recipients of these units suffer no ill effects, adverse reactions have been reported. No practical test is available to detect bacteria in units of blood. However, the Holland Laboratory is collaborating with a biotechnology firm to develop a test that can be performed on a unit of blood at the patient's bedside immediately before a transfusion.

These three examples represent proactive efforts by the American Red Cross to anticipate, study, and act upon emerging threats to the blood supply. While the focus of these hearings is on these potential threats, I join with my colleagues that we should not lose sight of the millions of men, women, and children who benefit from transfusions every year.

As a recipient of blood transfusions, I'm glad that voluntarily donated and properly screened blood was available for my needs. Our message to the American public must be clear. Blood is the gift of life, and when appropriately used, its benefits far outweigh its risks.

The blood supply has never been safer, but, as with any medical procedure, 100 percent safety is not realistic. Blood can only come from human beings, carrying with it the unpredictability inherent in all biological products. We rely on healthy, dedicated, fully screened volunteer donors as a cornerstone of blood safety.

As guardians of the Nation's blood supply, the American Red Cross will continue in partnership with medical professional and public health authorities to maintain and improve the safety of this precious national resource.

Again, we thank the subcommittee for the opportunity to speak today.

[The prepared statement of Dr. Davey follows:]

PREPARED STATEMENT OF RICHARD J. DAVEY, CHIEF MEDICAL OFFICER, AMERICAN RED CROSS BIOMEDICAL SERVICES

Thank you very much, Mr. Chairman, for the opportunity to speak to the subcommittee on the important issue of emerging infections. I am Dr. Richard Davey, Chief Medical Officer of the American Red Cross. Before joining the Red Cross, I was with the National Institutes of Health for 19 years, most recently as Chief of Laboratory Services with the Department of Transfusion Medicine. In that capacity I conducted research in transfusion medicine and cared for patients requiring blood. I have also been a medical officer with the World Health Organization, where I assisted developing African countries with organizing national blood transfusion systems. I am on the clinical faculty of Georgetown University Hospital and am active in the American Association of Blood Banks.

The American Red Cross collects approximately 45% of the nation's blood supply. We have an ongoing commitment to the American people to ensure that the blood and blood derivatives they may require are as safe as possible. Under the leadership of Elizabeth Dole, the Red Cross has undertaken a $162 million transformation of its blood program into a state-of-the-art system that can quickly incorporate medical information and technology as it evolves. That transformation is 80% complete. Our objective has been to transform 50 largely autonomous blood regions into a unified system with an FDA-accepted quality assurance program, standardized operating procedures, and strong, ongoing training programs. By the end of this year, we will have consolidated over 50 testing laboratories into nine national testing facilities suitable for the 21st century. In January, we will roll out a national computer system, linking all our facilities nationwide. We thank Secretary Shalala for her com-

ments earlier this month before this subcommittee, recognizing these accomplishments.

In its first hearing on blood safety, the Subcommittee heard testimony regarding major advances in safety. While the focus of these hearings is on potential threats to the blood supply, we should not lose sight of the millions of men, women and children who benefit from transfusions each year. As a former recipient of blood transfusions, I am glad that voluntarily donated and properly screened blood was available for my needs.

This substantial progress, while gratifying, does not diminish the horror that befell the hemophilia community and other recipients of blood transfusions infected with HIV in the early 1980s. The knowledge we gained from those years will help avoid repetition of that tragedy. In that context, the American Red Cross welcomes the appointment of Dr. Philip Lee to the newly created position of Blood Safety Director. We also support the creation of The Blood Safety Committee and the Advisory Council on Blood Safety and Availability announced by Secretary Shalala. Likewise, we look forward to our continued constructive relationship with the FDA, which is both a regulator of our operations and an important resource for medical and scientific information.

Secretary Shalala and the HHS Task Force recognized the complexity of blood safety issues, which involve a broad range of perspectives—medical, ethical, and societal. Hepatitis C lookback and the possibility of notifying those individuals who may have been exposed to the virus through transfused blood, represent such a complex issue. It is clear that while substantial progress has been made in reducing the risk of contracting hepatitis C through transfusion, this is an area that warrants a thorough review. To that end, the Red Cross was pleased to hear Dr. Lee testify before this Subcommittee that his Blood Safety Committee will take on that issue as a first order of business. The Red Cross looks forward to its participation in that much-needed discussion of this multifaceted issue.

Blood safety depends on three interlocking factors: carefully screened volunteer blood donors, careful testing of donated blood, and the appropriate use of blood and blood components by physicians. Refinements in each of these three areas have led to the major improvements achieved in blood safety in the last 10 years.

Central to the last of those factors, the appropriate use of blood, is the changing role of physicians in blood banking. As regional blood centers have moved to a more highly regulated environment, physicians are less involved with internal oversight of blood collection, processing and distribution. Instead, they are now able to better focus, within their communities, on the development of clinical services relating to transfusion medicine. For example, blood center physicians play a critical role in the development of life-saving transplantation services, and in ensuring the proper use of specialized blood components for patients with unusual transfusion needs.

Each of the 43 Red Cross regions has a medical director. One of my first actions was to establish a Medical Director's Council to assist in recruiting and retaining highly qualified physicians in our regional centers. As an organization that delivers biomedical services, a strong physician presence is essential to fulfill that role.

Now, looking to the future, as you have asked us to do, I would like to discuss measures to further improve blood safety. Careful vigilance and cooperation are required to detect and evaluate emerging threats to the blood supply. This cooperation already exists among blood banking organizations, the scientific community, the CDC, the FDA, and patient advocacy groups such as the National Hemophilia Foundation. The newly created Advisory Council and position of Blood Safety Director will further enhance this cooperative effort.

The Red Cross is involved in a range of epidemiologic and clinical studies of emerging threats. I chair the Red Cross Research and Development Committee, responsible for establishing our priorities in those areas. Many of these studies are conducted by our nationally recognized Jerome Holland Laboratory for Biomedical Research. Other studies are collaborative efforts with academic institutions or with biotechnology firms. For example, Red Cross centers in Atlanta, Baltimore and Detroit collaborate with blood centers in San Francisco and Oklahoma City in a surveillance effort funded by the National Heart, Lung and Blood Institute. This study, called the Retrovirus Epidemiology Donor Study, or REDS, evaluates a range of blood donor characteristics that may influence blood safety, such as the prevalence of disease markers, donor motivation and demographics. Importantly, when NIH funding for REDS ceases in 1998, the Red Cross will continue and expand our own surveillance system.

Improvements in blood safety invariably lead to the topic of eliminating from the blood supply viruses which cannot always be detected by screening or testing, an area of ongoing interest for the American Red Cross. In addition to the viral inactivation research conducted by our Holland Laboratory, last month we entered into

a strategic alliance with HemaSure Inc., to collaborate in the area of pathogen inactivation of blood components. The Red Cross views this partnership as yet another avenue for us to explore in providing the safest possible blood.

Another partnership we have entered into that holds promise is one where we are seeking to provide fresh frozen plasma that is virally inactivated using a solvent detergent process. Such a component, not yet available anywhere in the country, would provide an improvement in safety for people who have clotting factor deficiencies and problems and for those with severe liver problems.

I would now like to give three specific examples of how the Red Cross evaluates and responds to potential threats to the blood supply. The first is Chagas Disease, caused by a parasite passed to humans by the bite of infected insects. The disease is endemic in Latin America and can be transmitted by blood transfusion. Most people with Chagas Disease develop no ill effects. However, a small minority can develop severe heart and gastrointestinal disease many years later. As migration from Latin America to the United States increases, the blood banking community has become concerned about a possible threat to the nation's blood supply. To study this question, the Red Cross initiated a specialized screening study of donors at our Los Angeles and Miami blood centers in 1993. Questions were developed and subsequently refined to identify potentially high-risk donors. These donors are tested with a research test. Thirty of 196,832 donations, or 0.0015%, have tested positive for Chagas disease. This blood was discarded. None of the recipients of blood from earlier donations from these donors has tested positive for Chagas disease. This study is being expanded to other Red Cross centers under an FDA-approved protocol, and its results will permit informed decision-making about the management of Chagas Disease in the blood supply.

The second example is our approach to further reduce the already minimal risk of HIV transmission. The Red Cross supported the licensure and implementation of the HIV antigen test. We joined with the American Association of Blood Banks in recommending to the Blood Products Advisory Committee that it be licensed for blood donor screening. We will participate in studies evaluating this test after its implementation. For example, we will study its "magnet effect," that is the potential to draw high-risk individuals to a blood bank solely to be tested. This will provide additional data to assess the effectiveness of the test.

Finally, we are concerned about the infrequent but potentially serious problem of bacterial contamination. Data from a recent survey by Holland Laboratory scientists suggest that 1 in 2000 to 1 in 6000 units may contain bacteria. Although the overwhelming majority of recipients of these units suffer no ill effects, adverse reactions have been reported. No practical test is available to detect bacteria. However, our Holland Laboratory is collaborating with a biotechnology firm to develop a test that can be performed on the unit of blood at the patient's bedside immediately before transfusion. I have brought with me these small cassettes which are examples of what these test kits may look like.

These three examples represent proactive efforts by the American Red Cross to anticipate, study and act upon emerging threats. Our message to the American public must be clear. Blood is the gift of life—when appropriately used, its benefits far outweigh its risks. The blood supply has never been safer—but, as with any medical procedure, 100% safety is not realistic. Blood can only come from human beings, carrying with it the unpredictability inherent in all biological products. We rely on healthy, dedicated, fully screened volunteer donors as the cornerstone of blood safety. As guardians of the nation's blood supply, the American Red Cross will continue in partnership with medical professionals and public health authorities to maintain and improve the safety of this precious national resource.

Thank you.

Mr. DAVIS. Thank you very much. We have a vote on right now, but I'm going to try to get—Mr. Towns had some questions, and then we will recess and come back for more questions.

Mr. TOWNS. Yes. Thank you very much, Mr. Chairman. In testimony during the previous hearing, we heard that the restrictive and sometimes inflexible regulations implemented by the FDA have the potential to destroy this system of donation and blood banking as we know it. What is your response to that?

Dr. DAVEY. Perhaps I can speak to that. I'm going into a relationship with the FDA under a consent decree that you may be aware

of that was initiated in 1993. Working under the consent decree has been somewhat difficult, and it has been somewhat frustrating.

But, on balance, we feel that in the context of the transformation effort in the Red Cross, working with the FDA in this consent decree environment will result in a much stronger, a much leaner, a much better-positioned Red Cross to evaluate and deal with threats to the blood supply, both in the next few years and also into the next century. So we feel our relationship has been productive and professional, Congressman Towns.

Dr. SIMON. I might add that we have established a coalition for regulatory reform at the invitation of the Director of the Center for Biologics Evaluation and Research, with whom we work, and the American Association of Blood Banks, also, with the Red Cross's involvement, our organization and the American Blood Resources Association are working together to present to the agency ways in which we think the regulation of our organizations might be made more efficient and more flexible and help both parties.

Ms. LIPTON. I was just going to add, also, that there are a number of reform efforts before Congress this year, and we do support those. I think we've all been through a cultural change in the blood banking community, and we would encourage that same cultural change at the agency.

They have been working with us to do that, and I think when we speak of regulation, one of the things that is very frustrating is, we have a system now where we rarely replace things; we just add things on top of it without ever looking back at the entire system of regulation to see where we are today, what makes sense, and where you can eliminate the greatest risk, instead of just adding, perhaps, a new test, a new question.

That's something that we hope to be working on in the Association to present some of ideas to the FDA. We hope they will be receptive to those.

Mr. TOWNS. Thank you very, very much, Mr. Chairman.

Mr. DAVIS. Thank you very much. Mr. Souder has made a mad dash to the Capitol and has voted, and we'll hand the gavel over to him for continuing questions. Thank you.

Mr. SOUDER. After he catches his breath.

Mr. DAVIS. We'll give him a second. Thank you. We want to keep the hearing going, so Mr. Souder will continue the questions.

Mr. SOUDER [presiding]. Really a vote critical to the American Republic. It's called a journal vote, which means somebody didn't like what was going on and called for a parliamentary procedure motion. They obviously sent the youngest; I ran it. [Laughter.]

I wasn't the only one running, trying to keep hearings going on Capitol Hill at the same time.

I had some questions I wanted to follow up with on the first panel. I asked a question about the donors—did you get into that at all while I was gone—the advantage and disadvantage of paid volunteer donors. We earlier heard that there was some belief that having paid donors would expand the donor pool, and there were advantages to that.

Dr. Simon, in your statement, you said that safety would be improved by keeping the donor pool smaller. You also suggested that

volunteer donors may be safer than paid donors. Could you elaborate on some of that discussion?

Dr. SIMON. Historically, the United States has had two parallel systems. I think, since the early 1950's, the blood components—whole blood—have been provided primarily from volunteer donors, and this was increased further with the national blood policy in the early 1970's that supported the use of volunteer donors for whole blood donations.

The FDA also then regulated that blood had to be labeled as to being either from volunteer or paid donors, and this led to a dramatic increase in the percentage that was from volunteers. So, essentially, the blood and blood components that are provided by the blood centers are volunteer.

The panel that comes after us will talk about the plasma industry that historically has used paid donors. The rationale for that, historically, as I understand it, is these people were expected to subject themselves to a longer procedure of plasmapheresis, to come often twice a week, and often to have stimulation procedures done in order to produce the plasma.

So we've really had two parallel systems that have been developed. I think each system is trying to make its quality as high as possible and get the lowest possible risk within its system. I think that they're just different. We're providing blood that, by and large, remains in the community for the patients in that community. They're providing the starting material for pharmaceutical manufacture. So there is a difference between the two systems.

I don't mean by my testimony to pass judgment on the other system, but just to point out that we have spent, in the community blood centers, many years trying to develop the volunteer donor system to make it as safe as possible.

Ms. LIPTON. Could I add something to that?

Mr. SOUDER. Sure.

Ms. LIPTON. One of the things that I think that has come up is, I think we have that other system because we in the volunteer sector have not been able to fill that need, and so, to suddenly say we would need to go to an all-volunteer system for this entire program would not be possible.

I also think the other issue that needs to be raised is, we talk about paid versus nonpaid, but the real question here is one of donor incentives. What you always want to make sure is, whatever the incentive is for the donor to come in and donate, that that incentive is not somehow threatening the integrity of the donors, the safety of the donors.

So we are actually, and the Association had published a draft Association bulletin on donor incentives. We found it was very interesting, because it did generate a lot of controversy, and we are going to be doing further studies on what incentives are appropriate and at what point you may give someone an incentive that's not good to come in and donate.

I also think, as we become an increasingly pluralistic society, that it's very difficult to say, in one situation, that a paid donor is a less safe donor. I think it is entirely dependent upon communities and economic situations and how that donor is actually approached.

Mr. SOUDER. I apologize for some of my lack of familiarity with the history. My assumption has been that many volunteer donors will come because they've had an experience of either a family member or a friend who has had a problem, and therefore, they come into the stream as a donor, or they've heard something at work or somebody who is promoting a blood drive.

They were more or less, through guilt, encouraged to go the first time they did it, found out it wasn't so bad, and they continued to do it. Are those two major—what would be other places where people come in to the blood donor system in a voluntary way?

Dr. SIMON. Well, what we have tried to emphasize a lot in recent years is the educational part of it to get young people aware of the importance of volunteer donation as an act of a citizen.

So a lot of our emphasis has been on the school programs to get people to start to donate when they are in high school, so that the high school programs and the college programs are one of the ways that begin donation. And, of course, we have support from a broad segment of the community in trying to organize, to get people to blood drives to participate.

You're correct that often it's difficult to get the person in to begin with, but if you can get them in to begin with, give them a very positive experience, and then, if you can get them to repeat that experience, which is what we're trying to do more and more, and develop a repeat donor, then you have somebody who's really—part of their life is donating blood, and they will be with you for a long period of time. And, of course, they enhance the safety.

Dr. DAVEY. If I could make a comment, I would certainly agree with Dr. Simon. The overwhelming majority of the volunteer blood donors in the United States donate altruistically. They donate to give to others, and those are the kind of donors we like to encourage.

Again, as Dr. Simon has indicated, getting donors into the blood supply, either through connection with a family or a blood drive, is the major effort of all of our organizations, because once people donate blood, most of the time they feel pretty good about it, and they come back.

And the repeat donors we especially like to see, because they're donors who are already screened negative. They're pedigreed donors, if you will, and we encourage repeat blood donation throughout a person's lifetime.

Mr. SOUDER. My understanding is that roughly—if I have this statistic right—that 90-some percent of the problems in the blood supply come from the 4 percent who aren't voluntary, who are first-time donors. So, in that it puts a lot of pressure on the screening the first time through, what things are you doing or can be done to improve the blood donor screening process, if it's that disproportionate to those first-time donors?

Ms. LIPTON. Well, in fact, one of the things that we have looked at periodically is doing a different screening procedure for first-time donors, and when our committee is looking at this whole issue of sort of starting from scratch and building a donor questionnaire, that's one of the issues they will be looking at, as to whether you should be doing something different with first-time donors.

But I think we also have to keep in mind that that's as good as the diseases we know, and we've all heard today that the real threat, too, is for emerging diseases. So you have to be vigilant about keeping both types of questions. You could have the safest pedigreed donors in the world, but if something new comes into the blood supply, that same group could be bringing that in, too.

So you can't—I don't think you can totally fix the problem. I think you can probably focus on the diseases we know about. You really can't let down your guard with respect to the ones we don't know.

Mr. SOUDER. Well, if my statistic was correct, have you heard anything that counters that statistic, that over 90 percent of the problems come from the 4 percent who are—have you heard such a statistic as that?

Ms. LIPTON. I haven't heard 90 percent, and I think, in blood banking, we tend to speak more about specific diseases, so when you say 90 percent of the problems, we would probably break it down more into, is there a higher seropositive rate in a certain disease marker with first-time donors, and it's my understanding that there is.

Mr. SOUDER. Do you test first-time donors differently than you do repeat donors?

Dr. DAVEY. No, we don't. All of our donors, whether first-time or repeat, Congressman Souder, go through an extensive battery of questions that are actually quite difficult and somewhat intrusive. But all donors go through that process, and then, all are tested by the battery of highly sensitive tests that we now use to screen the blood supply.

But I think it's almost inherent in a first-time donor population that the markers will be a little bit higher. Those donors are then screened out, and so the repeat donors, I think almost by definition, will have a lower frequency of disease markers. So we want to make sure that we screen out risky donors at any point in the donation process, whether it's first time or later. But they'll be a slightly higher percentage of our first-time donors.

Mr. SOUDER. Do you hold the blood longer if it's a first-time donor, just to test it?

Dr. DAVEY. No, we don't. Blood, whether it's donated by a first-time donor or a repeat donor, Congressman Souder, is held until all screening tests are completed and that we're fully satisfied that the blood is safe for transfusion.

Mr. SOUDER. I yield for some additional questions.

Ms. PHELPS. In the interest of expediency, thank you. The question that was raised to the previous panel was the influence of cost on the development and issuance of new testing procedures.

What would you say would be the impact of cost consideration on the influx of new testing procedures in your industry—procedures, new technologies that might make the blood supply safer?

Ms. LIPTON. I think one thing that's important to remember is that all of us sitting at the table represent not-for-profits, so when we talk about costs, our operations are cost recovery. That means that we will charge for that unit what it costs us to process it.

So, in terms of the cost, it isn't something that we inherently feel, as much as it raises the cost of blood to people who might re-

ceive it. So we do get concerned about that, and I think that it has never really been the basis for a decision.

But we have an increasing sense from people that cost control, managed care—you know, finite resources are an issue for hospitals and for people who are receiving blood transfusions. So you can't say—I think, as was mentioned in the previous panel—you can't say it isn't something that you worry about. I don't think it has really been the deliberation that our groups have gone through when we've looked at these issues.

Dr. SIMON. I would agree. We certainly have a scientific review that's pretty much detached from those considerations, which then comes to a recommendation and a way to proceed. Then, I think, after that, the cost considerations come in.

Dr. DAVEY. I would agree. I think a good example, again, is the HIV antigen story, where the AABB and the Red Cross supported the licensure and implementation of antigen testing, even though this test will define and increase the safety of the blood supply by a very small degree. We feel that safety issues should come first.

However, we are in a situation now, these days, where new tests which may come to the fore are going to result in increasingly small increments in the safety of the blood supply. So I think issues such as safety, cost, and public policy may well be very useful bits of information for the new Blood Advisory Council, with Dr. Lee as head, to consider when, perhaps, new tests appear involving blood safety.

Ms. PHELPS. Thank you. Two more questions. Dr. McCurdy has suggested that there are some screening tests that have outlived their value. How would each of you respond to that remark?

Dr. SIMON. Well, we did have the one consensus development conference that resulted in dropping the ALT test as a requirement for transfusion, although, due to international harmonization issues, it's still required for our recovered plasma. It is difficult, once a test has been instituted, to look back and to try to review and determine if it no longer has utility.

That panel only recommended dropping that one test. There has been a lot of interest over the years in relooking at the syphilis test and its value, and there has been interest in looking at the Hepatitis B core antibody and its value. So I think that what we need is to continue to look at the value of these tests, collect data, and to try to reopen the consensus development mechanism for reviewing whether the test should be retained or can be dropped.

Dr. DAVEY. I would agree, again, with the ALT test. This was a test that was implemented as a surrogate test for non-A, non-B Hepatitis several years ago. We have a better test now. We have a very sensitive test for Hepatitis C. So, as Dr. McCurdy, I believe, explained, the value of the ALT test as a surrogate marker for that specific infection, became less important. So this was a test that we could safely drop.

But we would only, I think, consider modifying tests if the new tests or replacement tests that may be on the horizon provide an extra measure of safety that the old tests didn't provide.

Ms. LIPTON. I really have nothing to add to both of their statements.

Ms. PHELPS. How would you describe the benefits of the IOM recommendations, in terms of your activity?

Ms. LIPTON. I think we were very, very pleased with the recommendations. I think that what we all learned from the 1980's is that it really is that coordinating effort between the surveillance activities at Centers for Disease Control and, then, the research efforts of NIH and, then, the regulatory efforts of FDA that were very critical in knowing who played what role.

We rely very heavily on information that comes from the Centers for Disease Control, and we recognize that's their responsibility, but we can't make good decisions unless we have accurate information.

So we're very pleased with that, and I think we're looking forward to participating on the Public Health Advisory Council. I think it's a very good opportunity to bring in all of these issues that we were talking about and not confuse the issues that are before the FDA.

I think that we've struggled with that in the past couple of years because, as the issues become less scientific and technological, that's not where the arguments and the contention are. They really are in the issues of what are the priorities going to be, and, in view of limited resources, where are we going to put our resources, in what types of things?

Ms. PHELPS. So you believe the implementation of the IOM recommendations will help the prioritization of your efforts and Federal resources, as well as your own resources?

Ms. LIPTON. We do. I think we will continue—I think Dr. Simon mentioned we are pursuing our own parallel private initiative, where we would like to consider these issues in the blood banking community before we get to the Blood Safety Council or Public Advisory Council, so that we better understand, really, what we want to do. But yes, I think this will bring a good focus to all of our activities.

Dr. DAVEY. I would only say that the American Red Cross fully supported and joined with the American Association of Blood Banks in supporting the IOM report, and I agree fully with Ms. Lipton.

Dr. SIMON. I think that, from our point of view, pretty much in agreement with the other two speakers, the major impact of the IOM report is to highlight the issues at the Federal level and to help us achieve coordination from the important parts like NIH, CDC, FDA, and then, hopefully, relating to the community and the field, as well. So I think if it accomplishes that, it will be very valuable.

We were also interested—I know it's not a part of this committee's consideration—in the tort reform part of the report and have a pilot project for no-fault compensation in Arizona to go along with the IOM recommendation in that area. But we found them to be positive from that point of view.

Ms. PHELPS. Thank you. Thank you, Mr. Chairman.

Mr. SOUDER. I want to thank Ms. Phelps for letting us proceed in doing that. As someone who was formerly a staff director for a committee, I want to praise the staff work on this committee on both sides who have been very involved.

Now, as a Member, running between different things, if you didn't have the staff doing the in-depth research, working with the questions, we would look a lot dumber when we stand up here. So I'll say that for the record, because it happens to be true.

There's a couple of other questions we want to make sure that we have in our hearing record and would appreciate responses to. What are the benefits and challenges of the national computer system that's containing all the donor information?

Dr. SIMON. You mean a single?

Mr. SOUDER. Yes. If we had a national computer system with that donor information, what would be some of the pros and cons of such a system?

Ms. LIPTON. You mean specifically a national donor deferral registry? Is that what you're speaking of?

Dr. SIMON. I think the benefits, because we have a pluralistic system, would be that one could check for donors who had moved from one regional blood program to another, from one portion to another, and, for some reason or another, should not have their blood drawn.

The negative, of course, is trying to put something this complicated together and to have it work in an efficient manner so that we can utilize it in an ongoing fashion. So I think we've not solved that yet to figure out how we would put together such a system.

Dr. DAVEY. Or privacy questions.

Ms. LIPTON. I think there's another question here, and I think it's one from my experience. I think we should be looking at, really, the benefits that type of a system would bring. Is it something that really would increase the safety? I think that there is a very legitimate debate about that and that that's something that ought to be looked at before we would all make a determination to do that.

I think there is great concern over, logistically, how you would protect the sanctity of such a program. It probably could be done. The question is, is that the best place to put your resources in terms of protecting the safety of the blood supply?

Dr. SIMON. You were asking about privacy there, adding that on, and I think that is a serious consideration and would have to be taken into view. I also would agree that as a part of investigating it, the cost benefit would have to be looked at, because it would be a very small added benefit, and whether the cost would be prohibitive or not.

Dr. DAVEY. The American Red Cross does—we are going to be implementing a national computer system, linking our centers. But I concur with Dr. Simon and Ms. Lipton, a national donor deferral system, while appealing, and I think should be pursued in terms of its feasibility, does raise some problems.

Certainly the issue of donor confidentiality is major, how to keep the records of our deferred donors—sensitive records about test results—from falling into hands that are inappropriate.

Also, I think there are questions about the data that may go into this system, whether the data is uniformly of high quality, coming several different sources. These are important questions, and if we are to consider a national donor deferral registry, they have to be carefully considered.

Mr. SOUDER. Would a reduction in plasma pool size through plasma collection by plasmapheresis provide a greater safety for our Nation's hemophiliacs and other patients dependent on treatments derived from pool plasma?

Dr. DAVEY. We've talked a bit about the difference between plasma that is derived from plasmapheresis, which we will call source plasma, and in this country, source plasma from plasmapheresis tends to be from paid donors, as we've reviewed, Congressman Souder. Recovered plasma comes from units of blood that are donated in the volunteer blood supply, primarily.

I think it has been already reviewed to some extent, pools derived from recovered plasma tend to contain plasma from more donors than lots that are derived from plasmapheresis plasma derived from the paid donor population. However, there are no scientific data that I'm aware of, no data of any kind that indicate that the safety of one type of derivative versus the other is any different.

These derivative pools go through very extensive solvent detergent treatments and other heat treatments to render them very, very safe and free from infectious diseases. All the donors, whether they're from a paid source or the volunteer source, go through the same screening technologies.

So I think this is an issue that requires further study. Right now, it appears that these two sources for our plasma derivatives are equal on a very safe level.

Mr. SOUDER. Why have the blood bank accidents and error reports to FDA skyrocketed since 1990?

Ms. LIPTON. I think that's because we're looking more carefully, and, frankly, at the beginning, there was some confusion as to what constituted an error and an accident. I mean there are now new guidance coming out from the agency that I think will significantly reduce the number you see.

I think what's important about that is really that we continue to look at those internally. The most important piece of information is probably that the blood bank gets itself out of these, because it allows them to look at trends and where they think they have problems and need to fix them.

But I really think it's not that things are so terrible, it's that there was a misunderstanding about reporting, and I think any time you start looking at something, you will see a huge level until you say, "Oh, I understand. This is what's causing this issue," and then it paling down, and I think we're now into that phase.

Dr. SIMON. I would agree. Certainly, our members have put in much more extensive error management systems than they had in the past, and this has resulted in more errors being detected, which, in turn, I think, will help error resolution and quality improvement. But it does give you a period of time in which you have a greater number of reports, and I think we are expecting some guidance from the agency in perhaps reducing the reportable errors.

Dr. DAVEY. I would agree. If I can make one quick comment, I think the benefits of some of these reporting systems are becoming apparent. In the Red Cross system, we've seen now a 46 percent reduction in observations by the FDA in reviewing our centers from

fiscal 94 to fiscal 95. So we feel that the FDA is detecting fewer and fewer observations, and this may be as a result of our greater adherence to error and accident monitoring.

Mr. SOUDER. I had one other question for you, Dr. Davey. In your testimony, toward the end, you were talking about the HIV antigen test and its magnet effect. How would that test be different than other HIV tests? And also, how would you measure whether it indeed had a magnet effect? Would you compare it to the percentages that you're finding in current—or how would you do that?

Dr. DAVEY. That's a good question, and I think the REDS group that three of our centers and two other centers participate in are considering just how to ask that very important question.

REDS has already generated valuable information by doing surveys of blood donors after they've gone through the donation process, inquiring, "Why did you come to donate? What were the motivations that you came to donate?" This begins to get a handle on whether or not they come to donate altruistically or, a very small minority, come to get the test done.

Since the HIV antigen test will result in a very real, a very important, but a very small increment in blood safety, we're concerned and need to look at whether or not the fact that we have this new test, that donors may come to the blood centers to have this new test done that may be less safe. The best data that we have, from Dr. Bush and others, suggests that that will not be the case, but we do need to look at this more thoroughly after the test is implemented.

Dr. SIMON. One of the differences also, if I could just add, is that HIV antibody testing is available in alternative test sites, whereas the antigen test, as far as we know, the public health sector has no intention of testing for this at alternative sites. So the individual who's test-seeking could only get this, at least free of charge, at a blood center.

Mr. SOUDER. Ms. Phelps, did you have an additional question?

Ms. PHELPS. Yes, thank you. I want to follow up on the BPAC. All of your organizations were once members of the BPAC; is that correct?

Dr. SIMON. No.

Dr. DAVEY. No.

Ms. LIPTON. No.

Ms. PHELPS. Any of you?

Ms. LIPTON. Our membership would have been, but our institutions are not represented on the BPAC. It is individuals who would also be members of our organization or who might be employees of the American Red Cross.

Ms. PHELPS. I see. And they are no longer on the BPAC at this time; is that correct?

Ms. LIPTON. It's our understanding that, under the new rules, that anyone who has what is called an industry affiliation—and by that they mean anybody who is employed or has a financial interest in a regulated entity, an entity that's regulated by the FDA—will be precluded from being on the Blood Products Advisory Committee.

Ms. PHELPS. Right. But in the case of the new Advisory Council, the new Advisory Council that was established by HHS, your membership does have a seat at that table; is that correct?

Ms. LIPTON. Well, we haven't been specifically invited, but we understand that the recommendation was that that Public Health Advisory Council will have representatives from what has been called industry representatives from consumer interests and, then, ethicists. But it really hasn't been specifically defined as to how one gets a seat at that table or what qualifies you.

Ms. PHELPS. Right. But you do anticipate that someone from your industry would have a seat at the table.

Ms. Lipton. Well, we would certainly hope so, yes. We think we should be at that table.

Ms. PHELPS. The question would follow then, how would you reconcile that potential conflict of interest, being a regulated industry and then having a seat at the Council? Because I understand that was what led to the removal of some of your membership from the BPAC.

Ms. LIPTON. I think the difference between the Public Health Advisory Council is that the people who will participate in that will have interest. Consumer groups have vested interest, just as people from regulated entities have interest, and I think the whole point there is to try to get a very full discourse going on the issues that people need to engage in.

I think that, also, that's going to be an advisory council, as is the BPAC. We are frankly very disappointed that the FDA has chosen not to allow us seats or our members seats at the Blood Products Advisory Committee.

We think we're a very unusual group, because, unlike a lot of other entities that FDA regulates, the experts are both the people who are involved in the collection, processing, and distribution, and those who are the practitioners, those who transfuse. So to eliminate these groups, I think, really eliminates a huge number of people who have expertise in the area.

We've written to the FDA and explained that, that that is our concern. I think what we see right now is what's going to happen. I don't know whether they will really reevaluate their position. We hope they do.

Dr. DAVEY. I would certainly agree. It's very important that the scientists and health professionals in transfusion medicine—and those people who are represented by Dr. Simon, Ms. Lipton, and the Red Cross—that those people participate in the process that will be undertaken by the new Blood Advisory Committee.

We need to have a seat at the table, we need to participate, and I agree with Ms. Lipton, I share the disappointment that health professionals in this field were asked to withdraw from BPAC because of a perceived link with industry, and I think we lost some good scientific minds in that process.

Ms. PHELPS. Thank you.

Mr. SOUDER. I thank this panel very much for coming and being patient through our questioning and the going back and forth. If panel III could now come forward and stand for the swearing in. If you can remain standing, we need to swear in all witnesses.

For the record, our third panel is Mr. Michael Fournel, Dr. Edward Gomperts, Dr. Gene Tutwiler, Dr. Fred Feldman, and James Reilly. The only people who don't get sworn in at these things are Congressmen, because people don't expect us to tell the truth all the time.

[Witnesses sworn.]

Mr. SOUDER. Let the record show that all witnesses responded in the affirmative. You can go ahead and sit down.

Mr. Fournel, would you start with your testimony?

STATEMENT OF MICHAEL A. FOURNEL, VICE PRESIDENT, RESEARCH AND DEVELOPMENT, BAYER CORP.; EDWARD GOMPERTS, BAXTER HEALTHCARE CORP.; FRED FELDMAN, VICE PRESIDENT, TECHNICAL DEVELOPMENT, ARMOUR PHARMACEUTICAL CO.; GENE F. TUTWILER, ALPHA THERAPEUTICS CORP.; JAMES REILLY, PRESIDENT, AMERICAN BLOOD RESOURCES ASSOCIATION

Mr. FOURNEL. Mr. Chairman and members of the subcommittee, I would like to thank you on behalf of the Bayer Corp. for the opportunity to address you today. We share the subcommittee's commitment to the safety of the Nation's blood supply. We have submitted a detailed written statement, but, in the interests of time, I will summarize it here.

My name is Michael Fournel, vice president of research and development for biological products in the Pharmaceutical Division of Bayer Corp. In its Pharmaceutical Division, Bayer Corp. produces and markets biological products which are either derived from human plasma or from recombinant DNA technology, otherwise known as biotechnology.

Our products treat patients with serious, often life-threatening conditions, such as burn and accident victims and people with cancer, infections, genetic emphysema, and hemophilia.

It is important to note that plasma products, the realm of our involvement, are distinct from whole blood and blood components, especially because technologies applied in the processing of plasma products involve multiple inactivation or clearance steps that markedly enhance the safety of the final product relative to the starting material. Such technologies are not generally applicable to whole blood or other components, due to their sensitivity to harsh treatments.

Bayer's ability to deal with emerging dangers to the blood supply lies primarily in our scientific and technological capability. The robustness of our production methods and viral inactivation processes is absolutely critical to ensuring the safety of plasma-derived therapeutic agents.

While the screening of plasma has markedly reduced the risk of pathogen transmission, improvements in plasma processing have exerted additional, significant impacts on plasma product safety and will continue to do so in the future.

In addition, we have a role to play in efforts to safeguard the public health, not just as a recipient of government directives, but as partners in addressing the risks associated with the use of the products we provide.

The Institute of Medicine report contains several recommendations in this regard, which we support. As provided in our written statement, we were particularly pleased with recommendations 6, 7, and 8, which will enhance our ability to use our unique technological knowledge to assist regulatory agencies in their mission to protect the public health.

There are four main areas in which plasma product providers contribute to the safety and continued improvements in patient care. The first area is donor screening and plasma testing. This is an absolutely critical safeguard for whole blood supply and also plays an important role in plasma products safety.

At Bayer, we have rapidly incorporated new donor screening and plasma testing procedures as they have become available. For example, HIV antigen testing will be included once it is licensed.

The second area of contribution to product safety is when our plasma products are subjected to viral clearance and/or inactivation steps and other processing during manufacturing. Bayer is examining new techniques that will give us greater separation and clearance of pathogens from plasma products and new procedures for the inactivation of pathogens.

The third area is our ability to respond rapidly and responsively to new information and new threats. A good example of this was Bayer's response to a previously little-known pathogen known as Creutzfeldt-Jakob disease, or CJD.

Upon being notified by two of our suppliers that we had purchased some plasma intermediates obtained from a donor tentatively diagnosed with CJD, Bayer immediately initiated a voluntary withdrawal of all 20 lots of the product in which these intermediates could have been used.

At this time, Bayer also initiated its current policy to undertake a worldwide withdrawal of any plasma-derived product found to contain protein donated by healthy individuals who later were discovered to suffer from CJD. Bayer took these steps, even though it remains unclear whether and in what way CJD could be transmitted via blood or plasma products.

This is a prime example of why cooperation among plasma suppliers, manufacturers, researchers, and regulatory agencies is essential to ensure that decisions are made based on all available scientific information.

Finally, I would like to address the fourth area, our research and development activities and new treatment modality. Products derived from human plasma will continue to fill critical needs, despite the promise of biotechnology since it is unlikely that products developed through biotechnology will ever wholly replace plasma-derived therapeutic agents.

We continue to explore alternatives to plasma products where available, as exemplified by recombinant Factor VIII, and our investigation of alternatives such as transgenic animals and other sources for biological therapeutics. We point out, however, that no product source is without some risk.

In conclusion, I would like to state that our activities in these four areas I outlined above exemplify our commitment, both to the development of methods capable of meeting future challenges and an ethic that places ahead of everything else the health and safety

of patients who use our products. This concludes my formal comments, Mr. Chairman.

[The prepared statement of Mr. Fournel follows:]

PREPARED STATEMENT OF MICHAEL A. FOURNEL, VICE PRESIDENT, RESEARCH AND DEVELOPMENT, BAYER CORP.

INTRODUCTION

Mr. Chairman and members of the Subcommittee, I would like to thank you on behalf of Bayer Corporation for giving us this opportunity to address you today. We fully appreciate the level of the Subcommittee's commitment to the safety of the nation's blood supply. We share this commitment, particularly as it applies to the plasma fractionation industry, and we strongly commend your own public policy leadership, Chairman Shays, for launching this important examination of blood and plasma product safety issues.

My name is Michael Fournel, and I am Vice President of Research and Development for Biological Products in the Pharmaceutical Division of Bayer Corporation. I have conducted Research and Development efforts for Bayer in the field of plasma products for 20 years, during which time I have been responsible for the preclinical development of a number of presently marketed products derived from plasma fractionation or biotechnology sources. I assumed my present position one year ago.

AN OVERVIEW OF BAYER

Mr. Chairman, I would like to begin by describing my company and its role in this field.

Bayer Corporation, headquartered in Pittsburgh, is an American research-based company with major businesses in health care, chemicals, and imaging technologies. Bayer is the United States subsidiary of Bayer AG, the international chemical and health care company based in Leverkusen, Germany. Bayer Corporation, with 24,000 employees in the U.S. employed at more than 100 locations in over two dozen states, contributed almost a third of our parent company's worldwide sales.

Bayer's Pharmaceutical Division is based in West Haven, Connecticut, with additional operations in San Diego and Berkeley, California; and in Clayton, North Carolina. Within this division, Bayer manufactures and markets biological products which either are derived from human plasma or recombinant DNA technology (biotechnology). Our involvement in this field has a long and distinguished history. Our company was one of the first to pioneer plasma fractionation to support America's effort in World War II, and is the only one of the original fractionators still in operation.

Today the biological products component of our business, although relatively small in corporate terms, is an important part of Bayer. Bayer's commitment to providing patients with the safest and most up-to-date products is equally significant. Our products treat a range of serious conditions and diseases, such as general and specific immune disorders; hepatitis, tetanus, rabies exposure; genetic emphysema; and hemophilia. These life-saving therapies, along with those of other plasma fractionators, have saved millions of lives—accident and burn victims, people with immune deficiencies, cancer patients, people with hemophilia, and others with serious and debillitating illness.

A COMMENT ON THE INSTITUTE OF MEDICINE REPORT

Mr. Chairman, Bayer has been asked by the Subcommittee to provide our views on the role of blood and plasma products manufacturers in dealing with potential emerging dangers to the blood supply, and to discuss our application of new technologies toward improving product safety.

Bayer Corporation is a research and manufacturing organization, and as such our ability to have an impact on these areas lies primarily in our scientific and technological capabilities. The robustness of our manufacturing methods and viral inactivation processes, in particular, are absolutely critical to ensuring the safety of plasma-derived therapeutic agents. While the screening of plasma has markedly reduced the risk of pathogen transmission, manufacturing process improvements have exerted an additional significant impact on plasma product safety, and will continue to do so in the future.

It is important to note that plasma products (the realm of our involvement) are distinct from blood or blood products (e.g., components), especially because technologies applied in the manufacture of plasma products involve significant, multiple inactivation or clearance steps that markedly enhance the safety of final products

relative to the starting material. Such technologies are not generally applicable to blood or blood products due to the lability of blood and its sensitivity to harsh treatments.

That said, it is also important that we examine the interplay of our activities with those of others in our industry and the scientific community at large, and with regulatory and surveillance government agencies, including the U.S. Food and Drug Administration (FDA) and Centers for Disease Control (CDC). As a responsible member of industry, we have a role to play in efforts to safeguard the public health, not just as a recipient of government directives, but as partners in addressing the risks associated with the use of the products we manufacture. This isn't a new view on our part, yet it must be acknowledged that we are here today because it is critical to the future safety of the blood and plasma supply that we seek additional opportunities to work cooperatively.

A report of the Institute of Medicine (IoM) issued last July contains a number of recommendations in this regard which we enthusiastically support. The American Blood Resources Association (ABRA) has provided you with a statement regarding this report which we endorse.

In response to the IoM report, we understand that the Department of Health and Human Services (HHS) intends to implement key recommendations of its Task Force on Blood Safety in order to elevate blood safety issues to the highest levels of attention within HHS. Working with both Congress and HHS, we look forward to making a positive and substantive contribution to the deliberations of HHS's new Advisory Council on Blood Safety and Availability. While some aspects of the IoM report are subject to questioning we agree with the spirit of those recommendations which encourage implementation of partial solutions to problems for which complete information is not yet available (Recommendation #6), along with a subsequent review of such decisions when more information has been obtained (Recommendation #7)—as we will discuss later, such is the present situation with regard to Creutzfeldt-Jakob Disease (CJD). Recommendation #8 points to the need for clear directives from government agencies to regulated entities; it is in keeping with our stated goal of a collaborative relationship with government agencies, and our recognition that we must have access to clear guidance when decisions have the potential to affect the availability of products to patients who need them.

FOUR AREAS WHERE INDUSTRY CAN HAVE THE GREATEST IMPACT ON PRODUCT SAFETY

We believe there are four important areas in which plasma-product manufacturers can, and do, contribute to safety and continued improvements in patient care:

1) Screening of plasma donors and testing of plasma prior to manufacturing;
2) Continuing improvements in manufacturing processes and viral inactivation technologies;
3) Swift and responsible action in the event a potential pathogen is discovered; and
4) Research and development into new treatment modalities.

Each of these areas is important. Comprehensive donor screening, for example, is an absolutely critical safeguard for the whole blood supply, and also plays an important role—including from the standpoint of public perception—in plasma product safety. Swift and responsible action in the face of new threats is something this Subcommittee has been especially concerned about, and I will later give you an example of how we at Bayer are focusing on this as a main tenet of our commitment to safety. And, the future will indeed be shaped by all of the scientific expertise we can bring to bear on the research and development of new technologies and new products.

I want to emphasize, however, that in regard to plasma-derived therapeutics (as distinguished from whole blood donations), a major contribution to product safety is made when plasma is subjected to viral clearance and/or inactivation processes during manufacturing. This is an important element that distinguishes some of the safety issues related to plasma products from those related to whole blood, which cannot be subjected to viral inactivation processes such as heat treatment without destroying it.

1) Donor Screening and Plasma Testing

The first, critical steps in Bayer's effort to ensure the safety of plasma-derived products occur before the use of an plasma donation.

Prospective donors undergo a stringent screening process that includes identification and residency checks as well as mandatory medical history, physical exam, and blood testing. Our procedures meet in all cases the screening guidelines established by the FDA to protect the plasma supply.

Donor screening begins the moment a prospective donor walks into one of our plasma centers. To help ensure that all prospective donors are fully informed and respond accurately to screening questions, they are provided educational information they must read. An interactive videotape Bayer developed tests their understanding of donation restrictions and the process of plasma donation. During a confidential interview, the center's medical supervisor takes a detailed medical history and conducts a physical examination, with particular emphasis on identifying any factors that place the donor at a greater risk than the general population for contracting and carrying HIV or other infectious agents. Repeat donors are re-screened for many of these criteria at each donation. Finally, the donor is given the opportunity to inform the center on a confidential basis that his or her plasma should not be used.

During a process called plasmapheresis, plasma is obtained while other blood components (e.g., red blood cells) are infused back into the donor. Bayer primarily procures plasma through plasmapheresis from our own plasma centers and from plasma centers operating under contract to us, all of which are licensed and regularly inspected by the FDA. All of our owned and contract centers participate in our Automated Plasma Collection Program. Automated plasmapheresis accomplishes several goals at once: it increases the safety of the procedure by eliminating many steps in the process and the possibility of errors in documentation; it also saves time and is more convenient for donors. Plasmapheresis is the foundation for obtaining the large volumes of plasma necessary to meet the great demand for plasma derivatives.

A sample from every plasma donation is immediately fowarded to Bayer's plasma testing laboratory in San Diego, California, which is licensed under the Clinical Laboratories Improvement Act (CLIA) as well as by the FDA. The rest of each plasma donation is quick-frozen and stored at the plasma collection center until sample test results are received.

In the lab, every plasma sample is tested for HIV–1 and HIV–2 antibodies, hepatitis B (Hepatitis B Virus Surface Antigen, HBsAg) and hepatitis C (anti-HCV), liver disease (Alanine aminotransferase, ALT), and atypical antibodies (non ABO). Once licensed, HIV–1 antigen testing will be included in this panel.

If any of these test results or physical exam findings are positive, the potential donor's plasma is destroyed and the donor is permanently deferred from donating again. Similarly, if any test results are positive, the prospective donor's name is added to the National Donor Deferral Registry, a computerized database established by industry, which plasma centers can instantly access using an 800 number.

Plasma donor screening procedures are constantly updated and refined. As threats to the blood supply have materialized in recent years, we have rapidly incorporated new donor screening and plasma testing procedures to address these challenges. Recently, for example, we were confronted with a previously little-known disorder called Creutzfeldt-Jakob Disease (CJD) and its theoretical association with blood and plasma products. We immediately added questions about CJD to the donor education and medical history components of the screening process at all of our owned and contract plasma centers. In fact, the industry has added numerous new donor tests and screening requirements over the past decades.

Our responsiveness in this area will continue to play a central role in maintaining high quality plasma supplies.

2) Manufacturing Processes and Viral Inactivation Technologies

Within Bayer Corporation, biological product processing and manufacturing are located in two major research and manufacturing facilities, both of which are in the middle of significant expansions of their manufacturing capacity to address what is currently a desperate need for life-saving products that far outstrips the supply. Bayer Corporation is investing several hundred million dollars at each of these multi-purpose facilities to nearly double manufacturing capacity and support leading-edge research and development activities.

I should point out that although I will be referring to "manufacturing" in terms of therapies derived from plasma, the therapeutic agents are actually made in the bodies of plasma donors. We process the plasma to provide those therapeutic agents in a useful form.

The activities at Bayer's facility in Clayton, North Carolina are focused on plasma processing and manufacture. Scientists there are examining new techniques that will give us greater separation and clearance of pathogens from plasma products—for example, improvements in centrifugation and chromatographic partitioning techniques. In addition, new procedures are being explored for inactivation of pathogens, including chemical (e.g., solvent detergent) and thermal (e.g., dry heat and wet heat) inactivation processes. We are also putting redundant processing steps in place to

ensure product safety in the event of an inadvertent malfunction at any step in manufacturing.

One of the biggest shifts in our activities is the result of what we have learned in the last 20 years about the potential of previously unknown pathogens to threaten plasma supplies. In the past, we developed viral inactivation techniques targeted to specific pathogens (e.g., hepatitis B and hepatitis C). Now, we are working to develop techniques capable of targeting all known classes of pathogens—for example, lipid-enveloped versus non-enveloped viruses (e.g., parvo-virus). In this way we hope to anticipate currently unknown pathogens, and, should they appear, we will be better prepared to deal with them with methods already in place.

Bayer's facility in Berkeley, California is the worldwide headquarters of our biotechnology research and manufacturing activities. Biotechnology, to the extent that we can develop therapeutic agents to replace plasma-derived products, holds extraordinary promise for decreasing the risk of pathogen transmission. One example of this is our recombinant, genetically engineered clotting factor (Kogenate®).

3) Swift and Responsible Action

As long as we must rely on products derived from human plasma, there will always be a small chance that some pathogen may be presented in plasma used to produce therapeutic agents. In this context, our ability to respond rapidly and responsibly to new information and new threats is paramount. We must be positioned to make real-time decisions based on adequately disseminated facts and the unique circumstances of each situation—even if, as will often be the case, our information is incomplete. I believe we are positioned to respond in this way, both as a company and as an industry.

As an example of Bayer's approach, I would like to review Bayer's policy and actions relative to the emergence last year of Creutzfeld-Jakob Disease (CJD).

In November 1994, Bayer was notified by the American Red Cross (ARC) that one of its donors had been tentatively diagnosed with CJD, and we determined that some lots of a Bayer product—Prolastin®, a replacement therapy for a rare disorder called alpha-1 antitrypsin deficiency, or genetic emphysema—had been manufactured using plasma intermediates containing a plasma-derived protein donated by this individual. (In order to produce an adequate supply of Prolastin, Bayer must additionally obtain intermediate material—that is, by-products of other plasma products—from outside suppliers like ARC and other plasma manufacturers.)

Based on this information, Bayer initiated a voluntary withdrawal of 20 lots of Prolastin that had been produced from ARC plasma intermediaries. Over a period of just three days, Bayer did the following: notified key groups, including the four largest home health care companies and the Alpha-1 National Association (a patient advocacy organization) that there was a potential problem; issued withdrawal notices via overnight delivery (and, as a back-up measure, by facsimile) to approximately 800 customers who, according to company records, had received these lots; and simultaneously issued a public statement.

On November 21, 1994, Bayer was notified that a second ARC donor had been diagnosed with CJD, and that additional plasma-derived intermediates purchased by Bayer to manufacture Prolastin were affected. Bayer immediately issued another voluntary withdrawal—this time, of three lots of Prolastin produced from these intermediates. The next morning, Bayer's Recall Coordinator undertook a voluntary telephone campaign to everyone who had called the company with questions during the first withdrawal to notify them that three additional lots of Prolastin were being withdrawn. Bayer then notified all customers in writing, whether or not they had received the lots in question, to clarify facts relative to both voluntary withdrawals. During this period, Bayer fielded approximately 950 telephone calls, provided approximately 400 information packets to clinicians, and sent another 200 faxes.

At this time, Bayer adopted a clear policy with respect to any plasma-derived product that is found to contain protein donated by healthy individuals who are later discovered to suffer from CJD. In the event of such an occurrence, Bayer will initiate an immediate worldwide withdrawal of all lots of any product manufactured from such material.

Bayer took these steps in the absence of a solid scientific rationale for doing so—the jury is still out on whether and in what way CJD may be transmitted via blood, blood components, or plasma derivatives. And frankly, we have concerns about the effects of our current policy on the availability of life-saving products that are already in short supply. This is a prime example of why information sharing and a quick-response, coordinated approach among plasma suppliers, manufacturers, researchers and regulatory agencies is essential to ensure that good, responsible decisions are made based on all the available scientific information. Bayer Corporation's efforts in this case, however, exemplify the degree to which our industry's ability

to take swift and responsible action is one of the most critical ways we have of ensuring the safety of plasma-derived products.

4) Research and Development

We believe products derived from human plasma do and will continue to fill critical medical needs well into the foreseeable future, despite the promise and potential of biotechnology. The perspective gained from our experience with plasma products suggests that biotechnology is not risk-free (for example, cell culture can be permissive for some pathogens), and we are currently applying lessons learned from our plasma business to incorporate viral inactivation and clearance technologies into our biotechnology manufacturing processes, as well. Furthermore, it is unlikely that products developed through biotechnology will ever wholly replace plasma-derived therapeutic agents. The efficacy of some products, such as gamma globulin, depend on the diversity of antibodies that can be obtained only from a large donor pool. Recombinant factor VIII is viable as a biotechnology product because it is made and used in relatively small quantities; it is a much more formidable challenge to make proteins administered in high doses, like albumin, via biotechnology in a commercially feasible manner. Bayer Corporation believes that establishing the best possible safety profile for our products is our primary research objective.

As previously discussed, the history of the industry's efforts with regard to safety of products can be viewed as a continuum. Awareness of the potential of coagulation factor concentrates to transmit hepatitis led in the 1970's to the initiation of efforts which bore fruit in the 1980's with regard to inactivation of these specific viruses (HBV, HCV)—that is to say, specific virus targets were identified and specific methodologies studied. These efforts were not without problems, however, since there existed very real risks of significant product loss (in an era of acute products shortages, one that continues today) and neoantigenicity (for which demonstrated clinical experience exists), and there was insufficient knowledge to permit definitive conclusions.

The tragic occurrence of HIV infection in the blood supply ushered in a transitional period in this continuum—virus-specific methodologies were certainly applied but there was now an awareness that a previously unknown pathogen could suddenly appear in blood. This perspective led to a new concept in which classes of pathogens would now be studied and methods developed to inactivate or remove them (e.g., the solvent-detergent procedure for the inactivation of lipid-enveloped viruses such as HCV and HIV). Validation of production processes for clearance of viruses serving as markers for a class has also been undertaken such that strict compliance with "good manufacturing processes" (GMP) provides assurance that viruses are removed from products.

Today we consider blood and plasma as a safe resource but one into which unknown pathogens could appear without warning. Accordingly our strategy is to include steps in the collection and especially the manufacture of plasma products which are known to inactivate or remove entire classes of pathogens; to include multiple, even redundant, steps to ensure safety even if subtle differences between pathogens of similar class occur; and to investigate novel methodologies which augment current approaches. One example of the latter is the use of virucidal agents which have come from anti-viral drug research, which were too toxic for use in humans but which might be effective in a manufacturing process since they can be removed by downstream processing, thereby exerting the anti-viral effects without ever being present in the final products. We are examining other physical approaches as well (e.g., irradiation) and remain optimistic that new separation methodologies (especially chromatographic) will further advance our abilities to eliminate pathogens from plasma products.

Non-viral pathogens deserve special mention in this context. Often, blood borne pathogens are not a risk for plasma products since they either compartmentalize into cells (e.g., HTLV-1, malaria) or are extremely labile parasitic organisms which cannot survive even the initial stages of plasma products manufacture (e.g.,trypanosomes). However, concerns about the potential infection of blood and blood products by the agent responsible for CJD have recently been heightened, as discussed above. As several witnesses have already indicated there is currently no confirmed evidence for transmission from transfusions, but we as a company and an industry have initiated efforts to develop the necessary scientific evidence to allow for appropriate risk assessments. Several technical hurdles need to be overcome before this is possible—for example, the present lack of rapid, sensitive and generally accepted diagnostic screening and testing procedures; the absence of understanding of the infectious etiology; an unambiguous definition of the infectious agent; and the like. Our concerted efforts will hopefully permit better definition and answers to these technical challenges, thereby enabling a rigorous and scientifically

valid analysis of the risk to recipients of blood or plasma products associated with donations from individuals infected with CJD or other, currently unidentified agents responsible for transmissible spongiform encephalopathies.

We continue to explore alternatives to plasma products where available, as exemplified by recombinant FVIII; Bayer invested $300 million and over 10 years to make this product a reality. In addition to biotechnology, Bayer is examining alternative sources such as transgenic animals and non-human sources for biological therapeutics, but point out that no product source is without some risks. The chronic supply shortages which exist for nearly all of our plasma products, combined with the often life-threatening nature of the diseases they treat, argues compellingly for the continuation, even the expansion of efforts to produce safe plasma products. Our research and development efforts will continue to place safety from pathogen transmission as our primary objective so that this essential resource can be utilized by the medical community with a minimum of concern with regard to safety.

CONCLUSION

Our activities in the four areas I outlined above exemplify our commitment to both a scientific method capable of meeting future challenges, and an ethic that places ahead of everything else the health and safety of the patients who use our products.

Bayer Corporation will continue to disseminate the results of these efforts within both the medical and scientific community and in appropriate regulatory forums. In the past, we have discussed our products and processes and all of our plans with the FDA, and will continue to do so. We will continue to jointly develop testing, clinical trials and research is such a way as to encourage the continuation of that relationship. We look forward to participating in deliberations of the new Blood Safety Advisory Council to examine the broad public health and societal implications of blood safety issues.

This concludes our formal comments, Mr. Chairman. Thank you very much for your time and attention. I would now be happy to answer any questions you and other members of the Subcommittee may have.

Mr. SOUDER. Thank you very much for your testimony. Dr. Gomperts.

Dr. GOMPERTS. Mr. Chairman, members of the subcommittee, my name is Edward Gomperts. I'm a practicing physician with expertise in hematology and have special experience in the management of individuals with hemophilia and also HIV disease.

I'm also medical director and vice president of medical affairs and clinical development of the Baxter Healthcare Hyland Division, and as such, I have the responsibility for monitoring the safety and efficacy of our currently licensed products, as well as those therapeutic agents currently under clinical trial.

The Baxter Healthcare Hyland Division processes and markets various therapeutic biologic proteins. These are not pills or tablets; they are treatments derived from living sources. These include plasma-derived and recombinant source clotting factor concentrates for treatment of various forms of hemophilia, intravenous immunoglobulins for the treatment of various forms of immune deficiency and immune disorders, and also albumin, which is used to manage individuals with shock.

We have special capabilities in the purification of these delicate biological molecules, which are obtained from either human plasma or from cultures of genetically engineered cell lines.

We have played a leadership role in this therapeutic arena for many years. Hyland developed and marketed the first hemophilic clotting factor concentrate in 1967, the first licensed viral inactivated clotting factor concentrate early in 1983, was the first to use and market a second generation viral inactivation procedure for Factor VIII concentrate in 1987, and the first to market a ge-

netically engineered recombinant clotting Factor VIII concentrate in 1992.

We see Baxter continuing to play a leadership role as we look to the future and focus on extending the capabilities of our viral inactivation procedures to target the full spectrum of transmissible infectious agents. This is not a trivial undertaking, nor are we naive as we face the hurdles and challenges ahead, but Baxter is committed to this goal.

Simply put, what is good for the patient is good for Baxter. We're driven toward what might prove unattainable, that is, completely safe plasma-based therapeutic proteins. It is my opinion that we have already traveled a great distance toward that goal.

On looking at where we stand today, it is clear that there are a number of avenues for approaching viral inactivation and exclusion, and we believe that our plasma-based products are safer today than they ever have been. We have come a long way. Further, our recombinant Factor VIII manufacturing production process has opened a whole new avenue to explore as we move ahead toward our ideal therapeutic.

On considering the potential technologies that might be applied to our target, it is important to sound a cautionary note. We cannot allow ourselves to be totally and completely focused on the target because the therapeutics we process are not inert. They are complex molecules, and our patients dare not be harmed be a mindless, technologic-driven war on viruses.

Sure, we'll zap the bugs, but at what cost? What are the risks to the patient? Such an approach has indeed recently resulted in a mini-epidemic of a much feared adverse reaction in people with hemophilia in Europe.

Two European fractionators were recently instructed to withdraw their double viral-inactivated products from the European market because of a spate of unexpected inhibitor antibodies generated by a molecularly altered protein induced by aggressive physical and chemical techniques. The net result of this in these hemophilic patients was that bleeding could not be controlled.

At this juncture of my presentation, I and my colleagues at Baxter wish to acknowledge the pivotal role being played by this subcommittee. It is highly appropriate that government focus on the key issue of safety of the blood supply. It is also appropriate to air and debate the issues and impediments that impact the assurance of blood and blood product availability and supply.

As we at Baxter examine where we are today and where we need to be in 3 to 5 years, we believe that the fastest and most productive, intelligent approach to this issue is to marshal the resources and knowledge across our industry, by our governmental agencies and the outstanding capabilities of academicians across our country, as well as in the world.

As the only United States-based fractionator and as a major supplier of our therapeutics and technologies to Europe, Japan, as well as the rest of world, Hyland is able to perceive the potential of harvesting this diffuse knowledge base, as well as resources.

It is logical and virtually a no-brainer to recognize the potential and likely beneficial outcomes of a consortium of industry, academics, the CDC, the FDA, and other regulatory agencies across the

world. We firmly believe that such a collaborative interaction will bring us rapidly toward our goal.

There are, of course, impediments that Congress must recognize. One are the antitrust laws. An imaginative and creative approach can deal with this issue without harming the overall intent of these important antitrust laws. Second, academia, including the NIH, should have adequate biomedical research funding to meet these challenges.

Finally, one other approach will also assist us in our task, specifically the harmonization of regulatory requirements across the major geographies, with the overall objective of protecting the public welfare. And, of course, in the final analysis, this is why we're all there today. Thank you.

[The prepared statement of Dr. Gomperts follows:]

PREPARED STATEMENT OF EDWARD GOMPERTS, BAXTER HEALTHCARE CORP.

Mr. Chairman, Congressman Towns, and distinguished members of the Subcommittee, good morning. Baxter Healthcare Corporation is pleased to have been invited to appear before the Subcommittee today.

Baxter Healthcare Corporation is the principal domestic subsidiary of Baxter International Inc. Through its subsidiaries, Baxter is the leading manufacturer and marketer of health care products and services in nearly 100 countries worldwide. The company concentrates research-and-development programs in biotechnology, cardiovascular medicine, renal therapy and related medical fields.

The Baxter Healthcare Hyland Division processes and markets various therapeutic biologic proteins, these include plasma-derived and recombinant sourced clotting factor concentrates for the treatment of various forms of hemophilia, intravenous immunoglobulin for the treatment of various forms of immune deficiencies and abnormalities, and albumin. Hyland has special capabilities in the purification of delicate biologic molecules which are obtained from either human blood plasma or from cultures of genetically engineered cell lines. We have played a leadership role in this therapeutic arena for many years. Hyland developed and marketed the first hemophilia clotting factor concentrate in 1967, and the first licensed viral inactivated clotting factor concentrate early in 1983; was the first to apply and market a second generation viral inactivation procedure for these products in 1987; and the first to market a genetically engineered recombinant clotting Factor VIII concentrate in 1992.

We are here today to address future directions in the safety of therapeutic proteins. Therapeutic proteins, such as albumin, coagulation factors, and gamma globulin, are derived primarily from human plasma. However, as we will discuss in greater detail in a few moments, some of these proteins also have been derived using genetic engineering.

Over the past years and decades, many patients have benefited greatly from therapeutic proteins. Diseases which once cut short many lives now can be controlled, or reduced in severity, using therapeutic proteins.

The tremendous benefits of therapeutic proteins have resulted from research and development conducted by Baxter's Hyland Division as well as several of its competitors. This research and development has stemmed from the healthy workings of a competitive marketplace, as well as a genuine and deep concern for the well-being of patients. It has occurred without compulsion of the government, and will continue even without government urging.

In the recent past, there have been some stunning technological advances in the processing of therapeutic proteins, and Baxter has been at the forefront of those advances. These technological strides have brought with them significant gains in the safety of therapeutic proteins.

For example, Baxter has developed coagulation therapies—used to treat hemophilia—that are processed using genetic engineering. Baxter's Hemofil M® is processed using monoclonal antibodies that are "grown" using genetically-altered mouse cells. These cells are grown from a known cell that our scientists have been able to characterize all the way down to its DNA base, and which Baxter can replicate infinitely. Even more amazing is Baxter's Recombinate®, which contains anti-hemophilia clotting factor produced by hamster mammalian cells that our scientists have reprogrammed using human DNA.

In addition to genetic engineering, Baxter employs various forms of heat treatment, filtration, and solvent-detergent processes to remove or inactivate viruses and other pathogens that may appear in plasma from which therapeutic proteins are processed. The precise methods used vary depending upon which protein is being processed.

The processing methods used by Baxter to fractionate its therapeutic agents are capable of removing or inactivating a wide range of viruses and other pathogens. The solvent-detergent process, for example, inactivates HIV, Hepatitis C, bacterial contaminants, and other pathogens. But we continue, as will continue, to research and develop even better methods to remove or inactivate viruses. It is good business, and it is the right thing to do.

Baxter's goal is to develop completely safe plasma-based therapies by eliminating all infectious agents—and therefore all transmission of pathogens—from these therapies. We realize that we probably never can achieve this goal, but it gives us a good conceptual target at which to aim. We can move toward this goal through continued research and development of pathogen removal and inactivation methods. Indeed Baxter continues to research, evaluate, and develop chemical and physical methods of inactivating or removing viruses and other pathogens. We also continue to seek new applications of recombinant DNA technology, which may in some instances substitute for plasma fractionation.

As we strive for maximum levels of safety, we must remain cognizant of the delicate balance we face: Efforts to enhance safety may themselves impose risks, and at some point those risks may exceed the benefits of safety measures. These risks take two principal forms. First is the risk that new safety technologies may change therapeutic proteins so as to render them ineffective or harmful. Second is the risk that efforts to increase the safety of therapeutic proteins may reduce their supply, forcing patients to do without needed therapy.

The first type of potential risk from efforts to increase safety—that of reduced safety or efficacy—is most easily illustrated in the case of viruses. The "skeleton" of a virus—called its "capsid"—is made of protein. But the very therapies that patients need are also made of protein. So if we wiped out all proteins, we would get rid of viruses—but the medicinal value of the therapy would be destroyed as well. For this reason, efforts to remove or inactivate viruses require great care. In shooting at viruses, we do not want to hit the beneficial proteins as well, possibly rendering them ineffective or even harmful.

A particularly vexing question is how we respond to currently-unknown pathogens, which could emerge at any time. Because they are now unknown, we of course cannot predict with any certainty what form new pathogens might take, or how benign or harmful they might be. Nor can we determine, in advance, which method or methods might be used to defeat them, or what the risks and benefits of various measures to combat them might be. Until a risk is known, there simply is no good way to tell whether a given approach to that risk will or will not increase safety. The best response to currently-unknown risks well may be continued development of improved technologies, so that we are prepared to respond in relatively short order once we become aware of new pathogens.

The second type of potential risk presented by efforts to enhance safety is that such efforts sometimes may curtail the supply of therapeutic proteins. At some point, efforts to improve theoretical safety may threaten the availability of needed therapies, and actually harm the very patients who the safety measures were designed to protect. Therapies made from human sources such as plasma carry with them certain inherent risks. These risks, however, must be weighed against the tremendous savings of life and quality of life that plasma-based therapies make possible. Because a therapy that is not available cannot save lives, restrictions on availability—such as recalls or protracted licensure proceedings—must be based on sound scientific grounds.

Mr. Chairman, efforts to further enhance the safety of therapeutic proteins should continue to move forward on multiple fronts. In addition to Baxter, Baxter's competitors no doubt will push forward on their own to develop advanced safety mechanisms. Moreover, we undoubtedly will continue to see new ideas proposed and perhaps developed by individual inventors and scientists, as well as others who may wish to sell new technologies to the plasma processing companies. But we must ask whether there is some way for industry, together with academia and regulatory agencies throughout the world, to cooperate in advancing the safety of plasma-based therapeutics.

Because Baxter and the other plasma-processing companies are competitors, there obviously have been severe limits on our sharing of technology. Some of the ideas that no doubt are on various companies' drawing boards are trade secrets—their property—and rightfully so. In addition, the government has tended to frown upon

meetings in which representatives from all or most companies in an industry get together in a room and plan the industry's future in whole or in part. Even the perceived threat of antitrust action by government or private parties can deter cooperation within an industry.

But we do have the opportunity to forge ahead and create a new partnership between the public and private sectors. The plasma processing companies, such as Baxter, have knowledge, experience, research, and resources. The government has the ability to clear away antitrust barriers to collaborative research efforts by industry, and to seek international harmonization of regulations. It also has the capability of sharing, in real-time, information on emerging trends in diseases worldwide. Academia—both in the United States and throughout the world—has scores of scientists who possess, collectively, a vast storehouse of knowledge on virology, hematology, epidemiology, and other disciplines of relevance to therapeutic protein safety. If there were some way to pool these resources, perhaps all would benefit.

Mr. Chairman, we would like to tell you about actions that Baxter is taking now, in a forward-looking effort to further improve patient safety. Baxter continues to look forward, beyond therapeutic proteins. We would like, at some future point, to tell you that we have found cures for diseases such as hemophilia. It is far too early, however, for us to say that we have the cure in hand. But we are working on it now.

For example, Baxter's Gene Therapy Division has projects underway to move beyond clotting factor concentrates. Baxter is studying the possibility of an implantable device containing cells designed to produce clotting factors. If successful, such a device conceivably could eliminate the need for clotting factor injections for months at a time.

Lest we create false hope, we must make clear that potential full or partial cures are a long way off. But our efforts to develop technologies beyond therapeutic proteins are yet one more way in which Baxter seeks to enhance the safety and efficacy of treatment therapies available for patients. One day, perhaps, we may find a way—using genetic engineering—to cure diseases such as hemophilia. When that bright day arrives, we will have achieved the ultimate in safety.

Mr. Chairman, we should conclude with a few words about the role of government in the safety and availability of plasma-based therapeutic proteins. We in industry continue—without government compulsion—to evolve advanced safety technologies. Government collaboration, however, is essential.

There is a vital role for the Food and Drug Administration. When companies apply for licensure of new technologies and processes, the FDA must assess the safety implications of the submission. To do so, the FDA must examine both the safety pros and cons of any proposed process. Hence, while a new process or technology may be designed to further enhance safety, the FDA must also consider possible risks that the new process might present.

This creates a classical dilemma that all regulatory agencies face, in terms of both therapeutic proteins as well as pharmaceuticals and devices: How much study can and should the regulators require prior to deciding whether to approve a new drug, device, or biologic. There is no simple answer to this question, since there may be risks from either too little or too much study. Yet the FDA must grapple with this question every day.

In many instances it will be appropriate for the FDA to require, and then study, significant clinical research before approving changes to a process designed to enhance the safety or other aspects of a therapeutic. This will not always be the case, however. In some instances, it may be appropriate for the FDA to approve process changes based upon engineering information and chemical and physical principles, and without pre-market clinical investigation. Such approval could be coupled with rigorous post-market surveillance in order further to confirm safety, while reducing the lag time before the improved therapy is available to patients. We hope that this Subcommittee will encourage, rather than discourage, this kind of flexible response by the FDA in appropriate cases.

Mr. Chairman, the FDA's activities also should be assessed in light of FDA's mission and the government's resource constraints. The FDA is charged with protecting persons in the United States. Yet Baxter—the only U.S. plasma processor—finds itself subject to U.S. standards when it seeks to process therapeutic proteins in the United States and market them abroad. Perhaps the FDA's limited resources should be focused on people in this country, and the federal government should respect the rights of other sovereign nations to reach their own conclusions about what therapies are appropriate for their own populations. We must be vigilant lest domestic regulatory requirements damage the ability of companies based in America to compete in the worldwide markets.

Finally, Mr. Chairman, Secretary Shalala's appearance before this Subcommittee marked the announcement that Dr. Phil Lee will be appointed the first director of the new Blood Safety Council. Baxter is encouraged that this position will be occupied by an experienced professional. While the operational details of the new Council are not yet clear, Baxter assumes that it and other members of the plasma processing industry will be afforded the opportunity to make their views heard on issues that concern the industry. After all, the plasma processing companies have a wealth of expertise and knowledge on many of the very subjects to be addressed by the Blood Safety Council. Baxter looks forward to working cooperatively with Dr. Lee as he embarks on his new mission.

Mr. Chairman, thank you for inviting Baxter Healthcare Corporation to appear at this hearing, and for listening to the testimony of Dr. Gomperts, our Medical Director and Vice President of Medical and Clinical Affairs for our Hyland Division. Thank you also for your interest in safety, an issue that always has been a primary concern of Baxter's.

Mr. SHAYS [presiding]. I thank the gentleman. Dr. Feldman, I think you're next.

I want to apologize to the panelists. I have been working on issues of gift ban and lobby disclosure, and the Rules Committee was having a hearing, and I have been participating on that panel for the full time.

We scheduled this well in advance of that hearing, and so we couldn't change it, but I don't want you to think it's a reflection on what I think of this issue. I'm particularly grateful to have all of you gentlemen here. It's very important for us to hear from industry, as well. Dr. Feldman.

Mr. FELDMAN. Thank you. Mr. Chairman and members of the subcommittee, my name is Dr. Fred Feldman, and I am vice president of technical development for Armour Pharmaceutical Co. My Ph.D. is in biochemistry from Purdue University.

On behalf of my colleagues at Armour Pharmaceutical Co., I would like to express my appreciation to the subcommittee for the opportunity to share our views about the future safety of plasma-based therapies.

Specifically, the subcommittee asked me to address three complex and interrelated issues in my testimony today. One, emerging infectious agents in the blood supply and their impact on manufacturers; the role of this industry in ensuring the safety of plasma-based therapies; and three, industry quality standards in the application of new manufacturing technologies that may further improve product safety.

To fully understand and be prepared to deal with potential infection of blood or plasma therapies requires knowledge across a wide spectrum of science and technology. Our industry has devoted significant resources to acquiring that expertise over many years.

I can report that major progress has been made in understanding viruses and how to test for their presence. I am also proud to say that our understanding of the therapeutic proteins, the medicines we prepare from human plasma, and our knowledge of how to eliminate viruses which can contaminate these therapies has also increased dramatically.

In short, I want you and the patients who use our medicines to know that today this industry is better prepared to deal with the many unknowns which still exist and to devise strategies based on sound science for even better safety nets in the future.

It is impossible to adequately describe in brief testimony all that must be taken into account for science, technology, and regulation

to work together to control and enhance the safety of biological therapies in the future.

This important category of medicine spans from red blood cells or platelets or other cells for transfusion to biological therapies that come from plasma, the yellow fluid part of whole blood used to prepare coagulation factors for hemophilia, immune globulins for immune deficiency conditions, alpha-1-antitrypsin for treating congenital deficiency emphysema patients, or albumin for treating trauma patients in shock.

I would now include in this category, thanks to advances in science, those biological therapies that come from recombinant technologies applied to growing mammalian cells in laboratories.

The critical issues surrounding the safety of each of these therapies are complex, and I have prepared my thoughts, as you directed, on key elements surrounding today's and tomorrow's safety issues and concerns.

My colleagues and I believe that the safety of biological therapies depends on, and is the result of, combining the following technologies.

One, purifying the therapeutic protein products to high levels in order to remove infectious agents and at the same time make it easier to recognize product integrity and quality.

Two, stabilizing these therapeutic proteins without protecting viruses, so that the infectious agents can be inactivated without harming the medicine itself.

And three, combining multiple purification and inactivation methods to increase the overall power of removal and leave backup safety factors in place.

In doing all of these, we must have a thorough knowledge of the sensitivity of the therapeutics themselves in order to avoid damaging or dangerous alterations. In pursuit of our desire to improve safety, we must not render these agents clinically ineffective or otherwise dangerous.

This principle is a primary caution for my colleagues and me at Armour as we pursue the development of even safer biological products. Believe me when I saw that this is not simply an abstract academic worry.

As already indicated, inappropriate methods applied to a Factor VIII preparation made by the Dutch Red Cross to improve viral safety resulted in an outbreak of antibodies in Belgian patients which jeopardized their ongoing treatment and resulted in a recall of product and abandonment of the preparation.

Even today, an Austrian manufacturer's decision to combine two separately safe methods for viral inactivation of Factor VIII products has resulted in another major outbreak of antibodies for hemophilia treatment in Germany. That preparation is also now undergoing delicensure in various parts of Europe.

The lesson that must be learned from these examples is that as we continue to look for even more rigorous methods to ensure viral safety in biological medicines, careful research and clinical evaluation must be combined with open peer review to ensure that the best thinking is brought to bear to ensure not only viral safety, but also complete product safety and efficacy, as well.

However, the science and technology of methods for conferring viral safety is critically dependent on the availability of other knowledge that must be at hand in order for us to achieve progress without creating risk.

We must know which viruses can contaminate blood or plasma or the fluids used to grow other biological products in culture. We must have methods to detect their presence or absence, as well as methods to tell us if they are infectious when we do find them. And, if methods are not available for the viruses of concern, we must agree on model viruses or model test systems which can serve in their stead for the purpose of designing essential validation experiments.

These are absolutely critical issues for the future, because in creating international consensus on test viruses or test models, the scientific, technical, and regulatory communities will be able to provide the means for testing and handling disease agents which could yet threaten the blood supply.

We now have many scientific resources at hand to deal with infectious agents that we didn't have before. We have choices of several inactivation methods—heating or solvent treatments. We also have more powerful purification methods than we had before.

Mr. SHAYS. Could I ask you to summarize your conclusion here? I'll give you another minute or so, but I think we need to get to our next witness.

Mr. FELDMAN. Yes, sir. Thank you. I will. My company is proud of several contributions we've made which have been breakthroughs in this area and which have been licensed by the FDA. I have mentioned some of those in the written documents. We're particularly proud of the highly efficient ultrafiltration methods which we have developed that have been licensed by FDA which can separate viruses from proteins, including proteins for treating hemophilia B.

The second method that I talked about, the ultrafiltration method, is also important because it's been adapted by others and it has a potential for removing agents that we don't know of as yet, including the potential for removing agents such as the CJD agent.

In summarizing, I believe that to continually ensure provision of the safest therapies, those involved in the processing and regulation of biological medicines, that we must embrace a two-part mission.

First, we must combine an understanding of the structure, function, and integrity of therapeutic proteins with an understanding of how to stabilize them and remove them from the known agents of risk.

And second, we must also provide residual removal capacity, a safety net from yet unrealized disease agents while continuing to demonstrate consistent clinical efficacy and safety of biological therapies worldwide.

In attaining all these, those of us who make these kinds of medicines recognize the critical nature of GMP and the role that it plays to ensure manufacturing consistency, minimize human error, and to prevent contamination.

Last, I believe government also has a critical role to play in product safety by promoting the development of global regulatory guide-

lines, providing guidance to industry in appropriate use and control of emerging new sciences and technologies, and promoting international harmonization of regulatory and scientific opinion.

My colleagues and I believe that only open consensus gathering for regulation of new technologies with participation by all—industry, knowledgeable consumers, and scientific medical experts—can lead to a comprehensive understanding and control of risks from new agents and ensure public confidence that correct conclusions are obtained.

Thank you for allowing me the extra moment, and I would be happy to participate in answering questions.

[The prepared statement of Mr. Feldman follows:]

PREPARED STATEMENT OF FRED FELDMAN, VICE PRESIDENT, TECHNICAL DEVELOPMENT, ARMOUR PHARMACEUTICAL CO.

Mr. Chairman and members of the Subcommittee, my name is Dr. Fred Feldman and I am Vice President of Technical Development for Armour Pharmaceutical Company. I have a Bachelors Degree in Biochemistry from the University of Chicago and a Ph.D. in Biochemistry from Purdue University.

Based in Collegeville, PA, Armour Pharmaceutical is a worldwide provider of plasma protein therapies. Our company offers some of the most advanced treatments for hemophilia and other replacement therapies available today.

On behalf of my colleagues at Armour Pharmaceutical Company, I would like to express my appreciation to the Subcommittee for the opportunity to share our views about the future safety of plasma-based therapies.

Because the American Blood Resources Association, our national trade group, has provided the Subcommittee with specific comments about the recommendations contained in the Institute of Medicine report—comments that reflect Armour's viewpoint—my comments will focus on scientific, technical and regulatory issues that must be addressed to ensure that safe and effective plasma-based medicines are available to patients in the future.

Specifically, the Subcommittee asked me to address three complex and interrelated issues in my testimony today:

1. Emerging infectious agents in the blood supply and their impact on manufacturers.
2. The role of this industry in ensuring the safety of plasma-based therapies.
3. Industry quality standards and the application of new manufacturing technologies that may further improve product safety.

At the beginning of the 1970s, biological medicines were prepared, primarily, by using precipitation methods to separate proteins from each other. As increased knowledge of separation methods developed, the fractionation industry was able to add more powerful methods to its technical arsenal which resulted in purer biological therapies for treatment of a variety of medical problems, including hemophilia.

The kind of therapies that were available in the early 1970s used mainly a few rudimentary precipitation methods but were considered critical breakthroughs, especially in hemophilia care, because they provided the patient with direct access to preparations that could prevent bleeding. Prior to that time period, no such products were available.

Not until the late 1980s, did processes for separating beneficial plasma proteins include chromatography methods, which involve a sophisticated separation of proteins, one from another, by using the ionic differences between them.

It is important to note that knowledge of the structure and function of these beneficial proteins came very slowly. For example, hemophilia has been known as a disease for at least three thousand years; but, in fact, the underlying basis of the disease has been poorly understood.

Only in the last twenty years has there been any real progress made in understanding hemophilia, and really only in the last ten years has that knowledge enabled scientists to adapt the most modern techniques for separating proteins and providing them in pure form.

Providing proteins in pure form is important not just for medical treatment, but also because separation methods allow us to manipulate disease agents away from the therapeutic protein, itself.

However, to fully understand and be prepared to deal with potential infection of blood or plasma therapies requires knowledge across a wide spectrum of science and

technology. As I mentioned, our industry as a whole has devoted significant resources to acquiring that expertise over many years.

I can report that major progress has also been made in understanding viruses and how to test for their presence. I am also proud to say that our understanding of the therapeutic proteins—the medicines we prepare from human plasma—and our knowledge of how to eliminate viruses which can contaminate these therapies has also increased dramatically.

In addition to providing the degree of safety that biological therapies now offer, companies like Armour have been able to apply separation techniques that not only remove the disease agents that we know about today, but also provide broader safety nets that have the potential to remove disease agents that have not yet been identified—separating them from plasma derivatives and making these therapies safer for the patients that need them.

I want you and the patients who use our medicines to know that today, this industry is better prepared to deal with the many unknowns which still exist, and to devise strategies, based on sound science, for even better safety nets in the future.

However, it is impossible to adequately describe in this brief testimony all that must be taken into account for science, technology, and regulation to work together to control and enhance the safety of biological therapies in the future.

This important category of medicine spans from red blood cells or platelets or other cells for transfusion, to biological therapies that come from plasma—the yellow—fluid part of whole blood used to prepare coagulation factors for hemophilia, immune globulins for immune deficiency conditions, alpha-1-antitrypsin for treating congenital deficiency emphysema patients, or albumin for treating trauma patients in shock. I would now include in this category—thanks to advances in science—those biological therapies that come from recombinant technologies applied to growing mammalian cells in laboratories.

The critical issues surrounding the safety of each of these therapies are complex, and I have prepared my thoughts, as you directed, on key elements surrounding today's and tomorrow's safety issues and concerns.

My colleagues and I believe that the safety of biological therapies depends on, and is a result of, combining the following technologies:

1. Purifying the therapeutic protein products to high levels in order to remove infectious agents and at the same time make it easier to recognize product integrity and quality.
2. Stabilizing these therapeutic proteins (without protecting viruses) so that the infectious agents can be inactivated without harming the medicine itself.
3. Combining multiple purification and inactivation methods to increase the overall power of removal and leave backup safety factors in place.

In doing all of these, we must have a thorough knowledge of the sensitivity of the therapeutics themselves in order to avoid damaging or dangerous alterations. In pursuit of our desire to improve safety, we must not render these agents clinically ineffective or otherwise dangerous.

This principle is a primary concern for my colleagues and me at Armour as we pursue the development of even safer biological products. Believe me when I say that this is not simply an abstract academic worry.

For example, inappropriate methods applied to a factor VIII preparation made by the Dutch Red Cross to improve viral safety resulted in an outbreak of antibodies in Belgian patients which jeopardized their ongoing treatment and resulted in a recall of product, and abandonment of the preparation.

Even today, an Austrian manufacturer's decision to combine two separately safe methods for viral inactivation of factor VIII products has resulted in another major outbreak of antibodies compromising hemophilia treatment in Germany. That preparation is also now undergoing delicensure in various parts of Europe.

The lesson that must be learned from these examples is that as we continue to look for even more rigorous methods to ensure viral safety in biological medicines, careful research and clinical evaluation must be combined with open peer review to ensure that the best thinking is brought to bear to ensure not only viral safety, but also complete product safety and efficacy as well.

However, the science and technology of methods for conferring viral safety is critically dependent on the availability of other knowledge that must be at hand in order for us to achieve progress without creating risk.

We must know which viruses can contaminate blood or plasma or the fluids used to grow other biological products in culture. We must have methods to detect their presence or absence as well as methods to tell us if they are infectious when we do find them. And, if methods are not available for the viruses of concern, we must agree on "model viruses" or model test systems which can serve in their stead for the purpose of designing essential validation experiments.

These are absolutely critical issues for the future. Because in reaching international consensus on test models, as well as known viruses of concern, the scientific, technical and regulatory communities will be able to provide the means for testing and handling disease agents which could yet threaten the blood supply.

We now have many scientific resources at hand to deal with infectious agents that we did not have before. We have choices of several inactivation methods—heating, or solvent treatments which kill viruses by destroying the lipid coat that surrounds them. Many viruses, such as hepatitis B and C and HIV, have a lipid envelope. Some viruses, such as hepatitis A and parvovirus, have non-lipid envelopes and they require inactivation or removal by other methods. There are efforts under way to find methods for inactivating parvovirus, as well.

We also have more powerful purification choices than we had before.

My company is particularly proud of two contributions we have made in this area of product purity—the development of monoclonal antibody purification methods used to specifically remove the beneficial protein product we want from a sea of other proteins and potentially infectious agents. This development resulted in a safety breakthrough in hemophilia care when licensed by the FDA in 1987.

Secondly, the development of highly efficient ultrafiltration methods which have been licensed by the FDA. This process can separate viruses from proteins such as factor IX for hemophilia B through a molecular sieving process.

The ultrafiltration method is also important because it is even now being adapted by others around the world and explored for its potential to act as a generic removal step for a broad range of viruses—those we know, as well as others that may threaten humankind in the future. Methods such as these may be especially important in dealing with difficult, hardy viruses such as the parvovirus, or with agents such as the Creutzfeldt Jacob Disease agent (CJD) about which there its still no consensus on the world scene.

Armour has developed specific validation methods to allow us to verify the effectiveness of ultrafiltration in each and every batch treated by this method. We have already validated the utility of ultrafiltration for the removal of large viruses such as HIV, and for intermediate viruses like hepatitis B and hepatitis C. We have also accumulated data that shows that as we use ultrafiltration methods in production, even small viruses can be removed. My colleagues and I have published this information so that it can be applied across the industry—worldwide—to make therapies safe for use no matter where and how they are prepared.

Ensuring viral safety has required a lot of learning over a relatively brief period of time—brief for those of us who spend our time in laboratories. Key to providing safe biological therapies is an understanding of what viruses to characterize, what viruses to understand, as well as methods to test for the presence of viruses and for their inactivation. This knowledge did not exist for specific viruses of concern in the 1970s.

For example, there was no method for detecting hepatitis B and its potential infectivity in test tubes. Now, it requires either looking at animals like chimpanzees over long periods of time or looking at viruses that mimic hepatitis B, and that are representative of the kinds of viruses that could persist if hepatitis B were present.

Use of chimpanzees alone is inadequate, because not enough animals can be tested and the virus requires too long to incubate. And so with increased understanding of virology, we have, in some cases, learned how to test for viruses and look for their presence and their removal in different ways.

In the 1980s, we reached a point where specific inactivation and separation protocols could be established. Guidelines were put in place by manufacturers working together with the FDA that allowed us to examine removal methods and inactivation methods and their impact on panels of viruses that were either contaminates or predictive of contamination of the blood supply.

I believe that to continually ensure provision of the safest therapies, those involved in the processing and regulation of biologic medicines must embrace a two-part mission. First, we must:

> Combine an understanding of the structure, function and integrity of therapeutic proteins, with an understanding of how to stabilize them and remove them from the known agents of risk.

And we must also:

> Provide residual removal capacity—a safety net—from yet unrealized disease agents, while continuing to demonstrate consistent clinical efficacy and safety of biological therapies worldwide.

Even in attaining all the above, those of us who make biological medicines must recognize the critical nature of GMP (good manufacturing practice), as defined by the FDA, to ensure manufacturing consistency, minimize human error and prevent contamination. The sophistication of closed systems under automated computer

process control continues to increase and will be an even greater contributor to product safety in the future.

I believe that the United States is advanced in these areas. However, in other countries there is still much to be learned about GMP. It is critical that we share our knowledge on a world-wide basis and that we achieve a consensus on GMP so that regulations can be made uniform with respect to manufacturing practices.

I hope further that we do not see failures occurring outside the United States because of deficiencies in GMP which could raise concerns in this country about the use of similar products under good control. We should strive for the same high standards worldwide that we now have in this country.

Therefore, I believe that government also has a critical role to play in product safety by:

1. Promoting the development of global regulatory guidelines.
2. Providing guidance to industry in the appropriate use and control of emerging new sciences and technologies.
3. Promoting international harmonization of regulatory and scientific opinion.

Conflicting conclusions on disease agent risks and how to address them can significantly impede development progress, sap critical research resources and potentially delay reaching the right conclusion.

I believe, and my colleagues at Armour share this view, that it should be a priority of government to bring together for consensus gathering on an international basis the best minds on potential emerging infectious agents. That this is still not yet achieved in critical areas is apparent with regard to concern over the CJD agent, where there has been one conclusion reached in the U.S., but apparently a divergent conclusion reached in Europe.

It bears repeating. It is critically important that the best scientific and regulatory minds that exist today in the United States not only look at their own thinking and their own information on CJD, but also collaborate with the best minds that we have on this and other disciplines in international arenas so that manufacturers can have clear guidance on the direction that must be taken.

My colleagues and I believe further that only open consensus gathering for regulation of new technologies, with participation by all—industry, knowledgeable consumers and scientific/medical experts—can lead to a comprehensive understanding and control of risks from new agents and public confidence that correct conclusions are attained.

Only in an open forum can manufacturers contribute the knowledge that they have gained in the control of their manufacturing practices, and in the removal of disease agents. Only in an open forum can the consumer gain confidence that the best thinking is being applied to achieve our common goal of product safety.

One final observation. In order to ensure that we can protect against future disease agents, and provide safe and effective medicines to the people who need them, we must continue to expand our knowledge through scientific research and product development. I believe government has a role in funding and directing breakthrough research. Armour is absolutely committed to expanding its research efforts in the future—building on the knowledge that we have acquired.

Research conducted by companies and by the government should be published to the greatest extent possible to elicit peer review, manufacturer to manufacturer, scientist to scientist, scientist to manufacturer, so that nobody has a blind spot in what can be accomplished in the critical areas I have discussed today.

Given the scientific complexity of the technical issues involved in securing viral safety for biological therapeutics, I have attached a detailed outline of the eight areas we believe are critical to this discussion. The outline provides an evolution in safety improvements which have already occurred and opportunities available in the future.

Thank you for the opportunity to testify before you today.

IMPROVING SAFETY OF PLASMA PRODUCTS

- Development of High Purity Products
- Development of Product Stabilization Methods
- Development of Viral Validation Methodologies
- Development of Viral Removal and Viral Inactivation Methodologies
- The Combination of Methods for Improvement of Safety
- Evolution of Product Validation Understanding
- Evolution in GMP Control
- Development of Global Regulatory Guidelines

Development of High Purity Products

- Adding Chromatography to Precipitation methods
- Addition of Affinity and Immunoaffinity Purification Techniques
- Understanding Structure and Function
- Adapting Molecular Biology to Separation and Bio-Synthesis

Development of Product Stabilization Methods

- Freeze-Drying as a Stabilization Method
- Addition of Active Protective Agents
- Additions of Sugars and Salts as Nonspecific Protective Agents
- Finding Discriminating Protectants Between the Therapeutic and Infectious Agents

Development of Viral Validation Methodologies

- Characterization and Selection of Specific Viruses/Infectious Agents
- Development of Methods to Grow and Detect Viruses
- Development of Consensus Methods for Evaluation of Virus Reduction
- Uncertainties of Structural Modifications/Antibody Development

Development of Viral Removal and Viral Inactivation Methodologies

- Heat Treatment in the Lyophilized Protected Stage
- Heat Treatment During Stabilized Liquid Pasteurization
- Viral Inactivation by Destruction of Lipid Enveloped Viruses ("Solvent/Detergent Methods)
- Removal of Viruses by Separation Methods: Chromatography; Ultrafiltration

Combination of Methods for Improvement of Safety

- Combination of Purification and Heating
- High Temperature Heating Protocols
- Combination of Heating and Solvent Detergent Methods
- How Much is Enough; How Much is Too Much?

Evolution of Product Validation Understanding

- Combining:
  An Understanding of the Structure, Function, and Integrity of the Therapeutic Protein
  With an Understanding of How to Stabilize it Differentially
  And Remove It From the Known Agents of Risk
  While Providing Residual Removal Capacity From Yet Unrealized Risk Agents
  And Demonstrating Consistent Clinical Efficacy

Evolution in GMP Control

- Adapting Production to Closed Systems
- Institution of Automated Process Control
- Totally Controlling Facilities and Process
- Improving Documentation, Quality Assurance, and Validation

Development of Global Regulatory Guidelines

- Development of Critical Guidelines in the Use of New Technologies in Manufacturing
- International Harmonization of Regulatory and Scientific Opinion
- Open Consensus Gathering for Regulation of New Technologies
- Open Global Review of New Regulatory Guidelines

Mr. SHAYS. Thank you, Dr. Feldman, and your entire statement will be in the record. I appreciate your summarizing.

I think I'm going to go to you, Dr. Tutwiler. Am I pronouncing your name correctly?

Mr. TUTWILER. Yes, that's correct.

Mr. SHAYS. And then, Mr. Reilly, are you the last witness? Thank you.

Mr. TUTWILER. Mr. Chairman and members of the subcommittee, on behalf of Alpha Therapeutic Corp., we appreciate the opportunity to appear today to address issues related to the improvement and safety of plasma derivatives. My name is Gene F. Tutwiler. I am vice president of research and development.

Alpha has a proud history of providing high quality, efficacious, and safe blood plasma products for use by its worldwide customers. Alpha's history dates back to the 1940's, when we were known as Courtland Laboratories. Today, as in the past, Alpha is continuing to search for enhanced quality and safety in its products as we also pursue development of additional plasm derivatives with therapeutic value for expanded U.S. health care needs.

Alpha has always been on the leading edge of implementing new viral tests and ways to enhance viral removal and inactivation in our manufacturing process. Primary identification and discovery of new viruses for the plasma industry has actually come from the medical and scientific community in partnership with government agencies such as the Centers for Disease Control, NIH, and the FDA, as well as other related government entities.

Additionally, certain diagnostic companies which have extensive plasma screening test development capabilities have led in the development of large-scale viral testing reagents and related equipment.

Alpha, as well as other major plasma fractionators who are also here today, has researched and developed processes either to remove or inactivate viral and other contaminants that may be present in plasma source material. Alpha is committed, based upon prevailing scientific understanding, to ensure that its plasma-derived products are safe as humanly possible.

As this subcommittee knows very well, emerging infectious agents have had a significant and costly impact on plasma derivative products fractionated by our industry. Nevertheless, Alpha is committed to research and development programs which we believe can improve the safety of our plasma derivative products.

I would also like to now briefly outline some of the research and development in which our company is currently engaged.

First, viral detection. Alpha has implemented all FDA-approved initial and confirmatory tests for detection of viral agents in plasma as soon as these tests became available. In 1971, testing for Hepatitis B in donor plasma was initiated.

Then, in 1985, the antibody test for HIV became available for detection of infected donors. Upon FDA-approval of this antibody test, Alpha and the other members of this industry implemented this test for all plasma procurement. Viral screening of donor plasma has now been expanded to include HIV–2 and Hepatitis C virus.

More recently, the FDA has recommended the implementation of a new donor screening test for HIV–1 called HIV–1 antigen. Although this test was recommended on March 23, 1989, by the Blood Products Advisory Committee, it has not yet been licensed by the FDA and thus has not been available for implementation by our industry. Because current viral inactivation technology effectively destroys HIV, we question the additional potential benefit of this test. We have nevertheless accepted its implementation.

Now, in addition to the dramatic improvements in viral detection in plasma, there also have been considerable advances made in the manufacturing processes to remove and kill viruses.

We and other companies in this industry have found and published in peer review journals that many of the precipitation, column chromatography, and centrifugation steps used to fractionate

plasma not only purify the individual proteins but also greatly reduce the concentrations of contaminating viruses. This has clearly been shown for our intravenous gamma globulin product, our coagulation products, and new products that we have in development.

We also have made dramatic improvements in our ability to kill or inactivate viruses. At every stage, Alpha has implemented processes to inactivate potential contaminating viruses based on the best currently available scientific information.

For example, in 1984, Alpha introduced separate heating methods for Factor VIII and IX, respectively, and we and other fractionators clearly demonstrated that heat treatment is effective to inactivate the lipid-coated viruses such as HIV–1, HCV, and HBV. We have recently demonstrated heat treatment effectiveness, also, for the non-lipid-coated viruses.

In 1987, Alpha also implemented the chemical solvent detergent process that is very effective for inactivating the lipid-coated viruses such as HIV, while protecting the potency of the active protein drug.

Now, Alpha's goal is to develop, manufacturing processes which have the ability to remove more virus than one could ever imagine. For pathogenic lipid-coated viruses, heat and solvent detergent treatment and viral removal steps in the purification process have reduced the potential for contamination in many cases by over a billion fold.

Where studies have been completed on the newer non-lipid-coated virus, we have effected highly significant reductions in the potential for virus contamination. It should, however, be noted that the same treatments of processes may not be able to be used for every product, since the process might alter the protein or reduce the amount of beneficial protein contained in the products.

Now, the story of viral detection, removal, and inactivation, of course, does not end here. Alpha continues to invest in research and development in these areas and is studying new production processes for our current products and several new products. For example, Alpha is on the cutting edge of research into the use of DNA testing to identify viral agents. Specifically, we are reviewing the accuracy and sensitivity of the procedure known as polymerase chain reaction (PCR), which you've heard about earlier.

Alpha is also actively pursuing new and more effective viral removal steps such as Nanofiltration, which is the process by which we can eliminate viral agents based upon their molecular size.

In addition, we have continued the search for more effective viral killing processes, either using new chemicals or the use of alternative energy sources such as ultraviolet light or microwave. To date, these viral killing methodologies have either not been completely effective in viral removal, or they have destroyed the protein's potency. Nevertheless, Alpha will be vigilant in its quest to locate and implement effective viral inactivation methodologies.

In conclusion, Alpha manufactures products with safety and efficacy in mind. Our products are human proteins; they're used to treat human diseases. We attempt to eliminate all potential contaminants while maintaining the integrity and potency of the therapeutic proteins.

Our future in the production of plasma derivatives is dependent upon research and development into new methodologies, and we haven't stopped. We support the IOM recognition of the continuing importance of the full participation of the industry, government regulatory agencies, and government and academic scientists in the provision of safe and effective plasma products.

We further support the proposed role of BPAC as essential in this effort. However, we believe that it is vitally important for BPAC to include both industry and scientific representation on this committee so that decisions may be based on scientific rationale.

Finally, we are confident that our plasma derivative products have enhanced the lives of numerous patients. It is, of course, our goal with government and other members of our industry to do everything in our power to reduce risk and assure product availability.

Last but not least, Alpha endorses the concepts expressed in the American Blood Resources Association's response to the 14 IOM recommendations. We appreciate the opportunity to present our statement to you today. Thank you.

[The prepared statement of Mr. Tutwiler follows:]

PREPARED STATEMENT OF GENE F. TUTWILER, ALPHA THERAPEUTICS CORP.

Mr. Chairman and Members of the Subcommittee, on behalf of Alpha Therapeutic Corporation, we appreciate the opportunity to appear today to address issues related to the improvement and safety of plasma derivatives. My name is Gene F. Tutwiler, and I am Vice President of Research and Development.

Alpha has a proud history of providing high quality, efficacious and safe blood plasma products for use by its world-wide customers. Alpha's history dates back to the 1940's when we were known as Courtland Laboratories. Today, as in the past, Alpha is continuing to search for enhanced quality and safety in its products as we also pursue development of additional plasma derivatives with therapeutic value for expanded U.S. healthcare needs.

Alpha has always been on the leading edge of implementing new viral tests and ways to enhance viral removal and inactivation in our manufacturing process. Primary identification and discovery of new viruses for the plasma industry has actually come from the medical and scientific community in partnership with government agencies, such as the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH) and the Food and Drug Administration (FDA) as well as other related government entities. Additionally, certain diagnostic companies which have extensive plasma screening test development capabilities, have led in the development of large scale viral testing reagents and related equipment.

Alpha, as well as other major plasma fractionators who are also here today, has researched and developed processes either to remove or inactivate viral and other contaminants that may be present in plasma source material. Alpha is committed based upon prevailing scientific understanding to ensure that its plasma derived products are safe as humanly possible. As this Subcommittee knows very well, emerging infectious agents have had a significant and costly impact on plasma derivative products fractionated by our industry. Nevertheless, Alpha is committed to research and development programs which we believe can improve the safety of our plasma derivative products.

Additionally, our trade association, the American Blood Resources Association who will be speaking to you, has monitored the industry's self-imposed development of high standards for the collection of plasma and screening donors. Today, the plasma industry is completing its Quality Plasma Program which imposes inspections, specific donor exclusions, requires employee training and mandates other special procedures to assure the safety and quality of collected plasma.

I would like to briefly outline some of the programs in research and development in which our company is currently engaged:

Let me start off by reminding Congress that in the last few years advances made in molecular and genetic research have resulted in the discovery of previously unknown viruses. The discovery of the Human Immunodeficiency Virus (HIV) in March of 1984 represents the triggering event which brought tremendous attention

to and focus on the safety of plasma derived products and whole blood as never before. Our company, as well as the other members of our industry has implemented FDA-approved testing to screen out plasma containing infectious agents and to discover effective methods to remove and kill these agents. These agents include lipid coated viruses such as Hepatitis B, Hepatitis C, HIV-1 and HIV-2, non-lipid coated viruses such as Hepatitis A, parvovirus, and other newly identified pathogens such as Hepatitis E and G or Creutzfeldt-Jakob Disease. In this regard, we have placed strong emphasis on the following endeavors in our research and development programs.

A. Viral Detection—Alpha has implemented all FDA approved initial and confirmatory tests for detection of viral agents in plasma as soon as these tests became available. In 1971, testing for Hepatitis B in donor plasma was initiated. Then, in 1985, the antibody test for HIV became available for detection of infected donors. Upon FDA approval of this antibody test, Alpha and the other members of this industry implemented this test for all plasma procurement. Viral screening of donor plasma has now been expanded to include HIV-2 and Hepatitis C Virus (HCV).

More recently the FDA has recommended the implementation of a new donor screening test for HIV-1 called HIV-1 antigen. Although this test was recommended on March 23, 1989 by the Blood Products Advisory Committee (BPAC), it has not yet been licensed by the FDA and thus has not been available for implementation by our industry. Because current viral inactivation technology effectively destroys HIV, we question the additional potential benefit of this test. Moreover, we are concerned about potential misuse of this test as a self-diagnostic tool by prospective plasma donors. We have nevertheless accepted its implementation.

In addition to the dramatic improvements in viral detection in plasma, there also have been considerable advances made in manufacturing processes to remove and kill (or inactivate) viruses.

B. Viral Removal—We and other companies in this industry have found and have published in peer reviewed journals, that many of the precipitation, column chromatography and centrifugation steps used to fractionate plasma not only purify the individual proteins but also greatly reduce the concentrations of contaminating viruses. This has clearly been shown for our intravenous gamma globulin product, our coagulation products and new products in development.

C. Viral Inactivation—We have also made dramatic improvements in our ability to kill or inactivate viruses. At every stage, Alpha has implemented processes to inactivate potential contaminating viruses based on the best currently available scientific information. For example, in 1984 Alpha introduced separate heating methods for Factor VIII and Factor IX, respectively. We and other fractionators clearly demonstrated that heat treatment is effective to inactivate lipid coated viruses such as HIV-1, HCV and HBV. We have recently demonstrated heat treatment effectiveness for the non-lipid coated viruses, such as parvovirus.

In 1987, Alpha also implemented a chemical solvent detergent process that is very effective for inactivating the lipid coated viruses such as HIV, while protecting the potency of the active protein drug.

Alpha's goal is to develop manufacturing processes which have the ability to remove more virus than one could ever imagine. For pathogenic lipid-coated viruses, heat and solvent detergent treatment and viral removal steps in the purification process have reduced the potential for contamination in many cases by over a billion fold. Where studies have been completed on the newer non-lipid coated virus, we have effected highly significant reductions in the potential for viral contamination. It should however be noted that the same treatments or processes may not be able to be used for every product since the process might alter the protein or reduce the amount of the beneficial protein contained in the products.

The story of viral detection, removal and inactivation, of course, does not end here. Alpha continues to invest in research and development in these areas and is studying new production processes for our current products and several new products. For example, Alpha is on the cutting edge of research into the use of DNA testing to identify viral agents. Specifically, we are reviewing the accuracy and sensitivity of a procedure known as Polymerase Chain Reaction (PCR). Alpha is also actively pursuing new and more effective viral removal steps such as nanofiltration (that is, trying to eliminate viral agents based upon their molecular size). In addition, we have continued the search for more effective viral killing processes, using either new chemicals or the use of energy sources (such as ultraviolet light or microwave). To date, these new viral inactivation methodologies have either not been completely effective in viral removal or destroyed the product's potency. Nevertheless, Alpha will be vigilant in its quest to locate and implement effective viral inactivation methodologies.

Conclusion—In conclusion, Alpha manufactures products with safety and efficacy in mind. Our products are human proteins used to treat human diseases. We attempt to eliminate all potential contaminants while maintaining the integrity and potency of the therapeutic proteins.

Our future in the production of plasma derivatives is dependent upon research and development of new methodologies—we haven't stopped. We support the IOM's recognition of the continuing importance of the full participation of industry, government regulatory agencies, and government and academic scientists in the provision of safe and effective plasma products. We further support the proposed role of BPAC as essential in this effort. However, we believe that it is vitally important for BPAC to include both industry and scientific representation on this committee so that decisions may be based on scientific rationale.

Finally, we are confident that our plasma derivative products have enhanced the lives of numerous patients. It is, of course, our goal with Government and other members of our industry, to do everything in our power to reduce risk and assure product availability.

Last but not least, Alpha endorses the concepts expressed in the American Blood Resource Association's response to the 14 IOM Recommendations. As a reflection of our support for this response, we submit the ABRA recommendations to the Subcommittee with our statement.

We appreciate the opportunity to present our statement to you today. Thank you.

Mr. SHAYS. Thank you, Doctor. Mr. Reilly, I'm happy to hear from you, as well.

Mr. REILLY. Thank you, Mr. Chairman and members of the subcommittee. My name is Jim Reilly, and I'm the president of the American Blood Resources Association (ABRA), the national trade association representing the plasma collection and fractionation industry. On behalf of the membership of ABRA, I would like to express our appreciation to the subcommittee for the opportunity to submit our comments to you regarding the 14 recommendations.

Mr. SHAYS. I'm sorry. Are you going to go over the 14 recommendations right now?

Mr. REILLY. No, I was not going to go over them. They are an attachment to our specific comments.

Mr. SHAYS. What I would want to make very clear, from all the witnesses, which of these recommendations you agree with and which you don't. If you could incorporate it in your testimony, it would be helpful. Continue with your testimony, but ultimately I want that then answered.

Mr. REILLY. OK. Our testimony will include our comments regarding the 14 recommendations set forth by the Institute of Medicine, and we also provide the subcommittee with a sense of our accomplishments since the early 1980's and our continued commitment to safe and effective plasma-based therapies.

I would like to take this opportunity to briefly describe our industry to those of you who are unfamiliar with plasma and the therapies produced from plasma fractionation. In the United States, there are over 400 FDA-licensed plasma collection facilities and five principal pharmaceutical firms engaged in plasma fractionation.

U.S. plasma collection facilities perform approximately 13 million plasmapheresis donor collection procedures annually and provide 60 percent of the world's need for plasma. Source plasma is the noncellular fluid portion of the blood that is used as a raw material in the production of plasma-based therapies.

Plasma-based therapeutics are used in the treatment and diagnosis of many conditions, such as heart surgery, immune disorders,

hemophilia, burns, trauma, and to provide protection against diseases such as Hepatitis B, Rh disease, and tetanus.

With regard to the IOM report, our members have carefully analyzed its 14 recommendations. While we support in principle many of the IOM recommendations for improving prospective Federal regulation of blood and plasma-based therapeutics and do not wish to dwell on the negative, we must clearly state for the record that many of the IOM's findings and conclusions are without foundation and are incorrect.

We would like to ask the following qualifications be kept in mind. Throughout its report, the IOM variously refers to "industry" without distinguishing blood banking organizations, which collect blood for transfusion, from the ABRA membership, which collects plasma and processes plasma-based therapies used for treatment and diagnosis of many conditions previously mentioned. The IOM committee's confusion of these groups' identities has resulted in inaccuracies in the report.

The recommendations are largely a restatement of desirable activities, responsibilities, and objectives traditionally vested in them and pursued by the HHS agencies. Implementation of these activities, responsibilities, and objectives under the mechanisms proposed by the IOM recommendations could not have prevented the spread of HIV through blood and plasma-based therapeutics.

The essential truth is that it was a lack of information, not a lack of mechanism by which to process information, which was the central impediment faced by decisionmakers confronting the AIDS mystery in the early 1980's.

The practical value of any recommendations obviously will depend on the details of their implementation. We have attached, as I mentioned, our specific responses point by point to the recommendations, and I will go through them as is appropriate.

We would like to remind the subcommittee that the IOM report is a retrospective interpretation of events that occurred during the early 1980's. The IOM did not examine blood regulation or policy since 1986; that is, the report did not address all that has been achieved in the last 10 years.

Secretary of Health and Human Services Donna Shalala eloquently stated before this subcommittee that upon issuance of the report, IOM cautioned, "The danger of hindsight is unfairly finding fault with decisions that were made in the context of great uncertainty." We agree with the caution emphasized by the Secretary and support her desire not to examine the past to assign blame, but rather to ensure a safer blood supply in the future.

We will discuss the strides industry has made since the early 1980's. There are three general examples I would like to highlight our accomplishments.

Plasma collection facilities and fractionators have invested a significant amount of time, effort, and financial resources on proactive programs and standards which exceed FDA regulatory mandates.

Two programs which illuminate the strides that industry has made to further increase the safety of plasma-based therapies are the Quality Plasma Program (QPP) and the National Donor Deferral Registry, which we refer to as the NDDR.

QPP is a certification program developed by the industry to recognize plasma collection facilities which strive for the highest standards of excellence in their donor choices and facility operations.

To qualify for the QPP certification, a facility must comply with standards which exceeds FDA regulatory requirements, such as additional educational requirements to exclude potential high-risk donors, exclusive use of community-based donors, employee training standards, laboratory testing standards, viral marker rate limits, drug testing of all donors, and facility maintenance standards. QPP standards are enforced through a biannual inspection by independent third-party inspectors.

Additionally, all QPP-certified facilities must use a computer safety network called the National Donor Deferral Registry. The NDDR was designed by the industry to be used by plasma collection facilities to check all new donors against a computerized list of permanently deferred donors.

Plasma collection facilities access the NDDR via an 800 telephone number and are able to inquire if a potential donor is on the nationally list of permanently deferred donors through an automated system.

When checking a potential donor's status against the NDDR, users are informed whether or not the donor candidate is on the national deferral list. This national computerized system is an additional safety net designed by the plasma industry to further improve the safety and quality of plasma-based therapies.

Next, donor screening continues to be updated with the introduction of newer, more sensitive, and more accurate screening tests. Industry has implemented a new donor screening test on average every other year for the past decade.

Since the early 1980's, plasma collectors have implemented additional screening tests as they became available for ALT, as you heard earlier, which is now in controversy; HIV–1; subsequently, HIV–1 and 2; Hepatitis C; and, as soon as the test is licensed, we do anticipate compliance with HIV antigen, despite the controversy associated with plasma.

Research and development activity has not slowed since the advent of viral inactivation technology in the early 1980's. Industry has aggressively pursued, as you've heard, and implemented new, innovative viral inactivation and removal technologies, such as affinity chromatography purification, solvent detergent processes, and the same companies have, through breakthroughs in biotechnology, successfully developed and licensed recombinant coagulation concentrates.

Mr. SHAYS. If I could just interrupt, can you give me a sense of how much longer you have? I've tried to give you a little more liberty, since you are summarizing the view of the other four.

Mr. REILLY. I will try and run through this pretty quickly.

Mr. SHAYS. Yes, we really need to summarize that. Thank you.

Mr. REILLY. As the president of the national trade association representing the plasma collection and fractionation industry, I would like to outline the leadership role that the industry should play in formulation of blood policy.

The future of the safety of the American blood supply is an issue of tantamount importance to the plasma collection and fractionation industry, which relies on source plasma, a component of whole blood, as the raw material in processing plasma-based therapies. With regard to Federal blood policy, some of the recommendations of the IOM report provide fertile ground for the development of a better system to meet the challenges of the future.

The first two recommendations, in particular, address the most serious allegations of the report, that there was a lack of leadership at the various public health agencies during the early 1980's. To respond to this criticism, Secretary Shalala has appointed a Blood Safety Committee and an Advisory Council made up of representatives of industry, consumers, scientific experts, and ethicists.

ABRA embraces these steps made by the Secretary and looks forward to fully participating on the Advisory Council. Mr. Chairman, you have our pledge that we will fully cooperate and participate in all areas of blood policy decisionmaking as outlined by the Secretary.

Of course, we will continue to work with the Blood Products Advisory Committee, which advises FDA on blood policy. Please let me make one point clear, because it has been a subject of some confusion. The plasma industry does not currently and never has in the past had a voting membership on the Blood Products Advisory Committee.

However, please let me also make clear that we believe that plasma industry representation and expertise on BPAC is necessary and vital to sound decisionmaking on plasma collection and fractionation issues. Also, industry would like to have a formal liaison relationship with the Centers for Disease Control, which serves as the Nation's early warning system about threats to the blood supply.

Let me reassure you that the plasma collection and fractionation industry will continue to cooperate with this subcommittee and the Department of Health and Human Services and Food and Drug Administration to further improve regulatory decisionmaking, while the industry will remain vigilant in its own efforts to supply only the safest, most effective plasma-based therapies in the world.

I would like to thank you for the opportunity, and I'll conclude and take questions.

[The prepared statement of Mr. Reilly follows:]

PREPARED STATEMENT OF JAMES REILLY, PRESIDENT, AMERICAN BLOOD RESOURCES ASSOCIATION

Mr. Chairman and members of the Subcommittee, my name is James Reilly and I am the President of the American Blood Resources Association (ABRA), the national trade association representing the plasma collection and fractionation industry. On behalf of the membership of ABRA, I would like to express our appreciation to the Subcommittee for the opportunity to submit our comments to you regarding the fourteen recommendations set forth in the Institute of Medicine's Report entitled "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking." Also, I will provide the Subcommittee with a sense of our accomplishments since the early 1980s and our continued commitment to safe and effective plasma-based therapies.

I would like to take this opportunity to briefly describe our industry to those of you who are unfamiliar with plasma and the therapies produced from plasma fractionation. In the United States, there are over 400 FDA-licensed plasma collection facilities and five principle pharmaceutical firms engaged in plasma fractionation. US plasma collection facilities perform approximately 13 million plasmapheresis

donor collection procedures per year and provide 60% of the world's needs for plasma. Source plasma is the non-cellular fluid portion of blood that is used as the raw material in the production of plasma-based therapies. Plasma-based therapeutics are used in the treatment and diagnosis of many conditions, such as heart surgery, immune disorders, hemophilia, burns, trauma, and to provide protection against diseases such as hepatitis B, Rh disease, and tetanus.

With regard to the Institute of Medicine (IoM) report our members have carefully analyzed its fourteen recommendations. While we support in principle many of the IoM's recommendations for improving prospective federal regulation of blood and plasma-based therapeutics and do not wish to dwell on the negative, we must clearly state for the record that many of the IoM's "findings and conclusions" are without foundation and are incorrect. We would ask that the following qualifications be kept in mind:

- Throughout its report, the IoM variously refers to "industry" without distinguishing blood-banking organizations which collect blood for transfusions from the ABRA membership, which collects plasma and processes plasma-based therapies used for the treatment and diagnosis of the many conditions previously mentioned. The IoM committee's confusion of these groups' identities has resulted in inaccuracies in the report.
- The recommendations are largely a restatement of desirable activities, responsibilities, and objectives traditionally vested in and pursued by the HHS agencies. Implementation of these activities, responsibilities, and objectives under the mechanisms proposed by the IoM recommendations could not have prevented the spread of HIV through blood and plasma-based therapeutics. The essential truth is that it was a lack of information, not lack of a mechanism by which to process information, which was the central impediment faced by decisionmakers confronting the AIDS mystery in the early 1980s.
- The practical value of any recommendation will depend on the details of its implementation.

For more detailed information on our position on each of the fourteen recommendations we have provided a point by point statement which we have attached for your consideration and for submission to the record.

We would like to remind the Subcommittee that the IoM report is a retrospective interpretation of events that occurred during the early 1980s. The IoM did not examine blood regulation or policy since 1986 that is, the report did not address all that has been achieved in the last ten years. Secretary of Health and Human Services, Donna Shalala, eloquently stated before this Subcommittee that "Upon issuance of the report, IoM cautioned: 'The danger of hindsight is unfairly finding fault with decisions that were made in the context of great uncertainty.'" We agree with the caution emphasized by the Secretary and support her desire not to examine the past to assign blame but rather to ensure a safer blood supply in the future.

I will discuss the strides industry has made since the early 1980s. Here are three general examples which highlight our accomplishments:

- Plasma collection facilities and fractionators have invested a significant amount of time, effort, and financial resources on proactive programs and standards which exceed FDA regulatory mandates. Two such programs which illuminate the strides that industry has made to further increase the safety of plasma-based therapies are the Quality Plasma Program (QPP) and the National Donor Deferral Registry (NDDR).

  QPP is a certification program developed by the industry to recognize plasma collection facilities which strive for the highest standards of excellence in their donor choices and facility operations. To qualify for QPP certification a facility must comply with standards which exceed FDA regulatory requirements such as: additional education requirements to exclude potential high risk donors; exclusive use of community based donors; employee training standards; laboratory testing standards; viral marker rate limits; drug testing of all donors; and facility maintenance standards. QPP standards are enforced through bi-annual inspections by an independent third party inspector.

  All QPP certified facilities must use a computer safety network called the National Donor Deferral Registry (NDDR). The NDDR was designed by the industry to be used by plasma collection facilities to check all new donors against a computerized national list of permanently deferred donors. Plasma collection facilities access the NDDR via an 800 telephone number and are able to inquire if a potential donor is on the national list of permanently deferred donors through an automated system. When checking a potential donor's status against the NDDR, users are informed whether or not a donor candidate is on the national deferral list. This national computerized system is an additional safety

net designed by the plasma industry to further improve the safety and quality of plasma-based therapies.

• Donor screening continues to be updated with the introduction of newer, more sensitive, and more accurate screening tests. Industry has implemented a new donor screening test, on average, every other year for the past decade. Since the early 1980s plasma collectors have implemented additional screening tests as they became available for:

Alanine Aminotransferase (ALT)
HIV–1 Antibody (HIV–1)
HIV 1&2 Antibody (HIV 1–2)
Hepatitis C Antibody (HCV)
HIV–1 Antigen (HIV Antigen)

• Research and development activity has not slowed since the advent of viral inactivation technology in the early 1980s. Industry has aggressively pursued and implemented new innovative viral removal and inactivation technologies such as affinity chromatography purification, solvent detergent processes, and the same companies have, through breakthroughs in biotechnology, successfully developed and licensed recombinant coagulation concentrates. Industry has continually researched, updated, and improved viral removal and inactivation technologies and therapies as modern science would allow.

Finally, I will address the future of blood safety and the plasma industry's role in blood safety.

As the President of the national trade association representing the plasma collection and fractionation industry I will outline the leadership role that the industry will play in the formulation of blood policy. I will leave the details of our research and development of new and innovative fractionation technologies to the fractionation experts who sit before you on this panel.

The future safety of America's blood supply is an issue of tantamount importance to the plasma collection and fractionation industry which relies upon Source Plasma, a component of whole blood, as the raw material in the processing of plasma-based therapies. With regard to federal blood policy, some of the recommendations in the IoM report provide fertile ground for the development of a better system to meet the challenges of the future.

The first two recommendations address the most serious allegations of the report, that there was a lack of leadership at the various public health agencies during the early 1980s. To respond to this criticism the Secretary has taken firm steps by appointing a Blood Safety Director (Dr. Phil Lee, Assistant Secretary of Health), a Blood Safety Committee, and an Advisory Council made up of representatives from industry, consumers, scientific experts, and ethicists.

ABRA embraces these steps made by the Secretary and looks forward to fully participating on the Advisory Council. As the Chairman knows, this industry has a wealth of knowledge and expertise and we are eager to share this information in the hopes of formulating better blood policy based on sound science. Mr. Chairman you have our pledge that we will fully cooperate and participate in all areas of blood policy decisionmaking as outlined by the Secretary.

Of course industry will continue to work with the Blood Products Advisory Committee (BPAC) which advises the FDA on blood policy. Please let me make one point clear, because it has been the subject of some confusion, the plasma industry does not currently and has never in the past had a voting member on BPAC. However, please let me also make clear that we believe that plasma industry representation and expertise on BPAC is necessary and vital to sound decisionmaking on plasma collection and fractionation issues.

Also, industry would like to have a formal liaison relationship with the Centers for Disease Control (CDC) which serves as the nation's early warning system about threats to the blood supply. The plasma collection and fractionation industry would like to offer its services to the CDC working group on blood safety which the Secretary has developed to look at new or potential threats to the blood supply.

Let me reassure you that the plasma collection and fractionation industry will continue to cooperate with this Subcommittee, the Department of Health and Human Services, and the Food and Drug Administration to further improve regulatory decisionmaking. Meanwhile, industry will remain vigilant in its efforts to supply only the safest and most efficacious plasma-based therapies in the world.

Finally, ABRA and its members wish to acknowledge the loss and suffering that HIV has brought to the entire hemophilia community. We speak of this loss with reluctance, recognizing that only by personal experience can one appreciate its true magnitude.

Thank you for the opportunity to testify here today. If you have any questions I will be happy to attempt to answer them.

ABRA Response to the Fourteen Recommendations Included in the Institute of Medicine's (IoM) Report

INTRODUCTION

The American Blood Resources Association (ABRA), the national trade association representing the plasma collectors and fractionators, has analyzed the recommendations made by the Institute of Medicine (IoM) in its report entitled "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking." ABRA supports in principle many of the IoM's recommendations for improving prospective federal regulation of blood and plasma-based therapeutics. Yet the following qualifications must be kept in mind:

1. Many of IoM's "findings and conclusions" are without foundation and are incorrect. Consequently, ABRA cannot endorse them.
2. The practical value of any recommendation will depend on the details of its implementation.
3. Throughout its report, the IoM variously refers to "industry" without distinguishing blood banking organizations which collect blood for transfusions from the ABRA membership which collects plasma and processes plasma-based therapies used for the treatment and diagnosis of many conditions, including: burn, shock, heart surgery, immune disorders, hepatitis, and hemophilia. The IoM committee's confusion of these group's identities has resulted in inaccuracies in the report.
4. The recommendations are largely a restatement of desirable activities, responsibilities, and objectives traditionally vested in and pursued by the HHS agencies.
5. Implementation of these activities, responsibilities, and objectives under the mechanisms proposed by the IoM recommendations could not have prevented the spread of HIV. The essential truth is that it was a lack of information, not lack of a mechanism by which to process information, which was the central impediment faced by decisionmakers confronting the AIDS mystery in the early 1980s.

II. ABRA'S RESPONSE TO THE IOM RECOMMENDATIONS

Below is a response prepared by ABRA to each of the IoM's fourteen recommendations:

Recommendation 1: The Secretary of Health and Human Services should designate a Blood Safety Director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.

and

Recommendation 2: The Public Health Service (PHS) should establish a Blood Safety Council to assess current and potential future threats to the blood supply, to propose strategies for overcoming these threats, to evaluate the response of the PHS to these proposals, and to monitor the implementation of these strategies. The Council should report to the Blood Safety Director (see Recommendation 1). The Council should also serve to alert scientists about the needs and opportunities for research to maximize the safety of blood and blood products. The Blood Safety Council should take the lead to ensure the education of public health officials, clinicians, and the public about the nature of threats to our nation's blood supply and the public health strategies for dealing with these threats.

Response to Recommendations 1 and 2: ABRA, and surely others, support the concept of coordination between governmental agencies and the convenience of a single voice to express the collective views of the FDA, CDC, and NIH. It is not clear how the structure outlined by the IoM report would fit within the current organizational structure of HHS. For example, authority already exists within the PHS for meeting many of the tasks suggested by Recommendation 2. It is important that no proposed structure simply create an additional bureaucracy; rather, it should be implemented only if by thoughtful design it can be expected to expedite and further improve decisionmaking including the approval of vital new technologies and products (although this may not be included in the charter of the Blood Safety Council as recommended by IoM).

It must be recognized that the absence of a formally designated "single voice" did not prevent an effective response to the ill-defined threat of AIDS in the early 1980s. Inadequate human knowledge was the central impediment to confident decisionmaking of predictable impact.

Recommendation 3: The Federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products.

Response to Recommendation 3: The language provided in Recommendation 3 does not provide enough information for ABRA to take a position.

Recommendation 4: Other federal agencies must understand, support, and respond to the CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.

Response to Recommendation 4: ABRA agrees with the CDC role as described in Recommendation 4 and believes that the appropriate federal agencies including the CDC, sought to provide coordinated recommendations with respect to AIDS during the early 1980s, to the extent knowledge permitted.

Recommendation 5: The PHS should establish a surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products.

Response to Recommendation 5: The CDC did, in fact, play a substantial role in the early days of identifying the illness later to be called AIDS as something new and unique to be contended with. ABRA supports a surveillance system within CDC or in cooperation with the CDC and other organizations. It is important to note, however, that such a system could not have prevented the blood-borne transmission of HIV in the early 1980s since little was known about AIDS at that time. HIV—the causative agent for AIDS—was not even identified until 1984. Blood could not be tested for the presence of antibodies to the HIV virus until 1985.

Recommendation 6: Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

Response to Recommendation 6: ABRA agrees with the conclusion that the search for the complete solution to risk need not delay incremental steps to mitigate risk. For example, education of and voluntary exclusion of plasma donors were readily instituted by the plasma products industry members by 1983. IoM's Recommendation 6 makes the assumption that one can ascertain the existing level of risk and also the level of risk reduction that can be achieved by a particular action. AIDS is an example where such determinations could not be made.

Recommendation 7: The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

Response to Recommendation 7: ABRA supports this recommendation and believes such periodic review represents normal practice.

Recommendation 8: Because regulators must rely heavily on the performance of the industry to accomplish blood safety goals, the FDA must articulate its requests or requirements in forms that are understandable and implementable by regulated entities. In particular, when issuing instructions to regulated entities, the FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.

Response to Recommendation 8: ABRA believes that the federal agencies with jurisdiction over blood and plasma-based therapies should issue clear regulations and distinguish between mandated requirements and general guidance. At the same time, ABRA also recognizes that federal agencies need the flexibility to respond quickly to emergency situations.

Recommendation 9: The FDA should ensure that the composition of the Blood Products Advisory Committee reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.

Response to Recommendation 9: Unlike providers of whole blood, the plasma fractionators have never had a voting representative on the Blood Products Advisory Committee (BPAC). All parties affected by the regulation of blood and plasma-based therapies—including the fractionators—should be represented on BPAC. ABRA does not support the elimination of individuals simply because of their interest in a matter although their interest should be clearly articulated. In fact, such individuals' expertise is often essential to effective consideration of the issues which the Blood Products Advisory Committee must address. This IoM recommendation should be implemented in a manner which ensures that decisions are based on input from persons having the necessary scientific expertise, skill and knowledge.

Recommendation 10: The FDA should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.

Response to Recommendation 10: ABRA supports this recommendation and believes that such a dialogue has always taken place.

Recommendation 11: The PHS should develop reliable sources of the information that it needs to make decisions about the blood supply. The PHS should have its own capacity to analyze this information and to predict the effects of regulatory decisions.

Response to Recommendation 11: ABRA supports the concept that decisions about the blood supply and plasma-based therapies should be based on reliable sources of information if available. In the spring of 1983, the CDC, the NIH, and the FDA did just this—within the limits of what was then known—in issuing their joint recommendations for the prevention of AIDS (MMWR 3/4/83). ABRA understands that HHS has established a joint Task Force made up of representatives from the FDA, CDC and NIH to respond to the recommendations of the IoM report.

Recommendation 12: When faced with a decision in which the options all carry risk, especially if the amount of risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.

Response to Recommendation 12: ABRA recognizes that the role of the physician is critical in providing patients with information regarding the benefits and risks, to the extent they are known, associated with any course of treatment.

Recommendation 13: The Department of Health and Human Services should convene a standing expert panel to inform the providers of care and the public about the risks associated with blood and blood products, about alternatives to using them, and about treatments that have the support of the scientific record.

Response to Recommendation 13: ABRA agrees that providing forums for a discussion of various clinical approaches is desirable and recommends that the HHS Task Force evaluate mechanisms already in place to provide this function. We also suggest that the Task Force evaluate possible mechanisms for dissemination of useful literature and information.

Recommendation 14: Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgment, and otherwise act so as to earn the confidence of the public and patients.

Response to Recommendation 14: Members of ABRA have responded, and will continue to respond, to requests from voluntary organizations for earmarked funds to support such worthwhile projects as educational publications and summer camps for children with hemophilia. The IoM's apparent suggestion that funding such activities somehow taints these organizations is untrue and offensive.

Mr. SHAYS. I thank you. I want to say for the record that we appreciate your cooperation. This is a new area for this committee in some instances, not new for some of the staff, but new for me, in particular. Your industry has been very cooperative with the committee, and it's appreciated.

I'm going to start with Mr. Souder. I will just say that when I heard Dr. Satcher's comments, what I was struck with was the sense that we can have the danger of being overconfident in this area. I mean his testimony is replete with instances of concern about the sense that we thought we were on our way and find that we are—I use the analogy of a defense system—but that we're under heavy assault.

There's a sense of confidence that I'm getting from the panel, which I'm not quite sure I share, and I'm going to be interested in pursuing that a little bit. Mr. Souder.

Mr. SOUDER. How are the blood product manufacturers addressing the transmission of nonlipid enveloped viruses, such as the parvovirus, which are not affected by the current viral inactivation technologies? Dr. Feldman, do you want to start?

Mr. FELDMAN. Fred Feldman, Armour. Part of what I listed in my presentation was the effort to develop broad methods of removal beyond just inactivation steps. Since not all viruses are the same, some of them will be susceptible to one treatment, like a pasteurization step or a solvent detergent step, but others won't be.

In advance, to try to tailor a specific purification or therapeutic process to account for the future, we have to anticipate other cat-

egories of agents that might come in. And so, what we've tried to do is we've tried to bring into that wider safety nets.

One of these safety nets is purification processing that isn't designed specifically to handle the heat sensitivity of a virus or its lipid envelope. It's designed to separate the therapeutic we want and to remove potential contaminants, whether they're viruses that we know about or viruses that could yet come in that process.

The other method that we've tried to employ is the incorporation of ultrafiltration processing. It's something other manufacturers around the world are trying to incorporate. It's sometimes called Nanofiltration. The principle is simple. The principle is that the therapeutic that we want can be passed through a membrane. The pores are small enough to allow it passage, but viruses, especially larger viruses, are kept behind.

We have pioneered in how to do that. We have validated the process to the satisfaction not only of the USFDA but other international agencies, as well, and we believe that processes like these offer the best potential for protecting against future agents that we may not know how to characterize today.

Mr. SOUDER. Dr. Tutwiler, did you have anything?

Mr. TUTWILER. Well, I can add very little, except to confirm everything that he said. We're also looking at Nanofiltration in great detail. Of course, it's quite easy to do at the laboratory scale, and sometimes the challenge, of course, is to scale it up and make it applicable at the production scale.

Of course, we mentioned before that heat, itself, is quite effective against viral parvovirus and the nonlipid-coated viruses. The problem, of course, is that that often inactivates the actual therapeutic proteins.

So that's why we have been looking at other ways to commit energy during our production process separate from heat, such as microwave or ultraviolet light with certain chemicals, to see if they might be effective in killing those nonlipid-coated viruses.

To date, those processes haven't been particularly successful, and I would agree with my colleague that, in fact, separation techniques seem to be the most effective. We find that certain precipitation steps that we've been adding to our purification processes also are very, very effective in removing these nonlipid-coated viruses.

Mr. SOUDER. Dr. Gomperts.

Dr. GOMPERTS. Congressman Souder, Baxter believes that this is an important issue. There are no simple answers. Nanofiltration will certainly be effective for certain protein concentrates, and in the case of Factor VIII, for example, useless because of the size of the virus and the size of the protein.

These particular viruses tend to be particularly resistant and, therefore, simple physicochemical procedures to inactivate them clearly have the potential to damage the therapeutic proteins which I alluded to. Consequently, I feel that although I believe that our products are safe today, from the point of view of these agents, they at this time do not seem to be a major threat to the population at large.

However, it is an issue, and in order to develop technologies, apply them, evaluate them, the approach that I recommended, that

Baxter has recommended, from the point of view of collaboration and interaction to maximize the knowledge base, I believe is very important.

Mr. SOUDER. Thank you. Also, a number of you have touched in detail, some less so, but would you say which new safety measure each of you would cite as the most important to implement within the next 1 to 5 years? Mr. Fournel.

Mr. FOURNEL. Well, that's a difficult question to answer. It depends on the specific pathogen you're speaking about. It depends upon the specific product you're speaking about.

Certainly, at the moment, I believe we can say that thermal methods, heating, and solvent detergent type chemical treatments are the most effective methods that we currently know work in virtually all products they've been tested in, with the caveats that have been mentioned by others with respect to the potential for altering the particular protein in a way that then renders it ineffective or, in fact, even dangerous to the recipient.

But those two methodologies, along with a good GMP, a good manufacturing process for establishing and validating particular steps for the removal of particular agents are probably the most likely to be implemented. Many already have been, but are likely to be implemented in the short term for all of the processes we do.

Mr. SOUDER. Dr. Feldman.

Mr. FELDMAN. I agree that this is a difficult question. I guess the question could be divided into, are we trying to extend our methods toward the kind of viruses that we know about, or are we trying to address agents that may yet come that we can't characterize?

I feel that if we had to focus on only a few areas—and I think all of us need to focus on testing, inactivation, elimination, and monitoring of donor populations, all of them—that probably the most productive for dealing with agents that we don't know about are developing broader based methods for testing the donor population and working toward separation methods, as opposed to specific virus-killing methods.

I think we have good methods at hand for killing viruses, but I think what we have to assume for the future is that if we want to protect the blood supply and plasma products against worst-case scenarios, that those agents that could come at us are resistant to the methods that we know, are small, difficult to deal with, and that's we, I believe, all are trying to anticipate are broader based general methods to deal with the most difficult of the cases that there are.

Mr. SOUDER. Any of the others want to comment on what you think, where you think the priorities are? Mr. Chairman.

Mr. SHAYS. I thank the gentleman. One of the issues that concerns me is the reduction in the plasma pool size and the sense that it would have provided greater safety for hemophiliacs and other patients who are truly dependent on treatments involving a large pool of plasma.

What I'm interested in is the sense that the Institute of Medicine's report, that there are some issues you agree with and some that you don't agree with. One of their recommendations is that, potentially, you consider reducing the pool size. I would like each

of you to respond to why we wouldn't do that. Can we start with you?

Mr. FOURNEL. This is a very complicated issue, as I'm sure you're aware.

Mr. SHAYS. Can I just understand your definition of "complicated." Is it a complicated issue—and I don't mean any disrespect for this, because this is a factor in the process—but is it a difficult issue because of the finances involved in the cost of reducing it—which has to be considered—or is it a difficult issue for something else, some other reason?

Mr. FOURNEL. That, among other reasons.

Mr. SHAYS. OK. You need to tell me why it's a difficult issue.

Mr. FOURNEL. Sure. I don't know how much time you're going to allow me. Let me just say, we, of course, as our corporation, as well as, I'm sure, all of my colleagues, would never reject an opportunity to improve the safety of either the input material or the final product.

As you may be aware, what occurs in the processing of plasma is that, first of all, a large number of donors contribute to a single pool.

Mr. SHAYS. Right.

Mr. FOURNEL. And that pool is subjected to fractionation, during which time intermediates are collected and are subsequently pooled in the generation of a specific product. So one actually ends up with an amplification such that you can, in fact, get, as the IOM report cites.

Mr. SHAYS. Let me put it in my own words. You're saying, as you get this large pool and you take out parts of it, you need a large enough amount to be able to do that. Is that your comment to make?

Mr. FOURNEL. The intermediate, in and of themselves, may not be of sufficient volume to make it commercially feasible to produce the final product alone.

Mr. SHAYS. So you at least have to get to that threshold.

Mr. FOURNEL. That's right, yes.

Mr. SHAYS. OK.

Mr. FOURNEL. And then, as the IOM report sates, you can end up with many thousands of donors actually contributing to the content of one particular product.

Mr. SHAYS. Right.

Mr. FOURNEL. OK. So, with that in mind, it is clearly worthwhile to consider reducing a number of donors in a given pool in order to achieve a smaller number at the end, as I think was stated earlier.

However, it needs to be remembered that when a hemophiliac, for example, is receiving therapy, they receive it over their lifetime. So, in the course of a year, they receive a certain number of vials, let's say, from a certain number of batches of material.

Now, for example, if we had to go to smaller pool sizes or smaller final product donor contributions, the number of individual lots that we would have to make in order to provide the same supply would have to increase and, therefore, the likelihood that a given recipient would use more lots would also increase. So it's a very

complicated statistical or numerical equation that we have to balance here.

Having said that, let me say that we rely at Bayer—and, again, I believe the industry as a whole would agree—we rely upon the efficiency of our processes for manufacture to reduce the risk of pathogen transmission to the recipients. So these viral inactivation strategies, these purification methodologies, all of these technologies that we apply to the products, are really what we believe are the primary safeguard for the safety of the products that we provide to the individuals.

So, while we concur that screening of plasma is very important and it reduces the risk of transmission—and again, we are still looking at, and I don't want to say that we reject the idea of small pool sizes—but I want to say that our processes are really the ones that—or our process area is where we really rely on demonstrating safety.

I would want to point out that, particularly in hemophilia, as well as in most of the other cases for our company, at least, we simply cannot make enough of our lifesaving medicines to treat the demand that exists. We are doing everything we can to meet that demand, but right now, in virtually all—I think maybe one of our products—we are on, basically, an allocation. We can't supply the need.

Mr. SHAYS. And what's the cause of that? You can't get enough what? You don't have the production capacity?

Mr. FOURNEL. Part of it's the amount of plasma available. Part of it's our manufacturing capacity, yes.

Mr. SHAYS. OK.

Mr. FOURNEL. And so, if we go to smaller pool sizes, the ultimate consequence of that is that we'll probably have less material available, because we'll have to fractionate in smaller batches.

We'll have to do—the testing that we do remains the same, but if, instead of testing—if you take 200 vials, let's say, in order to do a test on a lot, if a lot is comprised of 10,000 vials currently, at the pool size that we're working with, you reduce the pool sizes now that a lot only has 1,000 vials in it, we still have to test 200 vials for safety, all of the quality assurance tests we do.

So it means, ultimately, less material is available for the patients at the end that really need it. So I'm not trying to say that we, at least, at Bayer, would reject the idea of smaller pool sizes, but I would simply want to illustrate that it's a very complicated issue.

The answer—and again, for us, the primary source of safety, we believe, in the product is in our manufacturing processes. That really mitigates to some degree against the advantages to a smaller pool size.

Mr. SHAYS. You're basically one of five companies in this business? I mean, are we looking at five, primarily?

Mr. FOURNEL. In the United States, yes.

Mr. SHAYS. Yes.

Dr. GOMPERTS. The issue of pool size is an important one that Baxter has looked at. Safety is foremost in our whole production and manufacturing of our products. However, when we look at the pool size issue, we have to look at it in somewhat detail and depth

and understand what the impact of reducing pool size will have on both the efficacy and the safety of our products.

This particularly applies to the intravenous immune globulin. What this product contains is antibodies from all these donors, and the larger the pool of donor, the more efficacious, the more active and more important to individuals who require these products, such as individuals with primary immune deficiency and other immune disorders.

And while the Hemophilia Foundation and hemophiliacs are very active, very strident, about decreasing donor pool size, the primary immune deficient individuals and their foundation are equally insistent about not decreasing pool size. So, as far as immunoglobulins are concerned, it would be a serious change in efficacy issues to decrease the pool size in this situation.

A second issue, from the point of view of safety. Our screening of donors, testing samples of plasma from them, the production process, the viral activation procedures, we believe, are particularly effective in the major blood-borne viral pathogens of HIV, HBV, and HCV. However, if one looks at the impact of, potentially, one individual with virus contributing to a small pool, the potential titer, the amount of virus in that pool, would be much higher than in a situation of a much larger pool. In other words, the dilution effect would be lost.

So we see, on the basis of the issue of efficacy of IVIG, and the potential dilution effect, that these are important issues. I must conclude in stating that Baxter is looking at this issue and, in fact, has taken steps to decrease pool size where efficacy and safety are not impacted.

Mr. SHAYS. Any additional kind of response? Yes.

Mr. FELDMAN. Mr. Chairman, if I could, I think that it's an important question, and the answers to you should be as direct and simple as possible.

Mr. SHAYS. I emphasize the simple part. [Laughter.]

Mr. FELDMAN. Simple. I disagree with nothing that has been said so far, but I believe that the answers really have to come to two questions that are parts of what you asked. The first question is, does it make it safer to make a smaller pool size? And the second question is, can we do it? What are our logistical problems?

With regard to, does it make it safer, I, myself, can't really provide you with data, but I can tell you that the best information that I've seen has come from a presentation given by the FDA this last summer in a Blood Product Advisory Committee. That presentation was given by Dr. Thomas Lynch, and it was a very thoughtful and statistical calculation of risks as a function of pool sizes.

My understanding of it was that, once you get above a certain size—and the size is very small, 100 donors or less—that when you get to 500 liters or 1,500 liters, or 15,000 liters or more, the risk has reached plateau, that there is no incremental benefit from going from current manufacturing scale batches to small scale. And, if you don't have that report, I would encourage you to obtain access to that.

The second question is, can't we do it anyway, even if, theoretically, it may not benefit? I feel so strongly on this issue that I've presented data to the Blood Product Advisory Committee and to

the FDA on the specifics of what it would do to the fractionation industry to move from our current batch sizes. Ours I know about specifically.

I've modeled a batch size of 15,000 liters progressively down in steps to 1,500 liters as a batch size or 500 liters as a batch size. Without going into detail, what I can tell you is that the annual capacity from a batch size of 15,000 liters, modeling what I know, would give you roughly a potential product availability for Factor VIII of around 344 million units, enough to treat a lot of patients.

By bringing the batch size down from 15,000 liters to 500 liters, the availability of supply under those modes of manufacture would give you only 12 million units per year, not enough to treat even a small proportion of the patients that there are today. Dropping down to that batch size would reduce product availability of that type from plasma by 96.5 percent. If there's interest in the detail of this, I'm more than happy to make the tables available.

Mr. SHAYS. Let me just understand something.

Mr. FELDMAN. Yes.

Mr. SHAYS. Under your present capacity, would you expand your capacity at this smaller batch size? I'm not getting that part of it.

Mr. FELDMAN. OK.

Mr. SHAYS. I mean if you said to me that it become unrealistic because then your cost of product goes up, that's a fair statement. The stupidest thing I could do would be to suggest you do something that makes it so economically unfeasible for a modest gain in safety, a tiny gain in safety. That's not my point of the question. I just want to understand it.

Mr. FELDMAN. Sir, the costs, no doubt, would increase. That's no part of my thinking at all. What I've tried to address is, if costs weren't an issue, were there barriers in place—I guess what I need to explain to you is that at 500 liter batch size—still, apparently, large size—you only get out, roughly, 75 vials for treatment. That's not enough. And that's before you do any testing.

Under the best scenario that I could envision, we would have to test 29 vials, 39 percent of the batch. It wouldn't leave enough to distribute to where the supply of product for patients in this country was solvable.

Mr. SHAYS. Well, see, you make an assumption that I knew that the product you test, you can't use. So anything that you test is not—OK.

Mr. FELDMAN. Testing is destructive.

Mr. SHAYS. Thank you. I hear you.

Mr. TUTWILER. Well, I would just say that Alpha really confirms our analysis of that same issue. I mean, almost point by point, all the points that have been made today, I would totally agree with.

Mr. REILLY. Just like to make a couple of additional statements.

Mr. SHAYS. Sure.

Mr. REILLY. The first point that I think should be considered, too, is that the issue really is patient exposure to donors. How do you reduce the number of donors that a patient is exposed to? Reducing the lot size, while, if you look at it in the context of a single lot, looks like a good outcome, one of the results is the patient then is exposed to multiple lots. And that calculation has not been assessed, whether they in fact really get lower exposures.

The second thing is that it's always important—we consider a supply to be a safety factor, and as Dr. Feldman has outlined, just the amount of product that has to go to lot testing moves from about 2 percent at 15,000 to 39 percent of the total production at 500 liters.

The last comment I wanted to make was with regard to cost, because it came up in the context of this discussion, and it also came up in previous panels. I think if you were to go back through the record for the plasma industry and look at where we've testified before Blood Products or in any other public arena, it would be very rare, if ever, that you would see us raising the issue of cost.

The question is science and technology. If the science and technology support that a product can be made safer, that's the direction we will go.

Mr. SHAYS. Let me ask you this. If you find that there is an infected pool, how often does that happen?

Mr. REILLY. I guess we have a difficult time defining exactly what an infected pool means.

Mr. SHAYS. Well, not usable.

Mr. REILLY. I think when we find that a unit has been introduced into a pool, through look-back procedures or some other method, an assessment is made whether having that unit in the pool jeopardizes the safety of that product, and then appropriate actions are taken in consultations with the FDA and other relevant parties.

Mr. SHAYS. I'm having a little trouble understanding. How often do you find that a pool, a particular unit, has been contaminated in some way? You know, I ask the industry this. I mean, is it so infrequent as to be a major event? With all the people that are contributing to this, I would think that this would happen periodically.

Mr. FELDMAN. Maybe I can have a try at that.

Mr. SHAYS. OK.

Mr. FELDMAN. All of us operate according to look-back procedures that are established by the FDA, which means that if a donor tests negatively and his product is incorporated, his plasma goes through the process of manufacture for processing, that we continue to process.

When a donor comes back—he's a repeat donor—and, on the 2nd trip, the 3rd trip, the 20th time that he comes to donate, that he's found to be positive for, for example, HIV, that the exercise we do is go back and look and see if that prior plasma that was negative is still within our control, if it's at our centers, if it's in our freezers, if it can be removed before processing, and if it can, then we remove it.

If we cannot, then we continue to process. But everything that has gone into the pool has already tested negative. Despite that—and, as I think, what you've heard from us as a whole is that we all assume that there can be an infectious unit in the pool, and, in order to guard against that, we have incorporated increasing layers of safety based on the mechanisms we've talked about—inactivation, virus elimination, and our attempting to increase the efficacy of those for other agents that there could still be.

Mr. SHAYS. How many donors contribute to a large pool? How many donors are we talking about?

Mr. FELDMAN. If you're addressing me, sir.

Mr. SHAYS. Yes.

Mr. FELDMAN. For our vat size, for a commercial factory, we operate at around 15,000 liters.

Mr. SHAYS. And 15,000 liters, is how many donors?

Mr. FELDMAN. Oh, around 18,000 donors.

Mr. SHAYS. OK.

Mr. FELDMAN. That's from plasmapheresed plasma. If we utilize plasma recovered from whole blood, because the volume that's collected is smaller, then that's an area we would have a pool size of around 60,000 donors.

Mr. SHAYS. Is that consistent for the industry, basically?

Dr. GOMPERTS. Approximately.

Mr. FELDMAN. Depending on whether we utilize plasma as a source or plasma recovered from whole blood.

Mr. SHAYS. But, basically, depending—it's 18,000 to 60,000. That's pretty much the industry?

Mr. TUTWILER. 11,000.

Mr. SHAYS. 11,000? OK. Is this proprietary knowledge, or is this basic stuff?

Mr. FELDMAN. I think we generally know that we all operate at industrial scales. The exact size, I think, none of us have really shared, but we've discussed that in open fora, including Blood Product Advisory Committee.

Mr. SHAYS. Which raises the question—I mean, I don't want to get off this question, because I really want to nail down one thing. If you had one donor who was HIV positive who somehow slipped into the system, would that mean that the entire vat was defective and infected?

Dr. GOMPERTS. Yes.

Mr. TUTWILER. You mean the plasma, itself, the pool of plasma?

Mr. SHAYS. Yes.

Mr. FOURNEL. Yes, before it has been processed.

Dr. GOMPERTS. Yes.

Mr. SHAYS. Well, after it has been processed.

Mr. FOURNEL. No, not after it has been processed.

Mr. FELDMAN. No.

Mr. SHAYS. OK.

Mr. FOURNEL. That's what I was saying earlier, that we rely on this manufacturing methodology to take care of the inadvertent accidents such as you described that might happen.

Mr. REILLY. One of the things you might want to understand is that the simple logistics of collecting it and shipping and of processing of plasma give you a window of opportunity to remove the unit. We know that the window of infectivity, for instance, for HIV is approximately 4 weeks.

If you have a donor who is a repeat donor, and you get a positive result, and you want to go backwards and pull the units which previously tested negative, you have an opportunity prior to pooling to pull those units.

So the likelihood that the unit that actually went in the pool was in fact infectious is very low, and we know that through out viral inactivation removal processes, we can clearly show the capacity to

kill whatever limited number of units might have gotten through that system.

Mr. SHAYS. Let me just ask you, on the issue of sharing, if one of you develops a breakthrough, why wouldn't it be in our Nation's best interest for you to share that with your competitors?

Dr. GOMPERTS. That does happen.

Mr. SHAYS. Give me an example.

Dr. GOMPERTS. The heat treated process that Baxter developed was shared. It's cross-licensed. The immunoaffinity chromatographic system that Baxter developed is cross-licensed with a large number of different fractionators across the world.

Mr. SHAYS. And you share them? Do you have a patented process that, then, you receive a benefit from? And then, are they being used by some of the other companies here?

Dr. GOMPERTS. Yes, that is correct.

Mr. SHAYS. Can others of you share?

Mr. FELDMAN. In fact, we obtained a patent for the immunoaffinity processing use of monoclonal antibodies that are used not only in today's plasma-derived products, but recombinant products, as well, and that is also being accessed by other fractionators. So it is not unusual for technology to be available to other manufacturers.

Mr. SHAYS. Do our antitrust laws prevent you in any way from sharing this kind of information? Is there anything the government does to make it more difficult in this way?

Dr. GOMPERTS. What the antitrust laws do prevent is industry sitting around sharing data, information, developing strategy, because of the potential fear that Department of Justice may see such interactions as contravening the antitrust laws.

Mr. SHAYS. Are your basic products all pretty much sold at the same price?

Dr. GOMPERTS. Approximately.

Mr. SHAYS. So does there become, if you develop a system which helps you reduce costs, does that become a challenge for you in terms of sharing that benefit with others?

Mr. REILLY. As a system that just reduces costs, I think that yes, it becomes a competitive issue.

Mr. SHAYS. Pardon me.

Mr. REILLY. If it's a system that simply reduces costs, yes, it's a competitive issue.

Mr. SHAYS. Yes. Then the challenge, though, is if it reduces costs and also provides a better screening process, then how would you deal with that?

Mr. REILLY. Well, I think what you've heard the gentlemen say here is that once the technique, whether it's a new technology or some scientific breakthrough, is developed and—fully developed, they do frequently cross-license, and they do cross-utilize the technology.

I think if you try to address the question of the antitrust laws, they're more a question of the up-front sharing, the question of joint research and sharing of information in advance of the technology being available.

Mr. SHAYS. Yes, Dr. Feldman.

Mr. FELDMAN. Mr. Chairman, this is an area where all of us publish and all of us want to be at the forefront of advances and want it to be understood that we're attempting to do those things. We're all alike in that respect.

I think what you would find, if you surveyed the literature or marketing activities, if you would, would be that as soon as we have something that looks good, we tell publishers, journals, scientific conferences, that we have a breakthrough, if it's in viral removal.

If it's a new process, there are publications in advance of licensing, oftentimes. Those are the opportunities for one company to go to another and to obtain a license for another process that looks like it brings some benefit and bring it into the common good. And I believe that that happens.

Mr. SHAYS. Let me ask you—I'm having some votes, and then I'll come back for the fourth panel. I'm not quite clear. There were some comments made at the beginning that just raised a question in my mind. You have tremendous demand for your products; correct? Are you meeting the demand or is the implication that you're actually almost having to farm it out to certain people in other organizations are not getting it? Is the entire demand being met?

Dr. GOMPERTS. By and large, yes.

Mr. SHAYS. Where isn't it being met?

Dr. GOMPERTS. Baxter is meeting the market demands as we see them, but we're also adding capacity.

Mr. SHAYS. You're adding what capacity?

Dr. GOMPERTS. We're adding manufacturing capacity, specifically for our recombinant Factor VIII product.

Mr. SHAYS. But are you all pretty much at peak capacity here?

Mr. FELDMAN. There are times when demand is not being met. There have been times this year, in 1995, when meeting demand has been difficult, and particularly in regard to the CJD recalls that occurred with the American Red Cross and the Canadian Red Cross, supply was a major problem. And because all of us are, I believe, at full capacity, those of us who didn't have a problem were able to meet those needs.

If we went to a volunteer donor source, if we went to small pool sizes, that kind of potential would disappear.

Mr. SHAYS. OK. Which raises a question that I wanted to ask, and that is, is there the danger that by depending not just on volunteers, but actually paying for the product, the base product, does that potentially endanger the supply?

Mr. FELDMAN. Absolutely. If we only were able to draw upon unpaid donors for plasma, and that plasma recovered from whole blood, we would not be able to have the kind of capacities we need and that the patients need.

The second question is, does it benefit the patient with regard to better viral safety, and would it have prevented the tragic contamination of Factor VIII concentrates that occurred?

The best record of that, I believe, is in Australia, where they had only volunteer donors, where they operated within industry under tight control by government, no importation of product from the United States, and where hemophiliacs there seroconverted to the same tragic extent as in the United States. There are better ways

to go, and there are things that we can do, but those two issues aren't part of the answer, I believe.

Mr. SHAYS. Let me just end, Mr. Reilly. I am concerned that we have the Secretary of Health and Human Services basically saying that she agrees with all the recommendations of IOM and you all making specific responses to the 12 recommendations and not being favorably inclined for a number of them.

I need to sort out with each of you—and I'm going to ask you to provide this to us in a written statement—where, specifically, each of your companies agree with each of the 12 recommendations and where you disagree. I don't want to depend on the association. Then I will just tell you, the basis for our next hearing will be to just really try to sort out that issue.

That's very important to this committee. The point would just be that that would be a question that I publicly asked for. So we may follow up in written request and would ask for your continued cooperation in that respect.

I'm very grateful for all of you being here and we'll just be at recess until I return from a vote. You all are done. Thank you very much; appreciate it.

[Recess.]

[Company responses follow:]

December 21, 1995

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
and Intergovernmental Relations
U.S. House of Representatives
B-372 Rayburn House Office Building
Washington, DC 20515

DEAR CHAIRMAN SHAYS:

During the November 2 hearing, "Protecting The Nation's Blood Supply: New Standards to Meet New Threats", you asked all witnesses on the industry panel for a formal comment on the Institute of Medicine report, "HIV and the Blood Supply: An Analysis of Crisis Decision making". Although Bayer Corporation included specific comments on this report in our written statement and oral testimony, we have given the subject additional consideration. In keeping with the spirit of your request, we respectfully offer the following thoughts.

First, we would like to commend you and the Subcommittee for your consistent and thoughtful attention to the safety of America's blood and plasma supply. All of us have an abiding interest in this subject, because each of us is a potential candidate for an unanticipated, yet critical, need for blood, blood components or plasma-derived therapies. Because the supply of these therapies is dependent on a limited natural resource for their base material, our society needs to ensure that this supply is not only as safe as it can possibly be, but also that is sufficient to meet the needs of those who may rely on it for their lives and health.

With respect to the Institute of Medicine report, we would like to start by stressing that our comments are limited to the 14 recommendations, which we understand are particularly relevant to the Subcommittee's interests. Overall, Bayer participated in the creation and endorses the responses of the American Blood Resources Association, which have been submitted to the Subcommittee for the record. Most important, we believe, is the impact of implementation on the success of these IoM recommendations.

In our testimony at the November 2 hearing, we stated our understanding that the Department of Health and Human Services (HHS) intends to implement key recommendations of it's Task Force in order to elevate blood safety issues to the highest levels of attention at HHS (in response to Recommendations #1 and #2). We also expressed our commitment to work with both the Congress and HHS to make a positive and substantive contribution to the deliberations of HHS's new Advisory Council on Blood Safety and Availability. However, we recognize the challenges the Council and Blood Safety Director will face in dealing with the complex issues that will confront us in the future. Keeping in mind the importance of proper implementation to the success of the recommendations, the Subcommittee may wish to statu-

torily establish the Council and Director and work with the Secretary of HHS on mutually agreeable objectives, responsibilities, and determinants and measurements of success.

Also at the November 2 hearing, Bayer singled out those recommendations which we believe focus most closely on the contributions private enterprises like ours can have on blood and plasma safety. We would like to reiterate our views here and at least point toward an issue on which the Subcommittee may be of assistance. In particular, Bayer supports the spirit of those recommendations which encourage the implementation of partial solutions to problems for which complete information is not yet available (Recommendation #6), along with a subsequent review of such decisions when more information has been obtained (Recommendation #7). We believe this is happening in the case of Creutzfeldt-Jakob Disease (CJD).

We also recognize that there are significant obstacles to implementation of Recommendation #6. For example, the IoM report suggested the possibility of a "phased recall" as a means of ameliorating the effects of withdrawals on the supply of product to patients (pages 8–18, 8–19). While this may make sense in theory, we believe that in practice the social, political, and legal environment makes it impossible. We think the Subcommittee may be able to provide some assistance in evaluating the problems with implementing this recommendation, perhaps using the above-mentioned CJD events as an analytical tool.

With respect to Recommendation #8, we reconfirm our support for clear directives from government agencies to regulated entities and reconfirm our commitment to a collaborative relationship with government agencies toward the interests of patients. Practically, we interpret all documents from the U.S. Food and Drug Administration which have a bearing on patient safety as directives. Such was the case with FDA's August 8 letter to manufacturers regarding plasma donors at high risk for CJD. Regarding Recommendation #13 concerning communication, as a matter of corporate policy and culture, Bayer is committed to proper and responsible communication to providers (and thereby patients) and has gone to great lengths within the bounds of law and regulations to communicate safety information. In this regard, we recognize and respect the law and regulations as authoritative guidelines of what is relevant to treatment/product use decisions. We hope you agree, Mr. Chairman, that our actions with respect to CJD are wholly in keeping with our stated commitment.

In closing, we respectfully suggest that, in evaluating actions contemplated as a result of the IoM report, it will be important to assess the contemporary environment (the period under review in the IoM report ended ten years ago). Our statement at the November 2 hearing was designed to outline our current activities, in the hope of providing some guidance for the Subcommittee's work.

We will continue to cooperate fully with you, Larry Halloran, and Anne Marie Finley of your superb senior legislative staff as you continue your important work on behalf of the millions of Americans who must rely on a safe and adequate supply of blood and plasma products. We share your commitment to the highest standards of healthcare.

With best wishes,

MICHAEL A. FOURNEL
Vice President
Research and Development, Biotechnology and Biological Products

---

January 3, 1996

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
and Intergovernmental Affairs
Committee on Government Reform and Oversight
United States House of Representatives
2157 Rayburn House Office Building
Washington, DC 20515–6143

DEAR CHAIRMAN SHAYS:

I am writing on behalf of Bayer Corporation regarding your December 18, 1995, letter to Michael Fournel requesting information on blood safety issues.

Your first question asked for a response to each of the recommendations contained in the Institute of Medicine's report, HIV and the Blood Supply: An Analysis of Crisis Decisionmaking. However, in response to your verbal request at the Subcommittee's November 2nd hearing, and in the spirit of cooperation with the Subcommittee, Bayer already had prepared a written comment which was sent prior to our receiving your December 18th letter. In our response, we focused only on those rec-

ommendations about which we felt Bayer could offer meaningful thoughts and on which the company has taken a point of view beyond that which was provided in the American Blood Resources Association's (ABRA's) position on October 3, 1995. Therefore our letter did not specifically respond in instances where we felt the IoM's recommendations dealt with internal government issues, or where had nothing to add to the ABRA response. Nevertheless, we hope you find our letter responsive to your needs and judge it a suitable response to your first question.

With respect to questions 2 and 3, Bayer respectfully requests a short extension to prepare a thorough response to your letter. I believe we can commit to providing the information you requested by no later than Friday, January 19.

We very much appreciate your consideration and look forward to assisting you and Anne Marie Finley in any way we can.

With best wishes,

Sincerely,

DANIEL J. MCINTYRE
Director Public Policy and Public Affairs

January 19, 1996

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources and Intergovernmental Affairs
Committee on Government Reform and Oversight
United States House of Representatives
2157 Rayburn House Office Building
Washington, DC 20516–6143

RE: Inquiry of the Subcommittee of December 18, 1995

DEAR CHAIRMAN SHAYS:

On behalf of Bayer Corporation, I am responding to the above-mentioned inquiry of the Subcommittee, in connection with your work relating to the safety of the nation's blood supply. This supplements our letter to you of December 22, 1995, which I trust is a sufficient response to question #1. Following is information relating to your other two requests:

> 2. Does your company currently import, or has your company ever imported, any plasma, albumin, blood, or blood products from any country other than the United States for use in the manufacture of any product sold in the United States? Please provide type of product, country of origin, and source.

During the early 1970's, Gutter/Miles imported a small amount of plasma from Haiti and Mexico. Plasma collection from Haiti and Mexico ceased in 1972 and 1973, respectively. Beginning in the mid-1970's, Cutter also collected plasma from a facility in Nicaragua, which was an FDA-inspected and licensed center. Plasma obtained from this center was subject to the strict procedures regarding screening and plasmapheresis center operations set out in the Cutter System of Plasmapheresis and Quality Assurance Procedures. The Cutter System of Plasmapheresis Procedures was approved by the FDA and is part of Cutter/Miles FDA license. We last imported plasma from Nicaragua in 1978. No other plasma collected from foreign countries went into coagulation products sold in the United States.

> 3. Does your company utilize, or has your company ever utilized, any plasma, albumin, blood, or blood products from prisoners or prison inmates in this country or any other country? If so, please provide all details such as dates, counties, and prison names.

At one time or another, prior to 1989, our company received plasma from FDA-licensed plasmapheresis centers located in various state prisons. Our company has at all times complied with the contemporaneous FDA regulations regarding the use of plasma from prison centers. (NOTE: Current recommendations are that inmates of correctional institutions and individuals incarcerated for more than 72 hours in the previous 12 months be excluded as donors for source plasma.)

From February 1983 onward, no plasma was collected from any prison facilities for use in factor concentrates. This action was taken in response to a request from the National Hemophilia Foundation and informal observations from regulatory authorities revealing that there was a perception that such plasma was undesirable.

We trust that the information in this letter is responsive to the Subcommittee's request. However, if you or your staff would like to review anything further, please let us know.

In closing, I would like to assure the Subcommittee of Bayer's commitment to working with you, through Mr. Halloran and Ms. Finley. If there is anything further

you need, either in connection to our response to the Subcommittee's request or other matters, please be assured that we stand ready to assist.

With best wishes,

Sincerely,

DAN MCINTYRE

February 14, 1996

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources and Intergovernmental Affairs
Committee on Government Reform and Oversight
United States House of Representatives
2157 Rayburn House Office Building
Washington, DC 20515–6143

RE: Subcommittee Inquiry of December 18, 1995

DEAR CHAIRMAN SHAYS:

You have asked us to expand upon our answers to questions #2 and #3 regarding the use of plasma from foreign and prison sources in plasma derivatives other than factor concentrates. We apologize for not providing the level of detail which you desired.

With respect to question #2, the only other plasma collected from a foreign source which went into plasma derivatives, other than described in our previous answer, was a small quantity of plasma obtained from the Bavarian Red Cross in Germany between 1992 and 1995. This center was an FDA-licensed facility, and a small amount of Bavarian Red Cross plasma was used in plasma derivatives other than factor concentrate. Some of this plasma may also have been incorporated into two lots of factor concentrate which were distributed in the U.S. in late 1993 or early 1994.

With respect to question #3 regarding the use of plasma from prison facilities, Cutter/Miles did obtain plasma from correctional facilities during the 1980s, which was used in plasma products, other than factor concentrates. As noted in our previous answer, plasma from prison facilities was not collected for use in factor concentrates after February of 1983.

With best wishes,

Sincerely,

DAN MCINTYRE

BAXTER HEALTHCARE CORPORATION'S RESPONSES TO THE HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE OF THE HOUSE GOVERNMENT REFORM AND OVERSIGHT COMMITTEE

QUESTION 1

Question: What is your company's response to each of the fourteen recommendations in the Institute of Medicine Report, "HIV and The Blood Supply: An Analysis of Crisis Decision Making"?

Baxter's Response: Baxter Healthcare Corporation (Baxter) considers the IOM Committee's recommendations valuable insofar as they stimulate productive debate on future directions in the safety of blood and plasma-based therapies. The recommendations, however, suffer from some serious limitations, the most salient of which—the limitations of hindsight—was acknowledged by the IOM Committee itself.

The IOM Committee was charged with reporting on events of the early 1980s. Toward this objective, the IOM examined the responses of various institutions to the AIDS crisis in the early 1980s, and theorized as to how those institutions could have been changed to function more effectively at the time. The IOM Committee did not examine the various institutions as they now exist. As the Committee itself explained, it "based its recommendations on the institutions as they existed in the early 1980s, not as they exist now." (page 8–9). Therefore, the relevance of many of the Committee's recommendations to today's world is unclear.

As the IOM Committee acknowledged, the early 1980s were characterized by ongoing debate and tremendous medical and scientific uncertainty about AIDS. Particularly in light of the limited knowledge possessed by humankind at the time, the Committee is correct in observing that "[t]he risk of hindsight is unfairly finding fault with decisions made by people who had to act long before scientific knowledge became available to dispel their uncertainty." (p. vi). Unfortunately, the IOM Com-

mittee—with the benefit of the 20–20 hindsight that it warns against using—draws a series of fundamentally erroneous conclusions from the history of the AIDS tragedy. The Committee offers selective and misleading presentations of the historical "facts," often without identifying the source of its "facts." The Committee then draws conclusions from these "facts" that are without any identified or supportable basis. The result is that the IOM Committee does indeed err in "unfairly finding fault" with those who faced daunting uncertainty during the early 1980s.

In addition, the IOM Committee's paradigm for "improving" regulation of blood and plasma-based therapies offers no panacea for the sort of crisis faced by the government, the medical community, and the fractionation industry in the early 1980s. The fundamental challenge confronting society during the early 1980s was a pure lack of information, not a flawed public or private response.

Recommendation 1: The Secretary of Health and Human Services should designate a Blood Safety Director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.

Baxter's Response: At the theoretical level, Baxter supports the notion of designating a "lead person" to coordinate the federal government's efforts regarding safety of blood and plasma-based therapies. In practice, however, such a designation could add an unnecessary level of bureaucracy, and could either advance or impede safety objectives. Baxter is pleased with the appointment of Dr. Phil Lee as the first Blood Safety Director, and will support him in his important mission.

Further Discussion: The designation of a single "czar" to oversee any area of policy does not guarantee better or more coordinated policy. Indeed, depending upon how the concept is implemented, it may simply add an additional layer of bureaucracy, delaying prompt action in crisis situations. At the same time, excessive emphasis on rapid responses in all situations may lead to rash actions which ultimately prove to have been more costly than careful, measured study and action.

Although Baxter does support the first recommendation of the IOM Committee, it does not endorse the "findings" of the Committee upon which its first recommendation is predicated. The IOM Committee's sweeping claim that there was a "failure of leadership" between 1980 and 1984 is incorrect. With the benefit of hindsight, one always can question the correctness of past policies and actions, and conclude that some things "should have been" done differently. But the policies and actions of the past are properly measured against the information available at the time, rather than what now is known. In the period from 1980 to 1984, there was no clearly "leading" view because there were so many unknowns. Conscientious and experienced experts simply differed (often quite strenuously) on many of the important issues. The IOM Committee's apparent notion that having a single "czar" to set policy in the face of conflicting views will itself avert any future tragedy like AIDS ignores the facts of scientific debate and uncertainty.

Recommendation 2: The Public Health Service (PHS) should establish a Blood Safety Council to assess current and potential future threats to the blood supply, and propose strategies for overcoming these threats, to evaluate the response of the PHS to these proposals, and to monitor the implementation of these strategies. The Council should report to the Blood Safety Director (see Recommendation 1). The Council should also serve to alert scientists about the needs and opportunities for research to maximize the safety of blood and blood products. The Blood Safety Council should take the lead to ensure the education of public health officials, clinicians, and the public about the nature of threats to our nation's blood supply and the public health strategies for dealing with these threats.

Baxter's Response: Baxter supports the concept of greater cooperation and coordination among groups concerned with the safety of the nation's supply of blood and plasma-based therapies.

Further Discussion: To the extent that the proposed Blood Safety Council will engage in study of possible "threats" to the supply of blood and plasma-based therapies, its mission appears largely uncontroversial, provided its methods of study are sound and science-based. The proposed role of the Council in education is, at the conceptual level, laudable, provided again that any education consists of disseminating the results of sound science. As with everything, however, the ultimate value of the Blood Safety Council will lie in its ability to foster scientific discussion, reach scientifically justified conclusions, and provide clear and timely communications to the public.

Baxter disagrees with the IOM Committee's conclusion that there was a lack of cooperation among responsible groups during the early 1980s, that these groups did not communicate effectively with physicians and the public, and that these groups were not publicly accountable. Minutes of the Blood Products Advisory Committee (BPAC), for example, evidence a tremendous effort to include and coordinate a vari-

ety of perspectives, and to weigh the many unknowns—while at the same time trying to maintain, for the sake of public health, the availability of lifesaving plasma-based therapies.

Baxter rejects the IOM Committee's guesswork about what a Blood Safety Council "would have" done had it existed in the early 1980s (p. 8–14). Assuming—as the IOM Committee does—that a hypothetical agency would have acted with prescience serves no useful function save to emphasize the Committee's misuse of hindsight.

Recommendation 3: The federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products.

Baxter's Response: Baxter agrees that this concept deserves further study.

Further Discussion: The IOM Committee offered few if any details of the "compensation system" it had in mind, perhaps because this recommendation fell well outside of the Committee's charge. Baxter's future support of, or opposition to, any particular scheme of "compensation" will depend upon the answers to a variety of questions about the specific program proposed.

The IOM Committee's suggestion that the government impose new taxes in order to fund a "compensation" scheme raises serious questions. Arguably, given society's interest in an adequate supply of blood and plasma-based therapies (p. 8–15), any "compensation" system should be funded from general federal revenues, as was the case for a portion of the vaccine fund.

American society well may decide that it wishes to spread among its members the costs of injuries due to blood and plasma-based therapies. There are a variety of ways to accomplish this end. Ultimately, however, the public and consumers of plasma-based therapies would bear the cost of any such compensation scheme. This result would be particularly pronounced were any "compensation" scheme not coupled with a restriction on civil lawsuits such as that found in state workers' compensation programs.

Baxter disagrees with the IOM Committee's attack on the judicial system of the United States. The comments made by the Committee not only appear critical of our judicial system and our reliance upon juries; they also challenge the judgments made by the legislatures of nearly every state seeking to define the appropriate standard of liability applicable to lifesaving blood, plasma-based therapies, and human tissue. The fact that persons with hemophilia who have resorted to the judicial system have not prevailed does not show that the common law tort system fails to protect the "rightful interests" of those who suffer injury from plasma-based therapies. In reality, the reason that HIV-infected persons with hemophilia have not recovered money in their lawsuits is that juries have found—after full trials—that the fractionators cannot be blamed for the AIDS tragedy.

The IOM Committee's recommendation No. 3 offers only a bare concept, and further evaluation of this concept will depend upon the answers to numerous questions that the IOM Committee did not address. Baxter's future support of, or opposition to, any particular system of "compensation" will depend upon how these questions are answered in concrete particular.

Recommendation 4: Other federal agencies must understand, support, and respond to CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.

Baxter's Response: Baxter supports this recommendation, as phrased. In fact, Baxter believes that the recommendation largely restates the current state of affairs.

Further Discussion: Baxter agrees that it is important that the nation have an "early warning system" for threats to the public health, and that the various federal agencies remain cognizant of early warnings as they occur. An early warning system can act, however, only as a beginning point of discussion.

Unless all components of the new scheme envisioned by the IOM Committee work together, public health might be disserved rather than advanced. This will require cooperation among the CDC in its role as a bellwether, the Blood Safety Council as an advisory panel, and the Blood Safety Director as the "lead person" in the area of blood and plasma-based therapy safety.

The IOM Committee's assertion that the CDC was "right" about the AIDS epidemic and how to prevent its spread—but was ignored by other federal agencies that were "wrong"—is not supported by fact. In truth, vehement scientific debate raged in, and among, all agencies—including the CDC—during the early 1980s.

Recommendation 5: The PHS should establish a surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products.

Baxter's Response: Baxter supports a surveillance system within CDC or in cooperation with the CDC and other organizations.

Further Discussion: At a conceptual level, the notion of a surveillance system seems uncontroversial. In Baxter's view, the question of which agency should operate such a surveillance system rests within the sound discretion of the various governmental agencies responsible for blood and plasma-based therapy safety.

Baxter disagrees with the IOM Committee's speculation that a different system of surveillance would have allowed a different response to AIDS in the early 1980s. The lack of knowledge in the early 1980s was not due to the absence of any particular form of surveillance, or to a lack of surveillance in general. Indeed, the CDC did play a substantial role in identifying the illness later to be called AIDS as a new phenomenon to be studied and, as knowledge permitted, attacked.

During the early 1980s, CDC did perform the early warning function advocated by the IOM Committee. The IOM Committee fails to acknowledge, however, that the CDC did not know what was causing the disease processes that CDC was warning about. Indeed, it was not until July of 1982 that symptoms later identified as AIDS were reported in any person with hemophilia. It was not until April of 1984 that the HHS was in a position to name the HTLV-III retrovirus (later named HIV) as the cause of AIDS. And it was not until 1985 that there was a commercially available way to test for AIDS.

In the future, action by the CDC or others to monitor and warn about reports of diseases as they arise (whether in isolation or in groups) will not necessarily allow the Blood Safety Director, the Blood Safety Council, or other governmental agencies to piece together enough of the factual puzzle rapidly enough to take the early, decisive action that the IOM Committee incorrectly claims was feasible regarding AIDS.

Recommendation 6: Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

Baxter's Response: In theory, Baxter supports recommendation 6. However, Baxter does so with serious reservations based upon the reality that the evaluation of the risks associated with the implementation of "partial solutions" is not foolproof, and may itself result in greater harms than those the partial solutions are designed to address. The IOM Committee is incorrect in its implicit assumption that human knowledge typically will permit accurate assessment both of existing risk levels and of the risks attendant to incremental steps.

Further Discussion: If the FDA can improve safety without causing any sort of harm, it should do so. However, where emerging infectious agents present science with great uncertainty, it will be difficult for the FDA to determine any way to increase safety without potentially causing harm.

In the early 1980s, the leading experts in this country—and around the world—believed that there were serious risks associated with all the potential courses of action. Decisions made at the time were based upon careful, indeed often agonizing, assessment of all the known and potential risks and benefits as they were understood at the time. It is difficult to see how regulators—or fractionators—could have designed a viable "partial solution" that would have "little risk of causing harm" in light of the then-existing base of knowledge.

Recommendation 7: The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

Baxter's Response: Baxter supports this recommendation, as phrased, and believes that such periodic review represents normal practice.

Recommendation 8: Because regulators must rely heavily upon the performance of the industry to accomplish blood safety goals, the FDA must articulate its requests or requirements in forms that are understandable and implementable by regulated entities. In particular, when issuing instructions to regulated entities, the FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.

Baxter's Response: Baxter agrees that federal agencies with jurisdiction over blood and plasma-based therapies should make it clear if any of the standards they set are not mandatory.

Recommendation 9: The FDA should ensure that the composition of the Blood Products Advisory Committee reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.

Baxter's Response: Baxter believes that all parties affected by regulation of blood and plasma-based therapies should be represented on BPAC. This includes fractionators such as Baxter, none of which has had a representative on BPAC.

Further Discussion: The presence of all parties affected by regulation will ensure that a mix of viewpoints is presented, and presented by persons who have both

knowledge of the subjects to be considered and who are invested in the subject of the regulation.

Baxter suggests that the interests of BPAC members should be disclosed. Hence, for example, if a BPAC member is an employee of a fractionator, or owns stock in a regulated entity, that interest should be disclosed. The same is true of those who may have interests directly opposed to those of regulated parties. For example, members of BPAC who have litigation pending against regulated parties should be required to disclose those interests in the same manner as other BPAC members must disclose their potential "conflicts." That way the interests of all involved will be open to public scrutiny.

BPAC should strive to consider the views of all qualified experts who wish to participate in its debates. Affiliation should not be a determining factor.

Recommendation 10: The FDA should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.

Baxter's Response: Baxter agrees with this recommendation. It believes that the FDA and its advisory committees have historically worked in the manner recommended.

Recommendation 11: The FDA should develop reliable sources of the information that it needs to make decisions about the blood supply. The FDA should have its own capacity to analyze this information and to predict the effects of regulatory decisions. It will, however, necessarily be limited by what information is obtainable at the time.

Baxter's Response: Baxter supports the concept that decisions about the blood supply and about plasma-based therapies should be based upon reliable sources, where such sources of information are available. Data collection and evaluation should at all times reflect sound science.

Recommendation 12: When faced with a decision in which the options all carry risk, especially if the amount of risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.

Baxter's Response: Baxter absolutely agrees that physicians and patients must discuss the risks and benefits of all treatment options, and that it is the responsibility of patients to be educated consumers, just as it is the responsibility of physicians to remain current on all information affecting their patients.

Further Discussion: The medical profession—through the education and training required of each prospective physician, and through the various professional codes and standards—establishes a number of standards of care for treaters to meet. Baxter of course advocates that individual treaters adhere to the standards appropriate to the administration of plasma-based therapies, including the discussion of risks and benefits.

Baxter does not agree with the IOM Committee's sweeping claim that physicians systematically kept their patients uninformed of the risks and benefits of factor concentrates as they were known during the early 1980s. The central problem was that nobody knew the real degree of risk from AIDS, and had to struggle with balancing an unknown and unquantifiable threat against the very real danger of death or other injury from a hemorrhage.

Recommendation 13: The Department of Health and Human Services should convene a standing expert panel to inform the providers of care and the public about the risks associated with blood and blood products, about alternatives to using them, and about treatments that have the support of the scientific record.

Baxter's Response: Baxter agrees that providing forums for discussion of various clinical approaches is desirable. It is not clear, however, that the creation of yet another governmental or quasi-governmental body is the appropriate method for facilitating such discussions. Baxter assumes that this role can be played by the Blood Safety Director, the CDC, the Blood Advisory Council, the PHS, the FDA, or another existing agency.

Further Discussion: In addition to government agencies, a number of organizations, including professional societies, already provide forums for exchange of research and views. Seminars and professional journals, for example, are common sources of information that treaters may draw upon in determining their courses of treatment.

Although Baxter sees tremendous value in development and dissemination of various clinical approaches, it has some concern that the IOM Committee's apparent call for development of "official" treatment modalities might, if implemented, stifle rather than foster innovation in treatment options related to blood and plasma-based therapies.

Recommendation 14: Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgment, and otherwise act so as to earn the confidence of the public and patients.

Baxter's Response: Baxter categorically rejects the IOM Committee's notion that humanitarian contributions by Baxter and others to aid the welfare of the hemophilia community somehow taint the recipients.

The assumption underlying the IOM Committee's recommendation is that voluntary organizations somehow become tarnished with "conflicts of interest" when they accept humanitarian donations from organizations and individuals that have an interest in the good works performed by these voluntary groups. This prejudice ignores the plain fact that most nonprofit organizations rely upon nongovernmental donations in order to reach the level of funding needed to provide services to their constituents. These contributions are neither secret nor nefarious.

The IOM Committee's assertion that the NHF was unduly influenced by the fractionation industry through financial support is groundless, and it is insulting to dedicated members of the NHF. These NHF members struggled—together with government, doctors, and industry—to understand the great uncertainty of AIDS in the early 1980s.

Baxter has in the past contributed, and in the future will continue to contribute, to a whole panoply of organizations. In particular, Baxter is proud of its financial contributions to the hemophilia community, and intends to continue making such contributions.

QUESTION 2

Question: Does your company currently import, or has your company ever imported, any plasma, albumin, blood or blood products from any country other than the United States for use in the manufacture of products sold in the United States? Please provide type of product, country of origin, and source.

Baxter's Response: Since the latter 1970s, Baxter has utilized only U.S.-sourced plasma in the plasma-based therapies it sells in the United States.

QUESTION 3

Question: Does your company utilize, or has your company ever utilized, any plasma, albumin, blood, or blood products from prisoners or prison inmates in this country or any other country? Is so, please provide all available details such as dates, countries, and prison names.

Baxter's Response: Baxter ceased utilizing plasma from incarcerated persons in 1983. Prior to that time, Baxter purchased plasma from a small number of plasma centers that collected plasma from incarcerated persons in Louisiana, Florida, and Tennessee. Once FDA licensing began, all such centers utilized by Baxter were FDA-licensed.

ARMOUR PHARMACEUTICAL COMPANY RESPONSE TO THE HOUSE GOVERNMENT REFORM AND OVERSIGHT SUBCOMMITTEE ON HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS

In response to a request by the House Government Reform and Oversight Subcommittee on Human Resources and Intergovernmental Relations, following is Armour's position on each of the 14 recommendations contained in the Institute of Medicine's (IoM) report entitled HIV and the Blood Supply: an Analysis of Crisis Decisionmaking. Please note that Armour concurs with the qualifications about the IoM report that were set forth in the statement submitted to the Subcommittee by the American Blood Resources Association (ABRA) on November 2, 1995. Specifically:

IOM REPORT QUALIFICATIONS

• Throughout its report, the IoM refers to "industry" without distinguishing blood-banking organizations, which collect blood for transfusions, from the ABRA membership, which collects plasma and processes plasma-based therapies used for the treatment and diagnosis of the many conditions previously mentioned [see ABRA statement]. The IoM Committee's confusion of these groups' identities has resulted in inaccuracies in the report.

• The recommendations are largely a restatement of desirable activities, responsibilities, and objectives traditionally vested in and pursued by the HHS agencies. Implementation of these activities, responsibilities, and objectives under the mechanisms proposed by the IoM recommendations could not have prevented the spread of HIV through blood and plasma-based therapeutics. The essential truth is that it was a lack of information, not the lack of a mechanism by which to process information, which was the central impediment faced by decisionmakers confronting the AIDS mystery in the early 1980's.

• The practical value of any recommendation will depend on the details of its implementation.

RESPONSE TO IOM RECOMMENDATIONS

IoM #1: The Secretary of Health and Human Services should designate a Blood Safety Director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.

Response: Armour supports this recommendation. We further recommend that the Blood Safety Director be charged with responsibility for:

• advocating the development of global regulatory guidelines;
• ensuring that guidance is provided to Industry in the appropriate use and control of emerging new sciences and technologies; and
• promoting international harmonization of regulatory and scientific opinion.

IoM #2: The Public Health Service (PHS) should establish a Blood Safety Council to assess current and potential future threats to the blood supply, to propose strategies for overcoming these threats, to evaluate the response of the PHS to these proposals, and to monitor the implementation of these strategies. The Council should report to the Blood Safety Director (see IoM #1). The Council should also serve to alert scientists about the needs and opportunities for research to maximize the safety of blood and blood products. The Blood Safety Council should take the lead to ensure the education of public health strategies for dealing with these threats.

Response: Armour supports efforts to enhance and expand coordination between all stakeholders responsible for the continued safety of the blood supply and therapies that are derived from blood components. Armour urges that it be made a priority of the federal government to bring together the world's experts on potential emerging infectious agents calling upon them to formulate unified opinions so that fractionators will have clear guidance on the direction that must be taken to effectively respond to future threats. The Blood Safety Council could certainly play a critical role in this regard.

IoM #3: The federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products.

Response: Until such time as specific information regarding the structure of such a system is presented, Armour can neither support nor oppose this recommendation. The Company, however, will provide a more definitive response to a fully developed policy proposal that specifies how a "no-fault compensation system" would be structured. Armour has four fundamental questions regarding such a system. The answers to these questions would, in large measure, determine Armour's reaction to a specific proposal:

1. Would the system adversely affect the supply of blood component therapies available to physicians and their patients?
2. Would the system adversely affect the cost of blood component therapies to the people who need them to survive?
3. Would the system limit the availability of funds for research and development of new and improved therapies?
4. How would the system define eligibility for compensation?

IoM #4: Other federal agencies must understand, support, and respond to the CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.

Response: Armour concurs with this observation.

IoM #5: The PHS should establish a surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products.

Response: Armour supports this recommendation. Such a system could prove effective in situations where adverse health effects have been linked to an identifiable causative agent whose presence can be detected in blood components. Armour notes that such a system would have had limited value in preventing the transmission of HIV in the early 1980's since HIV was not identified until 1984, and a test for the presence of HIV was not available until 1985.

IoM #6: Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

Response: Armour concurs with this observation. It is important to acknowledge, however, that there are risks inherent in blood and blood component therapies. While the goal of industry and government must always be to reduce risk, no credi-

ble authority would suggest that these inherent risks can be completely eliminated. Moreover, the dilemma often faced by government and industry officials trying to make the right decisions, is the absence of knowledge required to accurately quantify the risks attendant to partial solutions that may be available at the time.

IoM #7: The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

Response: Armour supports this recommendation and notes that periodic reviews have always been common practice within the government agencies charged with regulating the manufacture and distribution of blood component therapies.

IoM #8: Because regulators must rely heavily on the performance of the industry to accomplish blood safety goals, the FDA must articulate its requests or requirements in forms that are understandable and implementable by regulated entities. In particular, when issuing instructions to regulated entities, the FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.

Response: Armour supports this recommendation.

IoM #9: The FDA should ensure that the composition of the Blood Products Advisory Committee [BPAC] reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.

Response: Armour concurs with this recommendation and believes that the plasma fractionators' views are essential in developing rational policies. Armour also believes that the FDA must ensure that members of BPAC possess the scientific expertise and knowledge necessary for effective consideration of the many complex issues that must be addressed by the Committee. It should be noted that plasma fractionators have never had a voting position on BPAC.

IoM #10: The FDA should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.

Response: Armour concurs with this recommendation.

IoM #11: The PHS should develop reliable sources of the information that it needs to make decisions about the blood supply. The PHS should have its own capacity to analyze this information and to predict the effects of regulatory decisions.

Response: Armour supports this recommendation.

IoM #12: When faced with a decision in which the options all carry risk, especially if the amount of risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.

Response: Armour concurs with this observation.

IoM #13: The Department of Health and Human Services should convene a standing expert panel to inform the providers of care and the public about the risks associated with blood and blood products, about alternatives to using them, and about treatments that have the support of the scientific method.

Response: Armour supports this recommendation. However, Armour urges that the panel inform care providers and the public about not only the risks associated with blood and blood component therapies, but also the benefits attendant to these therapeutics. Effective and sound decision making requires a risk versus benefit comparison. Healthcare providers and the public must be informed of both the risks and benefits to make sound judgments about the use of blood and blood component therapies.

IoM #14: Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgment, and otherwise act so as to earn the confidence of the public and patients.

Response: Armour agrees with the principle expressed in this recommendation. However, Armour wishes to note that it, and other fractionators, have contributed funds to voluntary organizations in the past for humanitarian and educational purposes. If this recommendation is interpreted to mean that humanitarian and educational contributions to voluntary organizations represent a conflict of interest, then Armour would vigorously oppose, and categorically reject it.

RESPONSE TO QUESTIONS

The Subcommittee Chairman, Congressman Christopher Shays, posed to Armour the following two questions unrelated to the IoM report. Following is Armour's response to these questions:

Question 1: Does your company currently import, or has your company ever imported, any plasma, albumin, blood or blood products from any country other than the United States for use in the manufacture of any products sold in the United States? Please provide type of product, country of origin, and source.

Answer: Armour plasma therapies currently sold in the United States are processed using only source material collected in the United States. Therefore, Armour does not currently import into the United States any plasma, albumin, blood or blood components for use in the processing of any plasma therapies sold in the United States. The plasma used by Armour in the processing of its therapeutics sold in the United States has been collected predominantly by Armour's wholly owned collection affiliate, located in the United States, primarily in the mid-western states.

Information available to Armour at this time indicates that the company obtained limited shipments of plasma from collection centers located in the following countries in the indicated years: Belize (1973), Colombia (1972 and 1973), Haiti (1972), Mexico (1973 and 1974), Nicaragua (1973), and although not documented, the Dominican Republic. Armour did not receive any foreign plasma after early 1974, and by 1975, as a matter of corporate policy, Armour moved to obtain its plasma from Armour-controlled collection centers in the United States.

Question 2: Does your company utilize, or has your company ever utilized, any plasma, albumin, blood, or blood components from prisoners or prison inmates in this country or any other country? If so, please provide all available details such as dates countries and prison names.

Answer: No, Armour has never used plasma, albumin, blood, or blood components from prisoners or prison inmates in this or any other country. The material used in the processing of Armour plasma therapies sold in the United States has predominantly been collected by collection centers operated by Armour's affiliate, Plasma Alliance. Our plasma collection facilities are subject to the most stringent quality control and safety standards in the industry and together form the largest wholly owned commercial collection system in the world.

---

26 December 1995

The Honorable Christopher Shays, Chairman
Sub-Committee on Human Resources and
InterGovermental Relations
United States House of Representatives
2157 Rayburn House Office Building, Room B–372
Washington, DC 20515–6143

DEAR CHAIRMAN SHAYS:

The following is in response to your December 18, 1995 letter to Dr. Gene Tutwiler of Alpha Therapeutic Corporation. Our response is in accordance with the outline of your questions that were contained therein:

1. As you requested, you will find attached hereto, Alpha Therapeutic Corporation's response to the 14 recommendations made in the Intitute of Medicine's Report titled "HIV and the Blood Supply": An Analysis of Crisis Decisionmaking".

2. Your second question asks whether or not Alpha Therapeutic Corporation has ever imported, any plasma, albumin, blood or blood products from any country other than the U.S. for use in the manufacture of any products sold in the U.S. You further ask that Alpha provide the type of product, country of origin, and source. Our response to this question is that Alpha only acquired Plasma from outside the U.S. from a country called Belize. This plasma was acquired from an FDA-licensed center in Belize. This plasma was acquired prior to 1985. Further, it appears that this is the only source of plasma that was ever imported by Alpha.

3. The third question that has been directed to the company is whether or not Alpha has ever utilized, any plasma, albumin, blood or blood products from prisoners, prison inmates in this country or any other country. It is my understanding that Alpha has used prison-source plasma from prisons located in Louisiana. One prision that comes to mind is the Angola Prison located in Louisiana. It should be noted, however, that Alpha has never manufactured Factor VIII or Factor IX products (products used by hemophiliacs) from prison-source plasma. In addition, Alpha has never acquired any plasma, albumin, blood or other blood products from prisoners or prison inmates from sources outside the U.S. I would like to emphasize that I do not have the exact date that Alpha was acquiring plasma from prison centers in the U.S., but I believe that the company terminated this type of acquisition prior to 1985.

Should you have any questions or comments with respect to the above, please by all means contact me at 213 / 227–7605.

Very truly yours,

EDWARD A. COLTON
ALPHA THERAPEUTIC CORPORATION

ALPHA'S RESPONSE TO THE FOURTEEN RECOMMENDATIONS MADE IN THE INSTITUTE OF MEDICINE'S (IOM) REPORT

Alpha Therapeutic Corporation ("Alpha") has reviewed and carefully considered the Institute of Medicine's (IoM) Report titled: "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking." In his testimony and written statement provided to the Subcommittee on Human Resources and Intergovernmental Relations of the House Committee on Governmental Reform and Oversight, Dr. Gene Tutwiler of Alpha reaffirmed this company's support for many of the Recommendations contained in the IoM Report. On behalf of Alpha, Dr. Tutwiler incorporated the Response to the IoM's Fourteen Recommendations provided to the Subcommittee by ABRA, the national trade association which represents Alpha and the other plasma collectors and fractionators, into both his statement and testimony. At the request of the Subcommittee, Alpha is providing its own response to the IoM's Recommendations.

While the IoM's Recommendations are worthy of thoughtful consideration, Alpha has grave concerns about the accuracy of the "facts" and "conclusions" contained in the Report. First, unlike the fractionators and plasma collectors, the IoM had the benefit of making its decisions after all the relevant facts were known. Despite the IoM's recognition of that fact, it is not humanly possible when undertaking a retrospective review of the decisions made in the early days of the AIDS crisis to reach conclusions uncolored by the knowledge we have since gained about the natural history of AIDS and how it is transmitted. In several instances, it appears that the IoM's conclusions were not based on the state of the record at the time, but instead on the certainty that only hindsight can bestow.

With regard to the IoM Committee's fact-finding itself, some of the facts set forth in the IoM Report are inaccurate. It also appears that the IoM misinterpreted or simply did not consider evidence at its disposal that did not support its conclusions. For those reasons, Alpha cannot and does not endorse certain factual findings and conclusions that the IoM reached.

Regardless of the merits of those portions of the Report that Alpha cannot endorse, the IoM's goal of assuring the future safety of the blood and plasma derivatives supply is a vital one, and the Recommendations deserve evaluation for their own merit. Alpha's response to the Fourteen Recommendations follows.

Recommendation 1: The Secretary of Health and Human Services should designate a Blood Safety Director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.

and

Recommendation 2: The Public Health Service (PHS) should establish a Blood Safety Council to assess current and potential future threats to the blood supply, to propose strategies for overcoming these threats, to evaluate the response of the PHS to these proposals, and to monitor the implementation of these strategies. The Council should report to the Blood Safety Director (see Recommendation 1). The Council should also serve to alert scientists about the needs and opportunities for research to maximize the safety of blood and blood products. The Blood Safety Council should take the lead to ensure the education of public health officials, clinicians, and the public about the nature of threats to our nation's blood supply and the public health strategies for dealing with these threats.

Response to Recommendations 1 and 2: An issue as important as blood and blood product safety clearly requires coordination among all affected governmental agencies. Secretary Shalala has designated Dr. Philip Lee as Blood Safety Director, and Alpha is committed to working with Dr. Lee and the Blood Safety Council. Alpha remains concerned, however, that the Blood Safety Council be used to expedite, and not to delay, the important decisionmaking functions of the agencies responsible for the regulation of blood safety.

Recommendation 3: The Federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products.

Response to Recommendation 3: Alpha is unable to take a position with respect to this Recommendation because not enough information is provided, especially with respect to funding, to allow evaluation of the Recommendation.

Recommendation 4: Other federal agencies must understand, support, and respond to the CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.

Response to Recommendation 4: Alpha continues to support the CDC's role as described in this Recommendation, and also supports the ongoing efforts of the affected governmental agencies to provide coordinated responses to threats to the

blood supply, as was done with respect to AIDS to the extent knowledge at the time permitted.

Recommendation 5: The PHS should establish a surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products.

Response to Recommendation 5: Alpha endorses the maintenance of a surveillance system for consumers of blood and blood products, either within the CDC or on a cooperative basis between CDC and other governmental agencies. Alpha believes that the facts prove that such a surveillance system could not have prevented the spread of AIDS through recipients of blood and blood products in the early 1980s. Retrospective studies have established that the unknown causative agent of AIDS was in the blood supply long before the first cases of an immune deficiency syndrome were identified in male homosexuals in 1981. In addition, the lack of certainty about AIDS and its cause persisted until the spring of 1984. In fact, the Director of the CDC's Division of Host Diseases sent a series of letters to hemophilia treaters in the winter of 1984, stating that it was not then known whether AIDS was transmitted by a virus, and even if it was, it was not then known whether the disease could be transmitted through factor concentrates.

Recommendation 6: Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

Response to Recommendation 6: Alpha has always supported the use of incremental steps to decrease risk in its therapies when a complete solution has not been identified. For example, Alpha adopted direct questioning of plasma donors and encouraged self-deferral of donors in groups believed to be at increased risk for AIDS in late 1982, before such screening methods were mandated by the FDA. However, many of the "interim steps" proposed by the IoM would not have prevented the transmission of HIV through blood products, the benefit of those "interim steps"—if any—was far from clear, and in some instances, implementation of those steps might well have increased risks for users of other plasma derivatives.

Recommendation 7: The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

Response to Recommendation 7: Alpha endorses this practice, which it believes has been and is currently part of FDA procedure for plasma derivatives.

Recommendation 8: Because regulators must rely heavily on the performance of the industry to accomplish blood safety goals, the FDA must articulate its requests or requirements in forms that are understandable and implementable by regulated entities. In particular, when issuing instructions to regulated entities, the FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.

Response to Recommendation 8: Alpha believes that it is important for processors of plasma derivatives to have clear guidance from the agencies that regulate those products. While it is important that those agencies have the flexibility to respond appropriately in emergency situations, regulatory agencies should distinguish between general guidance and regulatory mandates.

Recommendation 9: The FDA should ensure that the composition of the Blood Products Advisory Committee reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.

Response to Recommendation 9: The goals of assuring the independence of BPAC membership, and of broad-based representation among BPAC membership, are commendable. At the same time, the essential function that BPAC provides to FDA is to assure that the agency has the necessary scientific and technical expertise to support its decisions. Those individuals who have the scientific expertise, skill and knowledge desirable when making decisions about plasma products are often connected with the blood products industry. Their elimination from BPAC would deprive the FDA of precisely the expertise required for meaningful decisionmaking. Alpha believes that open disclosure of the interests of BPAC members will assure that the decisionmaking process remains both scientifically based and unbiased.

It is important to reiterate that the plasma industry has never had a voting member on BPAC.

Recommendation 10: The FDA should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.

Response to Recommendation 10: Alpha supports this Recommendation and believes that this is a long-standing process between FDA and its advisory committees.

Recommendation 11: The PHS should develop reliable sources of the information that it needs to make decisions about the blood supply. The PHS should have its own capacity to analyze this information and to predict the effects of regulatory decisions.

Response to Recommendation 11: Alpha believes it is essential that decisions about the blood supply and plasma derivatives be based on reliable sources of information, as recommended by the IoM. At the same time, it is important to remember that reliable information about emerging situations is not always available, as was the case with AIDS. The Department of Health and Human Services' adoption of the Blood Safety Council and appointment of a Blood Safety Director should assist in effective governmental decisionmaking in those circumstances where reliable sources of information do exist.

Recommendation 12: When faced with a decision in which the options all carry risk, especially if the amount of risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.

Response to Recommendation 12: Alpha acknowledges the primary role physicians fill in providing their patients with information regarding the risks and benefits of any course of treatment, to the extent those risks and benefits are understood at the time.

Recommendation 13: The Department of Health and Human Services should convene a standing expert panel to inform the providers of care and the public about the risks associated with blood and blood products, about alternatives to using them, and about treatments that have the support of the scientific record.

Response to Recommendation 13: Alpha agrees that it is important to encourage discussion of various clinical approaches, and to permit the broadest possible dissemination of this information.

Recommendation 14: Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgment, and otherwise act so as to earn the confidence of the public and patients.

Response to Recommendation 14: Alpha has historically provided support to voluntary organizations that have requested funding for specific projects. For example, Alpha funded a project for the preparation of a list of hemophilia treaters throughout the US. This list provided easy reference to medical care, via hemophilia treaters, for hemophiliacs who chose to travel. The IoM's implication that funding projects such as this undermines the independence of voluntary organizations is untrue and offensive.

Mr. SHAYS. I would like to call this hearing to order and to welcome our final panel. I'm sorry to have held you up, Mark Philip from Immuno-U.S., Inc., and you're accompanied by Thomas Waytes. As is our custom, as you may know, we swear you in, and if you would both rise and raise your right hand.

[Witness sworn.]

Mr. SHAYS. I would just point out that you are part of the industry that we had before, but I made a decision that, given that you weren't in the market during the 1980's that was examined by the IOM, that we would have you come separately. There may be some other times that we would have you all collectively, but for this first hearing, we just decided to make that distinction.

I'm now very happy, Dr. Philip, to have you give your testimony, and then I'll have a few questions for you.

STATEMENT OF MARK A. PHILIP, CHIEF EXECUTIVE OFFICER, IMMUNO-U.S., INC.

Mr. PHILIP. Thank you, Mr. Chairman, members of the subcommittee. My name is Mark Philip. I have Dr. Thomas Waytes sitting next to me. He is the vice president of medical affairs for Immuno-U.S. and the medical director for our subsidiary, Community Bio-Resources, the plasma procurement company. Dr. Waytes, as I did, joined the company some 3 years ago. He joined from National Institutes of Health.

I am pleased to appear before you today to share with you some of the processes that we employ to help ensure the safety of our plasma derivatives. As indicated in our written testimony, we have never marketed a Factor VIII derivative in the U.S. and only began marketing a Factor IX derivative in 1993.

We distribute four products in the United States—FEIBA–VH for severe hemophiliacs that have developed antibodies to Factor VIII or IX; Bebulin-VH, a Factor IX product; IVEEGAM, which is the only licensed product for the treatment of a rare children's disorder known as Kawasaki's disease; and albumin, for the treatment of burns and shock.

All of our products are plasma derivatives and, therefore, the safety of our plasma supply is of paramount importance to us and our customers. At the heart of our safety program is the process that we refer to as the Immuno Quality System. This is shown on the flow charts that we've brought into the committee room, and I hope you can see it from where you are.

This system begins with careful screening and selection of plasma donors. Through our subsidiary, Community Bio-Resources, we operate 16 stale-of-the-art plasmapheresis centers.

Donors at these centers are rigorously screened, using a series of questions about possible high-risk behavior and past medical history, as well as receiving a comprehensive physical examination. Every unit of plasma from each donor undergoes a battery of tests, including those for the presence of HIV, Hepatitis viruses, and for elevation of ALT, a nonspecific test for liver function.

We realize that the safest units of plasma come from committed donors who return to the centers on a regular, frequent basis. We do everything we can to make the centers a pleasant and supportive environment, including the provision of child care in our newest centers. We have opened six new centers over the last few years, and several more are planned. Each new center that we construct requires a capital investment of approximately $1.6 million.

As a result of these initiatives, over the past 5 years we have seen an 88 percent decrease in viral marker rates for HIV among our donor population, with similar rate reductions for Hepatitis B and C. Obviously, anyone testing positively is permanently rejected and their plasma is destroyed.

However, as the subcommittee well knows, there is a "window period" during which a donor could be harboring a virus that could not be detected. This is particularly so with HIV.

In order to deal with this window period, we instituted in 1992, an inventory hold program of 2 months, later extended to 3 months, in which we store units of plasma which have been screened and found safe and usable for production according to FDA guidelines. If at any time a donor is found to be reactive to viral screening or surrogate tests, the plasma units held in inventory are destroyed.

Our data show that as a result of our 3-month inventory hold, we removed and destroyed 8 times more potentially risky plasma from these individuals than would have been removed without the benefit of this program. Because of the inventory hold program, we remove and destroy almost 1 percent of the plasma we collect which otherwise would be acceptable by FDA standards.

To further increase the margin of safety, we introduced in 1994, a first-time donor applicant rejection system. The basis of this approach is the well-known fact that first-time donor applicants present the greatest risk to the plasma and blood supply. Approximately 96 percent of all the plasma we receive are donated by repeat donors.

Mr. SHAYS. What was that number again?

Mr. PHILIP. 96 percent, and only 4 percent are from donor applicants. Of all the units of plasma that test positive for HIV or Hepatitis B or C, 95 percent come from these donor applicants. Under this policy, we destroy all plasma from donor applicants who do not return to make a second donation within 3 months and undergo the tests that we carry out repeated.

Mr. SHAYS. Say that again. I'm sorry. Since there's one witness, I feel a little more comfortable, and one person up here. What did you just say? You said that if they come back, you don't use their first donation until they've come back for a second visit?

Mr. PHILIP. Until they've come back for a second visit and been tested.

Mr. SHAYS. Are these voluntary donors?

Mr. PHILIP. No, these are paid donors.

Mr. SHAYS. So, basically, you use a paid system?

Mr. PHILIP. Yes.

Mr. SHAYS. OK.

Mr. PHILIP. Before we utilize the donated plasma in the manufacturing process, we carry out another test. Each plasma pool, prior to manufacture, is tested for virus genomes of HIV and Hepatitis B and C, using a polymerase chain reaction, or PCR test, developed in our laboratory. As you may know, PCR is a technique that allows for billion fold amplification of viral genomes that might otherwise be undetectable.

We use a system called laser-induced fluorescence PCR that incorporates a variety of internal and external controls that allows reliable detection of genome fragments of HIV and Hepatitis B and C. Our methods enable us to perform such testing on an industrial scale. Plasma that has passed the PCR testing is then fractionated.

During this process, we employ several viral removal and inactivation techniques that have been validated to be highly effective against various enveloped and non-enveloped viruses. Our proprietary vapor heating process, which has been effectively used for more than a decade, has resulted in a record of no confirmed transmission of HIV or Hepatitis B or C in Immuno's virally inactivated therapeutic products.

Finally, all batches of product are again subjected to PCR testing for HIV and Hepatitis B and C, with the commitment to destroy any positive batches before product is released. As of December 1994, all Immuno products sold worldwide have been PCR-tested before their release.

In our view, the Immuno Quality System has further increased the safety margin of our products. We have indicated our willingness to share our PCR technology with FDA and will entertain licensing discussions with other companies, should they be interested.

Many of the measures that I have described and that are set forth in this chart detailing the Immuno Quality System go well beyond the regulatory requirements of FDA. We are continuing research and evaluation of additional techniques that may further increase our safety margin. At Immuno, we have a deeply held commitment to the safety of our plasma derivatives. This is a philosophy that is ingrained throughout the company.

I would like to conclude by making a few remarks about the cost of measures like those adopted by Immuno. Steps that result in risk reduction are not cost free. As a result of the Immuno Quality System, our plasma derivatives cost a lot more to produce than they used to.

As this committee and other policymakers urge the adoption of policies that increase the margin of safety for these products, it is important to accept that cost may also increase. Society must be willing to bear this additional burden if it is to be assured of a safe and reliable high quality supply of plasma products in the future.

Thank you for your attention, and I would welcome any questions.

[The prepared statement of Mr. Philip follows:]

PREPARED STATEMENT OF MARK A. PHILIP, CHIEF EXECUTIVE OFFICER, IMMUNO-U.S., INC.

I am Dr. Mark Philip, Chief Executive Officer of Immuno-U.S., Inc. I would like to thank the Committee for the opportunity to testify today about steps that can be taken to help ensure the safety of the U.S. blood supply and plasma-derived therapeutic products marketed in the U.S. I will confine my remarks to (1) the Immuno Quality System, the process that Immuno has already implemented to guarantee the safest possible plasma derivatives for U.S. consumers, (2) Immuno's ongoing efforts to further improve the safety of its products, and (3) the company's active research program in the area of coagulant products, vaccines and immunoglobulins.

I am accompanied by Dr. Thomas Waytes, Vice President of Medical Affairs of Immuno-U.S. and Medical Director of Community Bio-Resources, Inc., the subsidiary of Immuno-U.S. which collects source plasma. Dr. Waytes has been at Immuno-U.S. since 1992. Before that he was with the National Institutes of Health (NIH), where he was a member of the Senior Medical Staff at the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Waytes also holds a position as Clinical Assistant Professor at Wayne State University School of Medicine in Detroit.

IMMUNO-U.S.—A RESEARCH-BASED COMPANY

Immuno-U.S. is a research-oriented, big-pharmaceutical company that develops, manufactures and distributes therapeutic biologic products used in the fight against rare and difficult-to-treat diseases such as hemophilia and immune disorders. We are a subsidiary of Zurich-based Immuno International, which is a global big-pharmaceutical company with operations in 18 countries. Immuno International is a worldwide leader in infectious disease research, the development of vaccines, and the manufacture of plasma-derived human therapeutic products.

Through our subsidiary, Community Bio-Resources, we operate 16 state-of-the-art plasmapheresis centers. Community Bio-Resources employs about 450 people. We are engaged in an aggressive plan to upgrade and expand our plasmapheresis centers. We have opened six new centers in the last few years and plan to open five to six more new centers in the next few years. Community Bio-Resources is a critical part of our effort to provide safe plasma deriatives, as will be evident when we describe in greater detail the Immuno Quality System.

Immuno-U.S. currently distributes four products in the United States: FEIBA-VH, which is used by severe hemophiliacs who have developed inhibitors to Factor VIII; Bebulin-VH, a Factor IX product; IVEEGAM™, the only intravenous immune globulin product licensed to treat children with Kawasaki Disease; and albumin, which reduces the effects of fluid loss in patients suffering from burns and shock.

Immuno-U.S. has never marketed in the United States a Factor VIII product—the antihemophilic factor used by 80 percent of hemophiliacs—and our virally inac-

tivated Factor IX concentrate was not introduced in the United States until 1993. At present, Immuno remains a relatively small player in the U.S., where our market share in plasma products is less than 1 percent.

We are, however, a growing company. Headquartered in Rochester, Michigan, we began operations in 1981 with four employees and we now employ about 150 people. We are in the middle of the first phase of an extensive capital investment plan that includes a $30 million expansion of our fractionation facilities in Rochester.

IMMUNO RESEARCH PROGRAM

Immuno has pioneered a number of viral inactivation technologies, including a two-step vapor heating process that has been proven in the laboratory to effectively destroy a wide range of viruses and has stood the test of time in clinical situations. Immuno has not seen any confirmed transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) in its virally inactivated therapeutic products.

The Immuno Group has developed several genetically engineered candidate AIDS vaccines and is working in collaboration with the National Institutes of Health (NIH) to test the recombinant gp 160 vaccines in clinical trials in humans. Currently in Phase II evaluation, the vaccines are being studied for both preventive and therapeutic benefit.

In 1988 Immuno and NIH established a Cooperative Research and Development Agreement (CRADA) to help accelerate and coordinate this very important research. If we are successful in developing an effective AIDS vaccine, we plan to build a state-of-the-art manufacturing facility for the vaccine in the United States.

Additionally, we are exploring the use of recombinant technology in the development of improved therapeutic agents, including coagulant replacement therapy. Other research projects of Immuno include surgical tissue sealants, specialty diagnostics, immune globulins and coagulant inhibitor therapies. We are particularly excited about the prospects of U.S. approval for our fibrin sealant, which is used to reduce blood loss during surgery or trauma. Our fibrin sealant has been used extensively in Europe for more than 15 years with excellent results and is also available in Canada. This application is currently pending regulatory review at the Food and Drug Administration (FDA).

IMMUNO QUALITY SYSTEM

Immuno has implemented a number of initiatives to obtain comprehensive quality and safety improvements at every stage of our process, from collection of source material to manufacture to viral inactivation and final product release. Immuno is committed to the highest level of safety and quality in its plasma-derived therapeutic products. The Institute of Medicine (IOM) report serves to focus the attention of this Committee and of industry on the safety of plasma products.

The safety measures that I will discuss with you today were already in place prior to release of the IOM report. Moreover, much of our program goes well beyond the IOM recommendations in fostering safety. In fact, we are proud that the Immuno Quality System meets or exceeds FDA's quality control requirements for plasma-based deriatives. Nevertheless, we will not rest on our laurels with respect to safety nor wait for government regulation, but instead will continue to refine our processes and procedures to improve further the safety of our products.

As noted above, since the institution of viral inactivation processes pioneered by Immuno, we have seen no confirmed case of transmission of HIV, HBV or HCV in our plasma deriatives. We have great confidence in the viral inactivation processes that we are currently using and the protection that they afford consumers. However, Immuno believes that we must look forward and try to develop measures that will anticipate other threats to plasma deriatives and those who depend on them. Therefore, the company has developed a stringent quality control program in addition to its viral inactivation procedures.

I would like to describe the Immuno Quality System in some detail. The system has several parts: selection of high quality donors with low viral marker rates; a three-month inventory hold program; a first-time donor applicant rejection program; polymerase chain reaction (PCR) testing of all plasma pools prior to fractionation; effective viral removal and inactivation; and PCR testing of batches of product prior to release for distribution. A flow chart describing the Immuno Quality System is attached to this statement.

A. Donor Selection and Screening

The plasmapheresis centers operated by Community Bio-Resources and other contractors follow stringent donor selection and screening procedures, with a goal of se-

curing healthy plasma donors who are free from infection and willing to become repeat donors. Screening of donors is an essential means of increasing the margin of safety for our products.

We rigorously screen our donors by asking a series of questions concerning possible high risk behavior and past medical history and by providing a comprehensive physical exam. Every unit of plasma from each donor undergoes a battery of tests, including those for the presence of HIV and hepatitis viruses and for elevations in ALT, a non-specific test for hepatitis and other infectious agents.

We realize that the safest units of plasma come from committed donors who return to the centers on a regular, frequent basis—people we know are healthy. We try to encourage this by continually educating and reminding donors of the important role that their plasma donations play in improving the lives of those patients who depend on them and by staffing our centers with professional, courteous and competent individuals. In order to facilitate donations, in our newer facilities we offer child care for parents who require it during the plasmapheresis process.

Because we want to encourage repeat donations, it is important that our centers be a pleasant and supportive environment in which to donate plasma. Our new centers are being constructed at a cost of approximately $1.5 million each; we believe the investment in these facilities is critical to securing a solid core of repeat donors. We make every effort to minimize any discomfort associated with plasma donation. Finally, we appeal to donors' sense of altruism. While we do in fact pay donors a modest fee for their time and trouble, an important motive in the decision to participate in plasma donation is the sincere desire to help those in need.

The impact of these efforts is clearly shown if we examine the viral reactive rates over the past five years. We have seen an 88% decrease in the donor population's viral market positivity for HIV, and similar decreases have been seen for HBV and HCV. Anyone with a positive result is permanently rejected as a donor, and any plasma collected from this person is destroyed.

We fully recognize that no matter now thoroughly one screens a plasma donor and tests the plasma, the possibility exists that a unit of plasma may still be obtained from a donor who is infectious but is nevertheless not detected in a serological test. This is referred to as the "window period." It is possible for an individual today to contract HIV but their infection will not be detectable by today's tests until 20 days later. Accordingly, there is a "window" when they may be infected but not detectable.

B. Inventory Hold Program

In order to reduce the chance of such a unit entering our plasma pools, we have instituted an inventory hold program, which was first implemented in 1992. In this program, we collect all units of plasma which have been screened to be safe and usable for production according to FDA guidelines and hold them for a period which is currently not less than three months. If at any time one of our donors is found to be reactive to viral screening or surrogate tests, we then have the ability to identify all plasma units previously obtained from this donor during the inventory hold period and remove them for destruction.

Our analysis reveals that, as a result of our three-month inventory hold, we removed and destroyed eight times more potentially risky plasma from these individuals than would have been removed without benefit of this program.

We have found that 97% of the plasma units collected by Community Bio-Resources for Immuno are followed by at least one additional donation by the same donor and thus have the benefit of this inventory hold follow-up. As a result of this program, we remove and destroy almost 1 percent of the plasma that we collect which otherwise would be acceptable for use by FDA standards. Almost half of the plasma units that we remove are from donors who are subsequently rejected because of an increase in ALT, and less than two percent are from donors who are subsequently found to be confirmed positive for HIV, HBV or HCV.

C. First-Time Donor Rejection System

Under our first-time donor rejection program introduced in 1994, we also destroy all plasma from donor applicants who do not return to make a second donation within three months. We decided to implement this policy because it is well known that first-time donors and donor applicants present the greatest risk to the plasma and blood supply. Approximately 96% of the plasma units we receive are donated by repeat donors, and only 4% are from donor applicants. Of all the units of plasma that test positive for HIV, HBV or HCV, 95% come from donor applicants and less than 5% from repeat donors. Any donor applicant who does not return to the center during this period is disqualified as a donor, and his or her plasma is removed and

destroyed. About 42% of the total units that we destroy are from non-returning donor applicants.

We cannot overemphasize the importance of rejecting our first-time donor applicants who do not return, or previous donations from donors who are rejected. Even though these plasma donations have passed all the necessary tests, we have decided to destroy this plasma because we believe that the risk is not warranted. This safety measure adds substantial cost to production of our final plasma products.

D. Laser Induced Fluorescence Polymerase Chain Reaction Test and Viral Removal and Inactivation

We have recently added an additional validation step to our system. To confirm that we have excluded HIV, HBV and HCV from the plasma we want to use, we now test each plasma pool using a specialized PCR system that was developed in our laboratory. PCR is a technique that allows for a billion-fold amplification of viral genomes which may otherwise exist at undetectable levels.

This system, called the Laser-Induced Fluorescence PCR, is unique in that it incorporates an array of internal and external controls that allow for the highly sensitive and specific detection of genome fragments from HIV, HBV and HCV, and allows the testing to be performed on an industrial scale. We have recently provided FDA with validation data concerning the performance of this test system. Plasma pools that are PCR reactive are destroyed.

The manufacturing of our plasma products incorporates the use of viral removal/inactivation techniques which have been validated to be highly effective against a variety of both enveloped and non-enveloped viruses. These techniques, including the vapor heating of our coagulation products and the immobilized hydrolase treatment of our intravenous immune globulin, IVEEGAM™, have been in use for decade.

All batches of product are again subjected to PCR testing for HIV, HBV and HCV, with the commitment that all positive batches will be destroyed. As of December 1994, all Immuno products sold worldwide have been PCR tested. Although to date there has been no transmission of HIV, HBV or HCV resulting from the use of our inactivated products, we believe these initiatives have improved the safety margin or our products.

In addition to the above measures, which surpass the regulatory requirements of any nation, Immuno also is aggressively developing and evaluating additional techniques that may further increase our ability to remove known and unknown viruses from products made from human plasma, as well as exploring applications of recombinant technology.

Research on Additional Safety Measures

Immuno supports an active research program to improve the safety of its products. We are investigating the use of global viral removal/inactivation processes such as (1) nanofiltration, (2) methods for removal of smaller non-enveloped viruses like parvovirus and (3) photodynamic destruction of genomic nucleic acids. We mention these activities, some of which are some distance from fruition, to give the Committee a sense of our long-term commitment to guaranteeing the safety of our products.

Balancing Risks and Costs

We will continue to engage in research and development and to manufacture our products with our first goal being safety and high quality. It is important, however, that Members of Congress and others involved in policymaking in this area recognize that industry cannot substantially improve its margins of safety for plasma products without incurring significant additional cost.

The measures I have described, which undeniably increase the margin of safety, also undeniably increase the final cost of the product. One of the issues that this Committee, consumers and others must confront is the inevitable burden that society must bear with incremental elimination of risk.

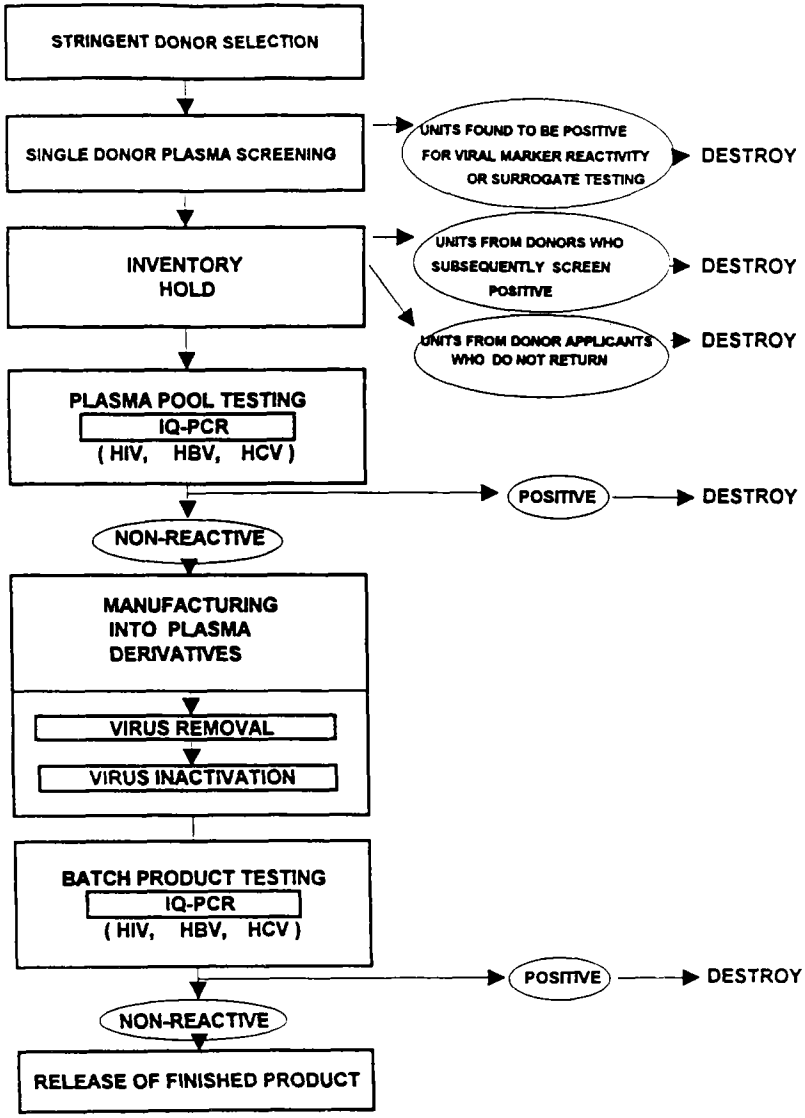
We want to be clear that we do not regard cost as a barrier to enhancing safety or a reason not to take such steps. However, once those costly steps are taken—as Immuno has done—manufacturers must be assured of a fair return on that investment, or, to put it differently, a fair price for their products that reflects the increased costs.

Making the safest possible products is not just a marketing strategy for Immuno, but a deeply held philosophy of the company, both in the United States and abroad, and we will continue to operate according to these principles. We are encouraged that this Committee is taking a serious look at blood and plasma safety and the barriers, cost and otherwise, to improving it.

As I have mentioned, we have spoken to FDA about these measures and offered them the technology for their evaluation. We are also willing to discuss licensing of these technologies to other companies.

We appreciate the opportunity to testify today and are looking forward to achieving our common goal of ensuring the safety of the blood supply, and in our case the plasma-derived therapeutics supply, in the United States.

IMMUNO QUALITY SYSTEM



Mr. SHAYS. What is unique about this process? Where along this process would you argue that you're unique or doing it differently?

Mr. PHILIP. I think the key steps are four in number. First of all, the commitment to develop plasma centers which are appealing for people to return to on a regular basis, which is a significant investment.

I think the second one is the use of a 3-month inventory hold, where the plasma is held in storage so that we can look at four donors who may seroconvert or become positive for one of the tests that we carry out, and if they do, that we can then remove all previous donations from the previous 3 months.

Mr. SHAYS. Run me through that process of a donor coming in 3 months ago. You've held his donation or her donation. They come in. What do you learn in the second visit that you didn't know in the first visit?

Mr. PHILIP. Well, for example, if someone was to seroconvert for HIV or for one of the Hepatitis viruses, and what we're able to do is take the plasma out of storage, which was stored, that they've previously donated. Even though that had tested negative, because we are concerned that the window period, which is the period when one may not be able to detect a virus with the current tests.

Mr. SHAYS. So it deals with the window period.

Mr. PHILIP. It deals with the window period. The third significant initiative is the first-time donor reject program we have where, as I said, we are very concerned about first-time donors. These are people we don't know.

We prefer, as other people do in the plasmapheresis industry, to have repeat donors, who, we know well. We know their health. We have a history of their health over, sometimes, a very long period, and those people we feel more trusting toward.

And, therefore, the first-time donor, who we don't know so well, we're not willing to risk a problem which may exist with that individual until we see them come back again and, hopefully, convert them into a repeat donor, as well.

Mr. SHAYS. When they come the second time, they could have contacted HIV between their first and second visit. Do you hold that second donation until their third visit?

Mr. PHILIP. This is also a concern for us, and this is why we instituted the PCR testing.

Mr. SHAYS. I want to make sure you answer my question first.

Mr. PHILIP. Yes, yes.

Mr. SHAYS. Yes or no?

Mr. PHILIP. No, we don't. We hold only the first-time donor for that period. If they've come back a second time, then it would be held in the 3-month hold, as usual. So if they came back again and were to seroconvert, we would find them.

Mr. SHAYS. But you would use it after 3 months, their second donation?

Mr. PHILIP. Yes, correct.

Dr. WAYTES. If I could add, when we've looked at the impact of the inventory hold, 96.6 percent of all plasma units that are donated and screened negative are followed up by at least one subsequent donation from that same donor. Thus over 96 percent of the

units in that inventory hold have the benefit of the subsequent donation to see if that unit might have been in the window period.

Mr. SHAYS. You're talking about even after the second visit?

Dr. WAYTES. Yes, of all units.

Mr. SHAYS. And you were saying, what is the fourth?

Mr. PHILIP. The fourth thing is the PCR test, because you can never be sure. Every time somebody comes in, essentially, they could have just previously seroconverted, so you can never be absolutely sure that you are totally free from that window period, and that's why the PCR test is used, which can detect extremely low levels of genome equivalents of virus particles.

And by doing that test on the pools of plasma prior to manufacture, we can be assured that we are not seeing any viral genomes entering that manufacturing process.

Mr. SHAYS. Percentage-wise, what do you discover in that fourth test?

Dr. WAYTES. If I could answer that question?

Mr. SHAYS. Sure.

Dr. WAYTES. When we first began to use this test to evaluate our plasma pools, our pools were about 1,500 liters at that stage. We found that about 5 percent of the pools were positive, primarily for HCV, not at all for HIV. We made the commitment to destroy those pools that were positive.

Mr. SHAYS. Destroy the entire pool?

Dr. WAYTES. Destroy the entire pool. What we have instituted since then is some pre-PCR screening, using smaller groups of plasma, we can eliminate those smaller pools before they're put into the large 1,500-liter pool. We see a reactive rate of about the same, that would have amounted to about 5 percent.

The thing is, now the final pools that we put together for PCR tests have all been nonreactive, because they've all been prescreened with PCR of the smaller pools.

Mr. SHAYS. Does one infected person—and what is your donor size in those pools, ultimately? Is that 11,000 or more?

Dr. WAYTES. Well, when you talk about a 1,500-liter pool, we're talking about, at maximum, 2,000 donations, because this is plasmapheresed plasma there may be two or three donations from the same donor in that pool. We're probably looking at a donor population in one of those pools of under 1,000.

Mr. SHAYS. Does one donor infect the whole batch?

Dr. WAYTES. Yes. One positive donor would, in fact, infect the whole batch. What you're asking, then, is would we be able to detect that?

Mr. SHAYS. No, no, I was going to drive somewhere else. That's where I'm confused about my questions to the previous panel, and I'm going to have to sort it out. It would strike me that a smaller pool would result in your having to destroy less.

Dr. WAYTES. Which is why we pre-PCR screen smaller pools.

Mr. SHAYS. Right, I understand why you do it.

Dr. WAYTES. Yes.

Mr. SHAYS. I was just trying to get a sense of how often a large pool becomes contaminated.

Dr. WAYTES. When we prescreen our smaller pools, we see no contamination of the larger pool. Before we started prescreening

smaller pools, we found about 5 percent of our 1,500-liter pools were positive.

Mr. SHAYS. And this is with the IQ–PCR test?

Dr. WAYTES. Yes.

Mr. SHAYS. Now, as far as you know, do any of your competitors do something similar, whether they call it this or not?

Dr. WAYTES. To our knowledge, we are the only ones that have incorporated PCR testing as part of product release criteria.

Mr. SHAYS. This final, last test?

Dr. WAYTES. The PCR testing.

Mr. SHAYS. Yeah. OK. I am going to invite—afterwards, I'm just going to invite any of the industry who is here, because I want to be fair to them, but I'm really trying to understand when an entire pool can be contaminated. From the testimony that you're giving me, I'm getting the sense that, had you not done this test, 5 percent of your batches would be—5 out of 100, 1 out of 20, would be contaminated.

Dr. WAYTES. I think it's important to note, as was stated earlier, that all the companies that make plasma derivatives use viral inactivation procedures that are very, very effective at removing the viruses.

Mr. SHAYS. But if you didn't do this test, you're saying that potentially 5 percent would be simply not usable.

Dr. WAYTES. No. What I'm saying is that without doing this test, 5 percent of our pools would have had at least some viral genomes present which, in all likelihood—in fact, we know—which would have been destroyed by the viral inactivation procedures that we use or the similar procedures that other companies all use.

Mr. SHAYS. I'm going to just use the word, "contamination." If part is contaminated, can you isolate that and just reclean your pool, or do you have to destroy your entire pool?

Dr. WAYTES. We've made a commitment, if the plasma pool is reactive in PCR, we will destroy that pool.

Mr. SHAYS. OK. I'm missing something here, then. I'm sorry. I'm really missing something. What I'm trying to understand is the significance of what you're telling me. I'm also trying to understand the economics of a large pool versus a small pool. I'm trying to understand, if a pool becomes contaminated, if you have to destroy the entire pool, or whether you have the scientific ability to cleanse it.

Dr. WAYTES. What you're asking, I believe, is do we and other companies have the ability to inactivate or destroy the viruses.

Mr. SHAYS. Right.

Dr. WAYTES. And the answer to that is yes.

Mr. SHAYS. But, that notwithstanding, you still destroy the pool?

Dr. WAYTES. We still destroy the pool.

Mr. SHAYS. OK.

Dr. WAYTES. It's just a matter of, even though we know that we have methods that have a billion fold reduction or inactivation of viruses, we still feel that this quality program offers an increase in the safety margin that we feel more comfortable with.

Mr. PHILIP. The key to the whole program is really to minimize the potential for virus going into the manufacturing process. As you've heard from the other manufacturers and ourselves, over the

last several years, the record has been very good in terms of ensuring safe materials. That's primarily because of the screening techniques used on donors and because of the viral inactivation capability that's used in manufacturing.

What some of these programs offer is an ability to reduce further the potential for virus getting into the manufacturing process and therefore increasing the safety margin or the kill capability of that manufacturing step.

Mr. SHAYS. Of these four tests, which is the one you think is the least likely to be used by others in the industry?

Mr. PHILIP. Least likely to be used?

Dr. WAYTES. I think they're all very valuable.

Mr. SHAYS. No, which ones are not being used by others? I'll ask them, as well. Let me just back up a second. My staff is going to kill me later for using this analogy, but one of the advantages you all have is that you're the new kids on the block who weren't there when, when we had some problems.

The analogy I'm going to use is, I got elected after 1974, and I saw what happened in Watergate, and I saw campaign finance, and I saw gift ban, and so on, and I haven't gone on golf trips when I could have—probably because I don't play—but tennis trips or whatever. But the bottom line is, if you got caught up in that, it's very difficult now to argue against it, even though their mindset says it should be.

The challenge that those in the industry have is candidly dealing with what they did without passing judgment that maybe it's bad, dealing with potential suits, et cetera, a whole host of not wanting to have memos that say, "Hey, I don't think this was a good idea," because some lawyer is going to find it, even if that memo is a meaningless memo.

That's the kind of mentality that I'm thinking. You don't have that problem. It's a great advantage. And I can say we can learn from potentially what you're doing. That's my mindset. Kill me later about the analogy. [Laughter.]

So, what I want to do is be clear as to what you think you do that is different than what others do, and, of the four you gave, which of the four do you think is unique to your company? All four? One of them?

Dr. WAYTES. I think basically the whole program is. This is not something that we just laid down and did.

Mr. SHAYS. You mean the critical mass of doing all four? They might do one or two, but they don't—or they don't do any of the four?

Dr. WAYTES. Well, I think in order to PCR your plasma pools, you have to have upstream more lower tech programs like the inventory hold and the rejection of nonreturning first-time donor applicants. You have to do everything you can to reduce the viral load of your initial plasma. Otherwise, what you would do is throw away so many of your plasma pools that you would go out of business. This is a program that evolved over a number of years.

Mr. SHAYS. But your argument is that it's based on safety. It's also based on sound economics.

Dr. WAYTES. We think it is.

Mr. SHAYS. Yes. I mean, that's the bottom line to it. Let me just go to one—if I were the Red Cross, I would be concerned that you're basically getting your entire supply from paid donors.

Dr. WAYTES. Yeah.

Mr. SHAYS. And first tell me, what is the financial incentive for someone? How are they compensated? What do they get?

Dr. WAYTES. I can tell you.

Mr. SHAYS. I like the bottom line, and then I like the story.

Dr. WAYTES. The bottom line is, now we pay between $15 and $20 for the time, the travel, and the effort for the donors to come in and donate plasma.

Mr. SHAYS. OK. You're not going to get rich on that, that's true.

Dr. WAYTES. No. In no way do we consider this payment for the plasma. I think everybody in this room would agree that the life-saving products that you can make from a unit of plasma are just priceless.

Mr. SHAYS. How often can someone donate?

Dr. WAYTES. A person in good health can donate up to twice a week.

Mr. SHAYS. Wow. Do you have some people who donate twice a week?

Dr. WAYTES. We do have some people that donate twice a week. We monitor them very carefully, like all of the other plasma procurers. We do hematocrits and total protein measurements on every visit to the center, and, on a regular basis, we do serum electrophoreses. Our patients have physical exams as they come in as donor applicants and, then, annually.

Mr. SHAYS. Let me just ask you, if it was logical for you to wait 3 months before you take or use their donation, and then until they come to their next visit, why wouldn't you do that for their second visit and their third and their fourth?

Dr. WAYTES. We do. Actually, the way the program works is we rely on committed repeating donors to continually come back to the center. So the first visit to the center, we want that donor to prove that he or she is wanting to come and join our program, as a committed, qualified donor, and we do this incredible battery of tests that you've heard about today.

Once that donor comes back, then we make the decision, "This donor's plasma is useable." If that donor doesn't make this commitment, we want nothing to do with the plasma that this donor had previously donated, and we destroy it. Every unit of plasma that we do collect that is negative for all the viral tests, we put in this inventory hold, and we hold for 3 months. 96 percent of those units are followed up by at least one other donation.

Mr. SHAYS. That's the part I don't understand. I'm sorry. What are the other percent that isn't? That's what I'm missing here. Why wouldn't it be 100 percent?

Dr. WAYTES. Because, at some point in time, someone might donate 5 times, 10 times, 15 times, and then decide to not participate in the program anymore. Those are the units that aren't followed up in the inventory hold. That is why, then, we go ahead and do the PCR testing of the plasma pool.

Mr. SHAYS. No, no, but why wouldn't the same logic apply? That's all I'm trying to say. Why wouldn't it be 100 percent?

Mr. PHILIP. It's more a question of the ability to record and track on an individual basis every single donor that would donate and every single unit that came in and maintained some sort of rolling check on that individual. We don't have the capability to do that.

Mr. SHAYS. Do you want to make any comment on any question that was asked by any of the Members here to the other panel? Is there any question you would have liked me to ask you?

Dr. WAYTES. Well, one question, I think, that we had started to get into just a minute ago was the idea of volunteer blood donors.

Mr. SHAYS. Right.

Dr. WAYTES. I would just like to say that the participation in a plasma program that would allow us to have the benefit of an inventory hold requires a committed, regular, repeat donor. I think that it would be impossible to expect somebody, without giving any reimbursement for time or effort, to come and participate to that degree.

Also, we follow our viral marker rates very, very carefully, and I can say that, of our units from our committed donors, the viral reactive rate is a fraction of what has been published for the volunteer industry. And so we don't see at all that we're compromising any quality whatsoever by making our products with our compensated donors.

Mr. SHAYS. I would like the Democratic staff director to ask a question.

Ms. PHELPS. Thank you, Mr. Chairman, for allowing me to ask some questions on behalf of the Democratic Members. At the risk of going over the same area again, I just need some clarity on your plasma pool. Your larger plasma pool, which has passed the prescreening, contains about 2,000 donors?

Dr. WAYTES. 2,000.

Ms. PHELPS. Individual donors?

Dr. WAYTES. It contains donations.

Ms. PHELPS. Individual donations?

Dr. WAYTES. Donations, yes.

Ms. PHELPS. So it's smaller in size than that which is used by the other manufacturers? Or are you saying that, because you have so many repeat donations, that it may be of the same size, but you use a lesser number of donors?

Dr. WAYTES. Depending on the products being made, these 1,500-liter pools may be processed into larger pools, depending on the product.

Ms. PHELPS. So, when you apply your manufacturing processes to derive your products, you're using about the equivalent size of a plasma pool that your industry competitors might use?

Dr. WAYTES. Yes, it's similar, probably not much different.

Ms. PHELPS. But the difference would be the number of donors who make contribution to that pool?

Dr. WAYTES. I think the question of the number of donors who contribute to a pool would apply throughout the industry, if one uses plasmapheresed source plasma versus recovered plasma from volunteer donations. The amount of plasma that you can obtain from plasmapheresis is about 3 times what is normally recovered from a unit of blood, because we return the cells to the donor.

Also, because donors do repeat on a regular basis, one particular lot, a shipment of plasma which is picked up at a plasma center, may contain two or three units on the average per donor. These units are then put into the same pool.

Ms. PHELPS. Thank you. Let me know if the questions I'm asking are getting into areas of propriety. What is your market share, as compared to your competitors?

Mr. PHILIP. Overall, we're less than 1 percent.

[NOTE.—After testimony, Mr. Philip stated that this statement was in error, and that stated as a percentage of total dollar value, the Immuno-U.S., Inc. market share is approximately 3.2% for 1995.]

Ms. PHELPS. Do you manufacture the same products?

Mr. PHILIP. No.

Ms. PHELPS. Do you manufacture a specialized type of product that will require these kind of stringent safeguards?

Mr. PHILIP. We manufacture some very specialized products which tend to address the sort of smaller, rare diseases in the area, specifically, of coagulation, as well as immune disorders.

Ms. PHELPS. So, then, would you advocate these same type of stringent activities in the larger industry, or, perhaps, in the Federal Government, that the Federal Government should enact some standards that raise the bar of safety?

Mr. PHILIP. I think what we're presenting today are a number of initiatives that we've taken, that we've just finished the measurement on those initiatives. We've just got the scientific data together. We've just finished the validation of our PCR tests. We've just presented this to the FDA, and we were just about to publish some of this material so it could be peer reviewed and other scientists can benefit from it.

I'm sure other companies are doing similar things, maybe different things. I think, to me, one of the most important things we do in this country is that we do allow individual companies and various research facilities, whether they're academic or whether they're government funded, to develop new ways and better ways to improve, in this case, the safety and quality of the blood supply.

Sharing of that information is important. We were just at the phase where we were about to share it before this committee called us to bring it, perhaps a little ahead of time, shall we say, and we're pleased to do that.

But I think it's very important that a lot of this information be weighed and evaluated carefully by FDA and by others to decide whether this is the sort of thing they want to do. We believe very strongly that these initiatives we've taken improve the safety margin of our products, and that's why we're doing them today.

Ms. PHELPS. Were you aware as you were developing your PCR—and I guess, actually, when you started using it in December 1994, then NIH was also in pursuit of this technology?

Mr. PHILIP. Yes, we were, and we have, in fact, now completed the data on our tests which we're presenting to FDA as a first step, and we would be more than happy to share it with the other agencies.

Ms. PHELPS. Is it often that you have industry and government duplicating each other's effort?

Mr. PHILIP. I'm not sure whether it's duplication. I think our technology is actually quite different to that developed or being worked on by the government and, probably, by other companies, too. I think it's true that other companies may have similar lines of research and development. Some work, some don't. Research is a very hard and expensive activity, as you know, and does not always pay off.

Ms. PHELPS. My last question, Mr. Chairman. You said in your testimony, Dr. Philip, that the Federal Government, I guess, the Members of Congress, should recognize that as the Federal agencies raise the bar of safety, they must recognize that someone will have to bear the increased cost burden. Right now, looking at your own experience, how are you looking at apportioning out the burden of that cost in the future.

And then, also, what recommendations would you make to Chairman Shays and other Members about how to best proceed?

Mr. PHILIP. I think, first of all, is the awareness that a lot of these activities do cost a lot of money, a lot of time, a lot of investment, and that we cannot, as a company or as an industry, for that matter, go on creating and improving and adding safety margins to the manufacturing process or the screening processes without coming back and recouping at least a proportion of that investment, and an awareness, at least, at this stage, and perhaps a more open discussion of that side of the business that we're in is very important.

And so I think the reality that research, quality, and future developments do come at a price, is very important.

Mr. SHAYS. Thank you. I would like to allow our Republicans staff member who focuses in on this area to ask a question or two, if you have one.

Ms. FINLEY. Thank you, Mr. Chairman. Dr. Philip, would PCR catch HIV O variant in your plasma pools?

Mr. PHILIP. I'll have to ask Dr. Waytes that question.

Dr. WAYTES. I'm not aware that it would.

Ms. FINLEY. So then it would not necessarily be more reliable than adjusted antibody tests?

Dr. WAYTES. Well, if you were talking—I can't say for sure whether or not. We use primers, which are the pieces of DNA that detect the segments of viral material that we're interested in that are specific to the gag gene. I really can't say whether or not these primers would detect the type O. I could find that out for you, but I would not want to make that claim.

Ms. FINLEY. We would welcome the information. Thank you, Mr. Chairman.

[The information follows:]

The specificity of a PCR is dependent on the primers that are used. We use the well-known gag-specific primers SK 38 and SK 39. To date, we do not have any documentation that would suggest that these primers would detect the HIV O variant.

Mr. SHAYS. I would like to thank both of you very much, so I will say that your panel is done. I'm not encouraging anyone from the previous panel to come up unless they feel it's imperative that they do. And so you all are excused. I thank you very much for attending. Is there anyone that feels inclined to testify from the past panel?

Mr. TUTWILER. Could I comment?

Mr. SHAYS. Sure. I gave you that invitation. I would be happy to. May I just remind you that you are still under oath.

Mr. TUTWILER. Yes.

Mr. SHAYS. Thank you, Dr. Tutwiler. You're helping me by sitting in the same seat.

Mr. TUTWILER. I'm Dr. Tutwiler.

Mr. SHAYS. If you had sat over here, it would have confused me. [Laughter.]

Mr. TUTWILER. I really have very little comment, except maybe just on this specific question of PCR testing, and just to remind one that, one, the PCR testing is not yet approved by the FDA, for actually doing this kind of testing on a routine basis to exclude it during the actual inventory process.

And the other thing is—and I would just caution. I haven't seen their results, haven't seen their test. It may be a wonderful test. But we've been looking at the reproduceability of these types of techniques, as well, the DNA testing techniques, and, quite honestly, what's important here is to look at the actual reproduceability.

I mean the possibility of getting false positives and false negatives is a critical issue here, especially, you've heard that we need to be able to supply these important products to the American public. And, of course, if you throw out a lot of plasma because of false positives, for instance, then, in fact, that would have a disastrous impact on product availability.

And I just need to also make note of the fact that just because there might be small pieces of DNA, this may or may not—this is something you need to look into. Of course, these don't mean that these, in fact, are infective in any way. In other words, you need a much larger piece of DNA for it to be, in fact, infective.

So PCR testing can be so sensitive that it may pick up so much positive plasma in terms of the—you may get so many positives.

Mr. SHAYS. Let me just say, though, I would make an assumption that a company that's using that system obviously is not going to want to have false positives.

Mr. TUTWILER. Right.

Mr. SHAYS. If your concern is that somehow this committee would weigh in on this issue and ask you to do something that we're not sure of, you don't need to worry about that.

Mr. TUTWILER. OK. So those were the only comments I had.

Mr. SHAYS. I appreciate it.

Dr. WAYTES. Could I respond?

Mr. SHAYS. If you want to respond, you definitely may. I'm going to try to conclude this. I had purposely tried to dismiss you so it wouldn't get into a debate. I want to be fair to both sides. I didn't say that would be the dialog. So if you get us in too much more controversy, then you're going to open it up for 2 hours.

Dr. WAYTES. What I wanted to say is that's absolutely correct.

Mr. SHAYS. OK.

Dr. WAYTES. That is if one did not have an assay that could adequately control for false positives and false negatives, it would be a disaster. There's a lot that can go wrong with PCR. That's why it took us a number of years to develop a system where we have

internal and external controls such that we can, we think, basically eliminate the chance of having false positives and false negatives.

[The information follows:]

January 5, 1996

Honorable Christopher Shays
Chairman
Subcommittee on Human Resources and Intergovernmental Relations
Committee on Government Reform and Oversight
United States Congress
B372 Rayburn House Office Building
Washington, D.C. 20515

RE: Additional Questions Per Your Correspondence of December 18, 1995

DEAR MR. CHAIRMAN:

As you requested in your letter of December 18, 1995, we are providing the following information for inclusion in the record of the November 2, 1995, Subcommittee hearing on blood safety issues.

IOM Report

As you know, Immuno-U.S., Inc. has never marketed a Factor VIII concentrate in the United States. The only Factor IX concentrate Immuno-U.S., Inc. has marketed was not introduced in the United States until 1993 and is, of course, virally inactivated. Therefore, Immuno-U.S., Inc. was not involved in the events that are detailed in the Institute of Medicine (IOM) report, HIV and the Blood Supply: An Analysis of Crisis Decisionmaking. We have reviewed the report and the recommendations and believe that they merit serious consideration and debate. We think it is vitally important to reinforce that public policy and federal regulations governing the nation's blood supply be based on solid scientific data and the accumulated guidance of properly gathered clinical evidence and experience.

Immuno's specific responses to each of the 14 IOM recommendations are attached.

Source of Products

All of the plasma products currently marketed in the United States by Immuno-U.S., Inc. are manufactured from Source Plasma collected in the United States. Immuno-U.S., Inc. marketed and markets products manufactured by the Osterreichisches Institut für Haemoderivate GES.M.B.H., another Immuno Group company. These imported products, FEIBA®), Bebulin®, and Iveegam®, are all manufactured from Source Plasma collected in the United States. The manufacture of these products in Europe is governed by their product licenses issued by the Center for Biologics Evaluation and Research of the United States Food and Drug Administration ("FDA"). The European manufacturing facilities also hold FDA Establishment Licenses and are regularly inspected by the agency. Albumin has also been, and is, manufactured from U.S.A. Source Plasma. Historically, it was manufactured by Osterreichisches Institut fur Haemoderivate GES.M.B.H., and more lately by Immuno-U.S., Inc. in Rochester.

Prison Plasma

Immuno has not utilized any material sourced from any prison plasma program in the United States or any other country.

Thank you once again for the opportunity to contribute to your investigation. Do not hesitate to contact me if you desire further information.

Sincerely,

MARK A. PHILIP, PH.D.,
Chief Executive Officer.

IMMUNO RESPONSES TO THE IOM RECOMMENDATIONS

Recommendation 1: The Secretary of Health and Human Services should designate a Blood Safety Director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.

Recommendation 2: The PHS should establish a Blood Safety Council to assess current and potential future threats to the blood supply, to propose strategies for overcoming these threats, to evaluate the response of the PHS to these proposals, and to monitor the implementation of these strategies. The Council should report to the Blood Safety Director (see Recommendation 1). The Council should also serve to alert scientists about the needs and opportunities for research to maximize the

safety of blood and blood products. The Blood Safety Council should take the lead to ensure the education of public health officials, clinicians, and the public about the nature of threats to our nation's blood supply and the public health strategies for dealing with these threats.

Immuno Response to Recommendations 1 and 2: Immuno does not object to the appointment of a new Blood Safety Council and a Blood Safety Director but believes caution must be exercised to ensure that these new entities do not simply result in an additional level of bureaucracy that slows decisionmaking and undermines the regulatory authority of the Food and Drug Administration (FDA). Immuno believes that reliance on the best available scientific evidence, rather than any particular decisionmaking structure. will ensure sound blood policy decisions.

Recommendation 3: The federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products.

Immuno Response to Recommendation 3: The IOM report recommendation for a no-fault compensation system has inadequate detail for Immuno to take a definitive position.

Recommendation 4: Other federal agencies must understand, support, and respond to the CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.

Immuno Response to Recommendation 4: Immuno supports Recommendation 4.

Recommendation 5: The PHS should establish a surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products.

Immuno Response to Recommendation 5: Immuno supports Recommendation 5. Immuno supports the improvement of clinical surveillance and reporting systems focused on adverse effects on recipients of blood products.

Recommendation 6: Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm.

Immuno Response to Recommendation 6: Immuno supports Recommendation 6 to the extent that it envisions FDA allowing implementation of partial solutions when they are based on sound scientific evidence.

Recommendation 7: The FDA should periodically review important decisions that it made when it was uncertain about the value of key decision variables.

Immuno Response to Recommendation 7: Immuno supports Recommendation 7.

Recommendation 8: Because regulators must rely heavily on the performance of the industry to accomplish blood safety goals, the FDA must articulate its requests or requirements in forms that are understandable and implementable by regulated entities. In particular, when issuing instructions to regulated entities, the FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.

Immuno Response to Recommendation 8: Immuno supports Recommendation 8. Immuno believes that the regulated industry will benefit if FDA clearly and consistently articulates its regulatory requirements.

Recommendation 9: The FDA should ensure that the composition of the Blood Products Advisory Committee (BPAC) reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.

Immuno Response to Recommendation 9: Immuno believes that members of the BPAC should be chosen for their knowledge, experience, and ability to contribute to the committee's deliberations and decisionmaking and should represent all involved interests and concerns. The BPAC should be constituted so that it will be able to make sound scientific decisions, and Immuno agrees that a balanced membership of qualified industrial and non-industrial members is appropriate.

Recommendation 10: The FDA should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.

Immuno Response to Recommendation 10: Immuno supports Recommendation 10.

Recommendation 11: The FDA should develop reliable sources of the information that it needs to make decisions about the blood supply. The FDA should have its own capacity to analyze this information and to predict the effects of regulatory decisions.

Immuno Response to Recommendation 11: Immuno supports decisionmaking based on the best available scientific evidence and agrees that FDA should have adequate expertise to make sound, evidence-based decisions. If the agency has that capacity, it will be able to judge the science that is presented to it and the recommendations of BPAC.

Recommendation 12: When faced with a decision in which the options all carry risk, especially if the amount of risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.

Immuno Response to Recommendation 12: Immuno recognizes the primacy of the treating physician in reviewing treatment options and communicating to the patient the risks and benefits of any recommended course of treatment, as does current law.

Recommendation 13: The Department of Health and Human Services should convene a standing expert panel to inform the providers of care and the public about the risks associated with blood and blood products, about alternatives to using them, and about treatments that have the support of the scientific record.

Immuno Response to Recommendation 13: Immuno supports the wide dissemination of information concerning treatment and believes that the federal government has an important role to play. There already exist some avenues for distributing information about treatments, and HHS should encourage further educational efforts, both through publicly funded programs and through cooperation with the private sector. Immuno is not convinced that a new standing expert panel is required to achieve the goal of enhanced public information.

Recommendation 14: Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgment, and otherwise act so as to earn the confidence of the public and patients.

Immuno Response to Recommendation 14: Immuno agrees that all involved in the blood and blood products industry, the treatment of patients, or the recommendation of products should avoid conflicts of interest and maintain independent judgment. When perceived or potential conflicts of interest occur, they should be fully disclosed to all interested parties and to the public. However, Immuno believes that the relationships between fractionators and voluntary organizations have been very productive ones that have led to the exchange of important information. These relationships can further contribute to improvements in the treatment of hemophiliacs and others with blood-related disorders and should be encouraged and fully disclosed.

Mr. SHAYS. I'll end on that positive note, all right? Thank you very much.

Let me, before closing, I want to thank the staff, both the Republican and Democratic staff that has helped us prepare for this, and to thank our reporter, Jan del Monte, for her work, as well, and just let all of you know that we're in this for the long haul.

We think this issue is extraordinarily important. We had enough wake-up call in the 80's. We aren't going to be complacent. This committee is part of the defense network that I described, as well as those who have come and testified. I will just emphasize again, this is such an important issue that I'm going to know more about this issue than I ever wanted. With that, I call us adjourned.

[Whereupon, at 1:50 p.m., the subcommittee meeting was adjourned.]

○