FDA REGULATION OF BLOOD SAFETY: NOTIFICATION, RECALL, AND ENFORCEMENT PRACTICES

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES

OF THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTH CONGRESS

FIRST SESSION

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FDA REGULATION OF BLOOD SAFETY: NOTIFICATION, RECALL, AND ENFORCEMENT PRACTICES

THURSDAY, JUNE 5, 1997

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

The subcommittee met, pursuant to notice, at 10 a.m., in room 2247, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Pappas, Towns, and Kucinich.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley, professional staff member; R. Jared Carpenter, clerk; and Cherri Branson, minority counsel.

Mr. SHAYS. I'd like to call this hearing to order. On July 25, 1996, the House Committee on Government Reform and Oversight adopted a report offered by this subcommittee entitled "Protecting the Nation's Blood Supply from Infectious Agents: The Need for New Standards to Meet New Threats." Forwarded to the House with broad bipartisan support, the report found the U.S. blood supply safer than ever, but recommended seven specific steps to maintain and improve the safety of the blood and plasma products used by more than 40 million people each year.

Two of those recommendations called for improvements in the Food and Drug Administration's—FDA's—regulatory approach to blood issues. Specifically we called for more rigorous inspections of blood banks and plasma facilities by the FDA's Center for Biologics Evaluation and Research [CBER] and for the development of a more effective system to notify patients when unsafe blood products must be recalled.

Today we ask, what has the FDA done to implement those recommendations?

Blood and plasma products must flow through a five-tier safety system before reaching patients: donor screening, donor deferral, blood testing, blood quarantine and compliance monitoring, which includes inspections and recalls.

In the inevitable event an infectious agent slips through the human and high-tech barriers of the first four layers, all that stands between a patient and potentially harmful, even fatal, therapy is vigilant, responsive regulatory inspections and recall. For some time, that final safety barrier against bad blood products has shown signs of leakage. Ten years ago FDA's own Office of Regu-

latory Affairs cited lapses and inefficiencies in CBER's inspection practices.

In 1988, the Presidential Commission on the Human Immunodeficiency Virus epidemic called FDA's dependent, nonconfrontational relationship with the blood industry an obstacle to progress toward improved safety. Before 1990, many thousands of people were infected with the hepatitis C virus through blood and blood products and never told of their exposure.

While significant blood safety improvements have made since the 1980's, some of the same regulatory policies and practices that failed to prevent the devastating spread of AIDS to blood product users, particularly hemophiliacs, are still in place today.

Then, as now, the lack of aggressive regulatory enforcement delays the detection of problems and delays the recall of potentially dangerous products, putting patients at risk. The number and scope of blood product recalls provides further evidence of a fraying regulatory safety net.

Since January, the FDA has announced 17 recalls, withdrawals, or quarantines of fractionated blood products for reasons including inadequate viral testing, product impurities and the use of plasma from persons with CJD, the human form of "Mad Cow Disease." Last October the FDA announced the largest blood product recall in U.S. history when one manufacturer of human products were found to be unsterile.

The Department of Health and Human Services—HHS—report on that recall concluded, "If FDA had been more aggressive about responding to its earlier inspections and if those earlier inspections were more encompassing, the incident probably would not have occurred." Even when a recall is not delayed by regulatory inattention, patients and their physicians still must rely on informal, voluntary, sometimes haphazard communication channels to learn their lifesaving therapies may be life threatening.

The current recall notification system seems more designed to pass the buck down the product distribution chain than the pass the word about unsafe blood products. The ineffectiveness of the recall notification system is especially important to hemophiliacs and other patient groups who rely on regular doses of blood and plasma products for disease control and to maintain their quality of life. In this era of global telecommunications, they wait at the end of a fragile network manned by nonprofit groups and volunteers. They wait for the call or the fax identifying a product lot that may transmit hepatitis or some new infectious agent. And they hope, they pray, they haven't already used it.

They are also waiting to hear from us. The subcommittee received thousands of letters from individuals and organizations representing thousands of blood product users, encouraging us to persist in our oversight of blood safety improvements. I ask these letters be made part of this hearing record. Theirs is compelling testimony on the need for strong enforcement and effective recall notification as the central parts of the blood safety system.

In February, the General Accounting Office—GAO—echoed our recommendations for strengthening blood and plasma facility inspections. At the subcommittee's request, the Department of Health and Human Services—HHS—Inspector General—IG—also

examined aspects of FDA's blood safety product. Their testimony and that of the FDA today should tell us and these patients how we can keep the U.S. blood supply among the safest in the world.

[Note.—Additional prepared statements can be found in subcommittee files.]

[The prepared statement of Hon. Christopher Shays and the information referred to follow:]

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ONE HUNDRED FIFTH CONGRESS

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Statement of Rep. Christopher Shays
June 5, 1997

On July 25, 1996, the House Committee on Government Reform and Oversight adopted a report, offered by this Subcommittee, entitled, "Protecting the Nation's Blood Supply from Infectious Agents: The Need for New Standards to Meet New Threats." Forwarded to the House with broad bi-partisan support, the report found the U.S. blood supply safer than ever, but recommended seven specific steps to maintain, and improve, the safety of the blood and plasma products used by more than 40 million people each year.

Two of those recommendations called for improvements in the Food and Drug Administration's (FDA) regulatory approach to blood issues. Specifically, we called for more rigorous inspections of blood banks and plasma facilities by the FDA's Center for Biologics Evaluation and Research (CBER), and for the development of a more effective system to notify patients when unsafe blood products must be recalled.

Today we ask: What has FDA done to implement those recommendations?

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In the inevitable event an infectious agent slips through the human and high-tech barriers of the first four layers, all that stands between a patient and a potentially harmful, even fatal, therapy is vigilant, responsive regulatory inspections and recall.

For some time that final safety barrier against bad blood products has shown signs of leakage. Ten years ago FDA's own Office of Regulatory Affairs cited lapses and inefficiencies in CBER's inspection practices. In 1988, the Presidential Commission on the Human Immunodeficiency Virus Epidemic called FDA's dependent, non-confrontational relationship with the blood industry an obstacle to progress toward improved safety.

Before 1990 many thousands of people were infected with the Hepatitis C virus through blood and blood products and never told of their exposure.

While significant blood safety improvements have been made since the 1980s, some of the same regulatory policies and practice that failed to prevent the devastating spread of AIDS to blood products users, particularly hemophiliacs, are still in place today. Then as now, the lack of aggressive regulatory enforcement delays the detection of problems and delays the recall of potentially dangerous products, putting patients at risk.

The number and scope of recent blood product recalls provides further evidence of a fraying regulatory safety net. Since January the FDA has announced 17 recalls, withdrawals or quarantines of fractionated blood products for reasons including inadequate viral testing, product impurities and the use of plasma from persons with Creutzfeldt-Jakob Disease (CJD, the human form of Mad Cow disease).

Last October the FDA announced the largest blood product recall in U.S. history when one manufacturer's albumin products were found to be unsterile. A Department of Health and Human Services (HHS) report on that recall concluded, "If FDA had been more aggressive about responding to its earlier inspections and if those earlier inspections were more encompassing, the ... incident probably would not have occurred."

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The effectiveness of the recall notification system is especially important to hemophiliacs and other patient groups who rely on regular doses of blood and plasma products for disease control and to maintain their quality of life. In this era of global telecommunications, they wait at the end of a fragile network manned by non-profit groups and volunteers. They wait for the call or the fax identifying a product lot that may transmit Hepatitis or some new infectious agent, and they hope, they pray, they haven't already used it.

They are also waiting to hear from us. This Subcommittee has received letters from individuals and organizations representing thousands of blood product users encouraging us to persist in our oversight of blood safety improvements. I ask these letters be made a part of this hearing record. Theirs is compelling testimony on the need for strong enforcement and effective recall notification as essential parts of the blood safety system.

In February, the General Accounting Office (GAO) echoed our recommendations for strengthened blood and plasma facility inspections. At the Subcommittee's request, the Department of Health and Human Services (HHS) Inspector General (IG) also examined aspects of FDA's blood safety program. Their testimony, and that of the FDA today, should tell us, and these patients, how we can keep the U.S. blood supply among the safest in the world.

May 28, 1997

Chairman Christopher Shays
Committee on Government Reform
Subcommittee on Human Resources
United States House of Representatives
Washington, D.C.

Dear Congressman Shays:

Your efforts to make the blood system safer are greatly appreciated. As a parent of two sons who died from AIDS and hepatitis, I only wish that such emphasis had taken place over twenty years ago. Nevertheless, it is critically important that such oversight continue with great vigilance.

In considering the current issues facing the blood system, I realize the complexity of the tradeoff. Nothing is free. Yet, the lives of those who rely on blood products much be considered as precious. While expense is always important, failure to be ever vigilant allows the system to not push for the greatest safety possible. For example, the evidence on whether Creutzfeldt-Jacob disease is transmitted by blood is not clear. Yet, waiting for conclusive evidence could cause the catastrophe of AIDS. Those of us in the hemophilia community will not be able to forget the damage caused by authorities not taking action until there was substantial evidence that the virus was transmitted by blood. Today, companies have been quarantining blood that might contain CJD and the companies complain that such quarantine is very expensive and it reduces the supply of blood products.

I understand these tradeoff. But there is a way to lessen the impact of the tradeoff. Companies have been increasing the size of the their plasma pools from which they make plasma derivatives. I assume the increased pools create economies of scale. However, if the increased pools result in huge losses because of quarantine, then the companies do not benefit from the larger pools. By returning to much smaller pools, withdrawals and quarantines will have a much smaller impact on costs. A reduced pool size would also make notification a much easier problem.

I encourage you to continue your efforts and hope your hearings are successful.

Sincerely,

Paul F. Haas

Paul F. Haas
873 Ferndale Ct.
Bowling Green, OH 43402

May 28, 1997

Congressman Christopher Shays, Chairman
Subcommittee on Human Resource
Committee on Government Reform and Oversight
Room B-372 Rayburn Building
Washington, DC 20515

Dear Congressman Shays:

As a consumer of blood products, I am very concerned with the present FDA recall and notification policy. The present policy is unacceptable as it is still the same policy promulgated in the early 1980's by which many of the blood product users were infected with HIV and Hepatitis due to lax enforcement. The FDA allowed the industry to voluntarily **withdraw** the products at their discretion when actually the products were considered a biohazard and warranted a **recall.**

Due to the voluntarily withdraw policies of the early 1980's, I am an HIV and Hepatitis C infected person and unknowingly tranmitted HIV to my wife who is now deceased from AIDS. Had a stricter recall policy been enforced, this tragedy surely would not have transpired.

It is paramount that a new recall and notification policy be promulgated which will provide for the ultimate safety of the consumer.

One other unresolved concern remains which needs to be addressed for the safety of the American people. Is high titer plasma, which is used for immuneglobulin treatment still being collected and pooled in the same pool being used to produce blood products and factor concentrates? If this collection practice still exists, it seems that it violates CFR 640.63 which promulgates the elimination of hepatitis from certain blood products, namely factor concentrate.

Thank you for your consideration and concern for the safety of the American blood supply.

Sincerely,

Dana A. Kuhn, Ph.D.

Finley, Anne Marie

From: Gary A. Marcil[SMTP:clion@minot.ndak.net]
Sent: Thursday, May 29, 1997 4:54 PM
To: Finley, Anne Marie
Cc: 'Hemophilia-Support'
Subject: Attention: Anne Marie Finley

To:Chairman Christopher Shays Subcommittee on Human Resources
& Intergovernmental Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Mr. Chairman,

I am not very good at writing letters or explaining myself very well, all the issues are of concern to me but today FDA enforcement of blood product withdrawal and recalls and for the establishment of a timely patient notification system is of great importance.

I just received a call from Caremark telling me that I had received a 'possibly' contaminated batch of Baxter Hemofil M. This batch was sent to me in February and today is May 29.

I have 1 out of 10 bottles left, meaning I injected 9 bottles of 'possibly' contaminated factor into my blood stream.

I am told I have been HIV positive since 82, but since that time the virus has mutated into different versions.

I am not part of the medical community and have no background in this illness but survival but if there are diferent versions of this bloody virus, how long before I get an aggressive enough version that will kill me?

It took them 4 months to find out and inform me. They are sending me a replacement vial for the one I have left and wish me to return the remaining vial of 'possibly' contaminated factor.

This is probably not what you wish to hear but this is my life and they are good at misdirection and covering their backsides.

We need help, especially for the children who are negative, no more deaths.

Gary A. Marcil
1201 4th St. S.W.
Minot, ND 58701

(701) 839-2683

STOP THE BLEEDING

HEMOPHILIA ASSOCIATION OF NEW YORK, INC. • 104 East 40th Street, Suite 506, New York, NY 10016
Tel: 212-682-5510
Fax: 212-983-1114

May 29, 1997

Chairman Christopher Shays
Subcommittee on Human Resources
and Intergovernmental Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Congressman Shays,

On behalf of the Hemophilia Association of New York I wish to applaud your interest in ensuring a more responsive blood safety system. Blood safety is of the greatest importance to all those with bleeding disorders -- people who rely on blood products to maintain life and health -- and to their families.

It has been made amply clear by the disastrous events surrounding the manufacture and distribution of contaminated clotting factor in the 1980's, as well as by the subsequent continual incidents of blood product hazards, that action is vital to establish clear guidelines for FDA enforcement of blood product withdrawal and recalls, and a timely consumer notification system.

The safety of products used in the treatment of bleeding disorders is a central concern of this organization which has represented thousands of persons with hemophilia and related disorders over more than 45 years. The immense size of the plasma pools continues to pose a threat as does the possibility of contaminants such as Creutzfeldt-Jacob and new strains of hepatitis. We see the necessity of greater incentives for the development of better viral inactivation methods.

We thank you for promoting, through the Government Reform and Oversight Committee, these measures that are essential to protecting the blood supply for all Americans.

Yours truly,

Edward G. Rogoff
President

EGR/dm

A copy of the latest annual report can be obtained from HANY or from the Secretary of State by writing to the Office of Charities Registration, Secretary of State, 162 Washington Avenue, Albany, NY 12231.

May 29,1997

Chairman Christopher Shays
Subcommittee on Human Resourses & Intergovernmental Relations
B372 Rayburn House Office Building
Washington , D.C. 20515

Dear Chairman Shays,

Please accept my personal thanks for the efforts you and your staff have made in regards to the need for more responsive blood safety from our government. It is through the diligent attention of committees such as Reform & Oversight that innocent citizens can be protected from catastropies like tainted blood products .

I have two brothers both of which are hemophiliacs and both were infected with HIV/AIDES in the early 80's as a result of contaminated blood products. As you can imagine, blood safety is of great importance to my family. We realize that it is too late for my brothers to avoid HIV/AIDES but they still must infuse blood products and those blood products must be "clean" to avoid any additional health or life treatening contaminates.

One of the main issues which continues to have dire ramifications is the timely patient notification of contaminated or even suspected contamination of any treatment products required for their health and well being. Sprecific FDA guidelines to enforce withdrawal and recall of dangerous blood products are crucial. The FDA has the ultimate obligation and responsibility for protecting our nation's blood supply to ensure it's safety for all Americans. The current system is much to informal in its communication with blood and blood product manufactures and the regulation of same.

Even with the recent increase in consumer representation, the FDA continues to address blood safety issues based on product availability verses cost. The 1980's proved how lethal those criteria were to over 10,000 persons effected with bleeding disorders. Those victums die one by one, day by day. Emerging threats such as Creutzfeldt-Jakob disease and new strains of hepatitis continue to plague the hemophilia community and other effected persons with blood disorders.

Chairman Shays, it is through your subcommittee that this more responsive patient notification system, developement of better viral inactivation methods and enhanced enforcement of these guidelines comes to the attention of the United States government. Please do all in your power to see that these issues recieve any and all benefit from the attentions of the Subcommittee on Human and Intergovernmental Relations. Kindly keep me informed as to what is happening and how I personally can be of assistance.

Respectfully,

Connie Etcheverry, 1554 N Sinova, Mesa, Az. 85205

Finley, Anne Marie

From: ebueso@warren.med.harvard.edu[SMTP:ebueso@warren.med.harvard.edu]
Sent: Thursday, May 29, 1997 2:00 PM
To: Finley, Anne Marie
Subject: blood safety reform

Dear Chairman Shays,

I am writing to you to express my concerns about a more responsive and safe blood system.

I am the parent of child with hemophilia and the sister of a brother with hemophilia and HIV. Because of this, the safety of the blood supply and the timely notification to consumers of a recall of a blood product that may be contaminated, is of the greatest interest to me.

Knowing that my son's and brother's health and well-being are totally dependent upon a blood system that CAN be safer and more responsive is a frightening thing. My brother's faith in the system has been shattered because of the contamination of the blood supply of HIV in the 80's. However, I know that this tragedy need not reoccur. NOW is the time to enact strict guidelines and procedures for recalls of blood products. NOW is the time for the FDA to construct a formal system of communication and enforcement of regulations with the blood manufacturers. NOW is the time to develop better viral inactivation methods.

While my family is directly and constantly effected by these issues, it is sobering to realize that the safety of the blood supply really is in EVERYONE'S best interest. No one ever knows if they, or a loved one, will need a blood transfusion some day or be dependent upon some sort of blood product.

Thank you for taking the time to read this letter and thank you for your efforts through the Government Reform and Oversight Committee to bring attention to these issues.

Sincerely yours,

Elizabeth Bueso
18 Mt. Calvary Rd.
Roslindale, MA 02131

Finley, Anne Marie

From: FTBR03A@prodigy.com[SMTP:FTBR03A@prodigy.com]
Sent: Thursday, May 29, 1997 8:00 PM
To: Finley, Anne Marie
Subject: Congressman Shays Recalls

I am the mother of a Hemophiliac and who has AIDS, Hep. C and B contracted through contaminated blood that was not monitored by the Industry or the FDA. The Hep. C was just contracted not more then three years ago. Through all of this my son has only 1/10th of his liver left. Blood safty is of great importance to me and my family as my grandson is also a hemophiliac and so far is HIV-. I could not bare to see him go through what my son has and is. As you see blood safety is of great importance to me and my family.

In the 80's the continued high frequency of recent incidents of blood products contamination demonstrate the urgency for clear guidelines to direct FDA enforcement of blood product withdrawal and recalls and for the establishment of a timely patient notification system. I also remain concnerned about the size of the plasma pools used to manufacture the clotting factor concentrates used by my son and grandson.

Blood safety is a shared responsibility, FDA has the ultimate obligation for protecting our nation's blood supply to ensure its safety for all Americans. The FDA currently relies on an informational system in communicating with blood and blood product manufactureres about enforcement of its regulations.

While consumer representation on the committee has increased in the past few years, the Committee often continues to address blood safety issues using the same framework - product availability versus cost as it use to in the 80's.

Enforcement is a more responsive patient notification system and greater incentives for the development of better viral inactivation method as well as for recombinant factors are all needed to prevent the recurrence of the HIV tragedy of the 80's and to protect the safety of the blood supply for all Americans.

Just last week the Hemophiliac Community received another recall of contaminated blood, but for some it was too late as they had used some if not all of the factor. You would think what happened in the 80's there would have to be no more recalls and we would not have to worry about contamination in our blood system. There has to be a way to stop this, bad blood is still getting through. The safety of the blood supply is oof great importance as threats such as Creutzfeldt=Jakob disease and new strains of hepatitis continue to plague the hemophila community and other users of blood products.

I want to thank you for your efforts through the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system. Please keep up the good efforts.

Joyce Grim
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Citrus Heights, CA 95621
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Prodigy ID# FTBR03A@Prodigy.COM

The Committee of Ten Thousand

918 Pensylvania Ave. SE, Washington D.C. 20003
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Advocates for Persons with HIV/AIDS

From the desk of:
Wayne L. Swindlehurst
Vice President
1705 Chief Okemos Circle
Suite 1
Okemos, Michigan 48864
Phone: & Fax (517) 381-9241

Chairman Christopher Shays
Subcommittee on Human Resources
& Intergovernmental Relations
B 372 Rayburn House Office Building
Washington, DC 20515

May 29, 1997

Dear Congressman Shays;

I am writing you today concerning your committees hearing concerning the timely patient notification and enforceable recall procedures for the users of blood and blood products.

I am a person with severe hemophilia and AIDS, I am forty seven years old and have lived through the many recalls, and the many instances of where there should have been a recall and for whatever reason, the recall did not take place. I have a great interest in the recall and notification problems that we in the hemophilia community , still face today. After the events of the early 1980's, it is unfathomable to me that we still have not put in place a recall system that errs on the side of safety of the users of blood and blood products.

The recent recalls are of great concern to me, these recalls have been handled in a very casual manner. The latest Baxter, American Red Cross recall is an example of the problems that we still face today. This recall was handled in a manner that suggests that there is still not a recall and notification system in place. The first the community learned about this recall came about because we have a community member on the Blood Products Advisory Committee, Mr. Corey Dubin. Mr. Dubin learned about the recall from the FDA and immediately issued a statement on behalf on The Committee of Ten Thousand (COTT) to the hemophilia community via the internet. Because this was not reported by other hemophilia organizations, or the FDA, many members of the community were confused. They tried to find out more about the recall by calling the FDA hotline, the hotline information had not been updated two days after the recall was issued. They tried calling the NHF to no avail,

the NHF was trying to determine if the community even needed to know about the recall. As of this date, I have still not been notified by anyone but The Committee of Ten Thousand about the recall. Thank god that this community has an organization like COTT in place, to relay important information to members of the bleeding disorder community. I have to wonder if we would have ever received the recall notification, without having Mr. Dubin on the BPAC, and his quick attention to the matter.

When the first CJD recall took place, by the time I received the notice, I had already taken seventy two vials of the contaminated factor. I blame the lack of notification on the FDA, and the United States Government for not having a system in place that would get information out to the consumers in a timely manner.

The events of the early 80's and the events of today, with the many recalls that have taken place, demonstrate the urgent need for clear guidelines to direct the FDA enforcement of blood product withdraw and recalls, and the establishment of a timely patient notification system. While the safety of the blood and blood products are a shared responsibility, I believe that the FDA has the ultimate responsibility to safeguard the nations blood and blood products. I also believe that it is past time for the FDA to take a proactive stance on the safety of blood and blood products, and stop relying on the manufactures to come to them with information. As far as I can see, the manufactures still put cost ahead of the regard for human lives. With what we now know about Creutzfeldt-Jakob disease and hepatitis, one or both will be the next epidemic. If the FDA doesn't act now, thousands upon thousands of lives will be lost in the future.

Please, I beg the United States Government to put in place a system that can save lives, a system that will notify consumers in a timely manner, a system that will err on the side of human lives, not on the side of profit.

Thank you for your concern,

Sincerely,

Wayne I. Swindlehurst
Vice President, Committee of Ten Thousand

National Organization for Rare Disorders, Inc.®

NORD • 100 Rt. 37, P.O. Box 8923 • New Fairfield, CT 06812-8923
(203) 746-6518 • FAX : (203) 746-6481 •TDD: (203) 746-6927
http://www.nord-rdb.com/~orphan • e-mail: orphan@nord-rdb.com

May 30, 1997

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
& Intergovernmental Relations
United States House of Representatives
Room B-372 Rayburn Building
Washington, DC 20515

Dear Representative Shays:

We are pleased that you will be holding a hearing on June 5 regarding the adequacy of FDA's enforcement practices to ensure the safety of the blood and plasma supply. As you know, many rare disorders are treated with blood and plasma products such as Factor VIII for hemophilia, alpha-1-antitrypsin for the hereditary form of emphysema, intravenous immunoglobulins for immune deficiencies, etc.

It is discomforting to the patient community to know that Americans cannot rely on a continuous supply of important biologics because they are often unpredictably recalled from the market. Without warning patients find that treatments are temporarily unavailable, which can cause great anxiety, medical deterioration and sometimes life-threatening events. Even more discomforting is the knowledge that unsafe products are often on the biologics' market for some time before the FDA recalls them. As a result, too many Americans are put at risk each year because contaminated products may be distributed before FDA finds out that they may be contaminated.

Mr. Shays, we urge you to investigate this problem and require the FDA to put in place a reliable inspection system, an improved reporting system, and a public notification system that alerts patients and physicians of potentially unsafe products. It is most important that FDA monitors blood facilities closely to prevent these types of problems from recurring. Patients must rely on the uninterrupted availability of these lifesaving products. It is inhumane to periodically experience periods when some biologics are not available because FDA reacted after the fact, rather than preventing manufacturing deficiencies in the first place.

Very truly yours,

Abbey S. Meyers
President

ASM:aa

Member Organizations:
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Unavailable, only listing membership. For specific listing, please contact the NORD office.

Dedicated to Helping People with Orphan Diseases

Finley, Anne Marie

From: Joyce Lawson[SMTP:jlawson@mounet.com]
Sent: Friday, May 30, 1997 3:13 PM
To: Finley, Anne Marie
Subject: HEARING: For Blood Safety

Joyce S. Lawson
2017 Holly Street
Kingsport, TN 37660

Chairman Christopher Shays
Subcommittee On Human Resources
& Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman and Committee Members:

I am writing concerning the hearing on June 5, 1997, concerning the progress of industry's and the FDA's development of guidelines concerning timely patient notification and enforceable verifyable recall procedures for violative biologicals. Thank you for your efforts through the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system.

I was the wife of a man with hemophilia for almost 27 years. My husband, Ron, died September 6, 1994, as the result of my infusing him, unknowingly, with contaminated blood factor products. Ron died a horrible, agonizing death with HIV/AIDS while our two children, grandchild, and I watched. Ron was a wonderful christian man who loved his family and God. He struggled for over two years to live, for he enjoyed life and his family, putting himself through torment with full-blown AIDS. My children and I have went through emotional distress for over seven years since finding out about Ron's HIV diagnosis.

As a mother of a daughter, Joy, who is a carrier of hemophilia and having many friends in the hemophilia community, I want to voice my concern about the blood supply safety and all the recalls of the factor product that are happening. This concern is of great importance to me and I have devoted my life to helping the hemophilia community and working toward a safer blood supply. The events of the 1980s and the continued high frequency of recent incidents of blood products contamination demonstrate the urgency for clear guidelines to direct FDA enforcement of blood product withdrawal and recalls and for the establishment of a timely patient notification system. My concern is also about the size of the plasma pools used to manufacture the clotting factor concentrates. While blood safety is a shared responsibility, FDA has the ultimate obligation for protecting our nation's blood supply to ensure its safety for all Americans. The FDA currently relies on an informal system in communicating with blood and blood product manufacturers about enforcement of its regulations. The FDA also relies on the Blood Product Advisory Committee in formulating blood safety policy. While consumer representation on the committee has increased in the past few years, the Committee often continues to address blood safety issues using the same detrimental decisions of the 1980s - product availability versus cost.

We need a stricter enforcement of these products, delaying of releasing these products till they have been tested and retested again so we can eliminate in the first place the numerous recalls. When I first found out about my husbands' diagnosis, I spent numerous hours and days at my local library researching, going back into the early 40s, found that even then our government knew our blood supply was not safe. Our country have done many marvelous inventions, for instance, sending individuals to the moon which in my opinion is not necessary, but something that 1 out of 6 Americans at sometime in their life will receive in the form of transfusion

and it's still unsafe! In our day of great technology that we have I think it is inexcusable that our blood supply is not safer.

As the mother of an 18 years old daughter being a carrier of hemophilia I am very concern that if she has a son(s) with hemophilia, my family and I will have to live in constant fear of my grandchild(ren) being infected by viruses from contaminated products as Ron was. Already, she saids, "No, way, will I have children for I don't want to watch my child(ren) die as I watch my father did" and to me it's unthinkable that she as a teenager is worrying and feeling deprived in the future of having, most everyone's desires, children.

Please, I pray, be urgent, in protecting our blood supply for all Americans, in bringing stricter enforcements to prevent the recurrence of the HIV tragedy of the 1980s. Think, Chairman Shays, it just might be you or your loved ones this happens to just as it happened to my beloved husband and thousands of people with hemophila. I trust you will make the right decisions and I along with others will be watching for your urgent response to this problem.

Sincerely,

Joyce S. Lawson

Finley, Anne Marie

From: global.mgt@internetmci.com[SMTP:global.mgt@internetmci.com]
Sent: Friday, May 30, 1997 4:52 PM
To: Finley, Anne Marie
Cc: Hemophilia-support@web-depot.com
Subject: Blood Safety

Chairman Christopher Shays
Subcommittee On Human resources
& International Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman:

I would like to take this opportunity and thank you for your efforts through the government reform and oversight committee to bring greater attention to the need
for a more responsive blood safety system.

As a hemophiliac/ blood product consumer, blood safety is of great importance to me and my family. So the FDA's development of guidelines concerning timely patient notification and enforceable verifiable recall procedures is an impertinent
issue of serious consequences and of importance.

Enhanced enforcement, a more responsive patient notification system and a better incentive for the development of better viral inactivation methods as well as for recombinant factors are all needed to prevent the recurrence of the hiv tragedy
of the 1980's and to protect the safety of the blood supply for all.

Thank you for your time and I look forward to your positive reply.

Regards,
Mohamed Shaaban
18 Chelsea court
Ramsey, NJ 07446
Shaaban@prodigy.net

Finley, Anne Marie

From: CNeveu@aol.com[SMTP:CNeveu@aol.com]
Sent: Friday, May 30, 1997 6:48 PM
To: Finley, Anne Marie
Subject: Blood Safety

Dear Ms. Finley and Chairman Shays;

My name is Cindy Neveu and i am a woman with a rare bleeding disorder who contracted HIv from a blood transfusion in the early 1980's. I am aware that there are several levels of responsibility in this disaster within the nation's blood supply as well as numerous blood collection/distribution and manufacturing agencies ivolved in the blood industry.

It is absolutely imperative that there be one overseeing body of legislation to monitor the blood supply and notify consumers and providers of devective products. I use a product that comes from local blood banks and is called cryoprecipitate. This product is unable to be heat or chemically purified and depends entirely on state of the art screening of donors. Because of this, cryo users like myself are extremely vulnerable to contamination and most of us who have been using these products regularly have already been infected with several forms of hepatitis, HIV and who knows what else...and we continue to depend on these products with not alternatives.

The FDA needs to be responsible for the monitoring and notification of issues surrounding our blood supply. The timely notification of tainted product can mean the difference between life and death, and its too important to be left up to pharmaceutical companies to "get around" to notifying consumers or removing potenially hazardous products at the risk of losing profits.

Please pass these concerns along to the committee members and do whatever is possible to ensure the future safety of our blood supply. Its not just about hemophiliacs, its about anyone and everyone who may need to depend on blood products at some time in their lives!

Thanks for your attention. If there is any other way that I can be of assistance in pleading for this issue, please do not hesitate to contact me!

Sincerely,
Cindy Neveu

742 Wesley Way #2A
Oakland, CA 94610
510-832-0813
510-832-5223 FAX
CNeveu@aol.com

Finley, Anne Marie

From: sharon@www.pgsm.com[SMTP:sharon@www.pgsm.com]
Sent: Friday, May 30, 1997 8:15 PM
To: Finley, Anne Marie
Subject: contaminated blood

Dear Ms Finley,
It is very hard to believe that in this day and age and all the technology that is available and we still have a contaminated blood supply. How is this possible? In the early 80s a virus was discovered in the blood supply. This is 1997 and there should be absolutly nothing in the blood now. You know what to look for, you are suppose to be intellegent people. I do not understand how bad blood can still be around. Its seems the only way to fix it would be to store a few pints of our own blood at our hospitals and have it CLEARLY labled who it belongs to and then we won't have to worry about our friends and family dying of a horrible desease.
Lets get our act together here and show the population just how intellengent we are and STOP passing out the contaminated blood. We are not backwards people who don't know any better. CHECK the blood supply and DOUBLE check again. And keep in mind of getting people to store their own blood especially the ones who get it on a regular basis.
You may notice that I'm from Canada and believe me, our blood suppy is just as bad. One incident awhile back almost cost the Canadian Red Cross to fold, then where we would we be?
Thank you for taking the time to read my letter

Sincerly
Sharon Moore
R.R.#3
Picton, Ontario
Canada
K0K 1G0
sharon@home.pgsm.com

Attn: Anne Marie Dunley 5/30/97
Chairman Christopher Shays
Sub Committee on Human Resources and
Intergovernmental Relations
B 372 Rayburn House Office Bldg.
Washington D.C. 20515

Dear Chairman Shays,

As a father and mother of two sons, born with Hemophilia, who became infected with the HIV virus in the 1980's as a result of tainted blood products, we want to thank you for your efforts thus you and your staff have made to bring attention to the need for a better blood safety system. We realize that it is too late for our sons, but if it can protect other families from the pain, suffering, financial burden and certain early termination of life, we urge you to continue putting pressure on the F.D.A. who has the ultimate obligation of protecting our nations blood supply to assure safety for all Americans. The safety of the blood supply is of great importance as emerging threats of new strains of Hepatitis and Creutzfeld-Jacob disease continue to plague the hemophilia Community and other users of blood supply.

Our heartfelt thanks
Harley & Connie Green

Chairman Christopher Shays
Subcommittee on Human Resources & Intergovermental Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

May 31, 1997

Dear Chairman Shays;

Thank you for your efforts through the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system.

As a parent of two children with hemophilia, blood safety is of great importance to me and my family. The events of the 80's and the continued high frequency of recent incidents of blood products contamination demonstrate the urgency for clear guidelines to direct FDA enforcement of blood product withdrawal and recalls and for the establishment of a timely patient notification system. I also remain concerned about the size of the plasma pools used to manufacture the clotting factor concentrates used by my children.

Thanks for your help in this matter.

Sincerely,

Thomas J. Ondreyka
52 Zaleski Dr.
Sayreville, New Jersey 08872

Finley, Anne Marie

From: CTStwo@aol.com[SMTP:CTStwo@aol.com]
Sent: Saturday, May 31, 1997 1:15 AM
To: Finley, Anne Marie
Subject: Blood Safety

Chairman Christopher Shays
Subcommittee On Human Resources
& International Relations
B372 Rayburn House Office Building
Washington, DC 20515

To the Honorable Chairman Shays

I would like to take this opportunity and thank you for your efforts through the government reform and oversight committee to bring greater attention to the need for a more responsive blood safety system.

As a manager for a home care company, I am concerned with the safety of blood products for the thousands of people we serve. I am interested in obtaining a copy of the FDA's development of guidelines concerning timely patient notification and enforceable verifiable recall procedures. Many people have suffered from the consequences of improper notification and there is still poor record keeping and slow notification.

Thank you for your time and I look forward to your positive reply.

Tamara Kato
Marketing Manager

May 31, 1997

James S. Haley
1175 Hillard Road
Glendale, MO
63122-3255

Chairman Christopher Shays
Subcommittee on Human Resources
& Intergovernmental Relations

Dear Chairman Shays:

I have Hemophilia. Because blood products I have used over the years have been contaminated with disease organisms, I have suffered five (5) episodes of hepatitis and now am struggling with AIDS. The cost of treating these diseases has to be astronomical to say nothing of the human suffering they cause. I have learned that your subcommittee is studying ways to increase blood safety. Bravo! Only two days ago I saw a product recall notice of Baxter Hemofil M a product I now use. I saw this notice only because I have access to the Internet on my home computer. It is my understanding that very few hemophiliacs have such Internet access. This recall notice tells me that after all the travail of the AIDS epidemic, these manufacturers are still making mistakes and there is no requirement to notify me when such mistakes are made. New horrible diseases are coming along all the time (e.g. Creutzfeldt-Jakob Disease). The FDA needs to regulate these companies

so keep them from causing more morbidity. Research for better methods of purification of blood products should be funded. And a system of patient notification should be mandated when defective products are recalled. Your assistance on these matters is greatly needed.

Sincerely yours,
James L. Haley

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Worcester, MA

Diane W. Wara, M.D.
UCSF Medical Center
San Francisco, CA

IMMUNE DEFICIENCY FOUNDATION

The National Organization Devoted To Research And Education For The Primary Immune Deficiency Diseases

June 1, 1997

The Honorable Christopher Shayes
Chairman
Subcommittee on Human Resources
and Intergovernmental Relations
Room B-372 Rayburn Building
Washington, DC 20515-6143

Dear Congressman Shayes,

The Immune Deficiency Foundation represents the estimated 30,000 to 40,000 persons with Primary Immune Deficiency diseases throughout the United States. Primary Immune Deficiency diseases include over 50 conditions resulting from inherent defects of the immune system thereby rendering patients incapable of fighting off infection and vulnerable to both routine and rare infectious agents. Over 75% of Primary Immunodeficient patients rely on regular (e.g., monthly) infusions of fractionated blood products called immune globulins to maintain an adequate health status. Ironically, the compromised immune systems of our patients leave them especially vulnerable to blood-transmitted diseases while simultaneously relying on immune globulins to boost resistance to illness.

The Immune Deficiency Foundation has three main public policy priorities with respect to the concerns of the Subcommittee :

1) Overall safety of the nation's blood supply and the specific safety and therapeutic features of immune globulins.

2) The necessity of an effective patient notification system of product recalls and withdrawals. Routine users of blood products must be rapidly notified of potential problems with these products, including notification prior to use whenever possible.

3) Formal membership of representatives of primary immunodeficient patients on the FDA Blood Product Advisory Committee and the HHS Advisory Committee on Blood Safety and Availability.

25 W. CHESAPEAKE AVENUE • SUITE 206 • TOWSON, MD 21204 • (410) 321-6647 • 1-800-296-4433 • FAX (410) 321-9165

The Immune Deficiency Foundation will be attending the hearing on Thursday, June 5, 1997 and respectfully requests that this letter with attachments illustrating our positions on issues of interest to the Subcommittee be included in the official record and be made available to distribute at the hearing. Please feel free to have the appropriate staff contact me directly to facilitate this request. The Immune Deficiency Foundation would be very grateful if it might be included in future deliberations of the Subcommittee in order to educate Subcommittee members regarding the unique circumstances of our members and their valuable perspectives on blood safety.

Sincerely,

Thomas L. Moran
President
Immune Deficiency Foundation

IMMUNE DEFICIENCY FOUNDATION

The National Organization Devoted To Research And Education For The Primary Immune Deficiency Diseases.

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Texas Children's Hospital
Houston, TX

E. Richard Stiehm, M.D.
UCLA School of Medicine
Los Angeles, CA

John L. Sullivan, M.D.
University of Massachusetts
Medical Center
Worcester, MA

Diane W. Wara, M.D.
UCSF Medical Center
San Francisco, CA

May 15, 1997

Robert Rilley
Executive Director
International Plasma Products Industry Association
1100 New York Avenue, Suite 1080
Washington DC 20005

Dear Mr. Rilley,

On behalf of the Immune Deficiency Foundation, I am pleased to offer our response to the IPPIA's presentation to the Blood Products Advisory Committee on March 13, 1997. The IDF represents primary immunodeficient persons, the majority of whom regularly receive immunoglobulin therapy to maintain their health. IGIV infusions occur in a variety of settings and under the medical supervision of a large number of practitioners. In fact, based upon a partially-completed national survey, 1509 physicians report treating 21,338 primary immunodeficient persons, the large majority of whom are receiving regular infusions of IGIV. These preliminary results represent a fraction of the actual numbers of patients and treating physicians Furthermore, IGIV infusions occur in the home, in outpatient clinics, physicians' offices, managed care organizations, and other settings. These facts support the IPPIA's statement that some plasma-derived products have a "wider network of entities involved in the distribution process."

The IDF agrees in general that the proposal offered by IPPIA on March 13, 1997 to the Blood Products Advisory Committee is, in the words of the Association "...a constructive step in moving forward...It is not a final step; that will require that all interested parties, including the FDA, work toward the common goal: the most effective product recall system possible and a patient notification system that gets critical information to patients."

25 W. CHESAPEAKE AVENUE • SUITE 205 • TOWSON, MD 21204 • (410) 321-6647 • 1-800-296-4433 • FAX (410) 321-9165

Specifically, the IDF supports industry in obtaining effective FDA guidelines, and rules if necessary, requiring industry to include contractual requirements with distributors stipulating timely notice of recalls and withdrawals, including lot numbers, to all entities dispensing IGIV down to and including pharmacies and treating physicians. Further, IDF endorses IPPIA's recommendation that FDA require such dispensing entities to notify patients when an appropriate order has been issued from FDA. IDF believes that FDA monitoring and enforcement of such a system is essential to its success.

Although there are similar protocols currently in place for other products, a significant effort will be needed to heighten awareness and to educate pharmacies, physicians, and patients about the importance of rapid patient notification of recalls and withdrawals. All parties, including patients, must recognize the importance of the role they are being asked to assume. The IDF is willing to work with industry to help insure that the intended benefits of the proposed recommendations do indeed occur. Further, it must be recognized that the steps being proposed will take some time to implement, therefore it is incumbent upon industry and patient groups to begin immediately to improve patient notification in ways that are currently feasible and consistent with the approach you are recommending.

IDF is strongly committed to the concept that consumers of plasma derivatives have the right to be informed in a timely manner of conditions and situations which might have significant health consequences as a result of their use of these products. All parties in the manufacture, distribution, dispensing, and regulation of these products bear an ethical responsibility to insure that this occurs. The Immune Deficiency Foundation is willing to play a constructive role in assisting all parties in meeting this responsibility.

Sincerely,

Thomas L. Moran
President

cc: Marcia Boyle, Chairman, IDF Board of Trustees
Jerry Winkelstein MD, Chairman, IDF Medical Advisory Committee

FDA INFORMATIONAL MEETING
NOVEMBER 19, 1996
WITHDRAWALS AND RECALLS

STATEMENT PROVIDED BY THE IMMUNE DEFICIENCY FOUNDATION

The Immune Deficiency Foundation represents over 20,000 patients with primary immune deficiency diseases. The great majority of these patients rely on IVIG to prevent life threatening illness and enjoy a decent quality of life. Except for recently-experienced and well-documented problems with Hepatitis C, primary immune deficient patients have had a fortunate experience with these products. However, the Hepatitis C experience, recent voluntary withdrawals related to CJD, and the potential of new, as of yet unknown infectious agents has increased the level of concern of IVIG users. Our increased interest in withdrawal practices stems from the fact that fractionated plasma is a blood product. Resolving the problem in the recall and withdrawal system deserves the highest priority.

The current notification process is not working. Notifications are not reaching the end user, the patient. Simply stated, IDF would like to see a system in place where all primary immune deficient patients receiving immune globulins and health professionals involved in these treatments receive rapid notification of voluntary withdrawals and product recalls. Second, we need a system where all patients are able to record easily lot numbers for themselves or to obtain the lot numbers from the source of their infusion, whether that infusion took place in an outpatient clinic, physicians office, hospital, HMO or at home. Finally, product in the pipeline subject to recall or withdrawal needs to be immediately removed.

IDF recognizes that accomplishing these simple objectives is a difficult task best achieved by introducing innovative approaches, worked out in an atmosphere of mutual understanding.

Many suggestions have already been made and others will be made today to accomplish these goals. Some are under consideration by IDF. For example, the notification process could be improved by reaching physicians directly. IDF is currently conducting a national patient survey of immune deficient patients. We are currently working through a data-base of 17,500 physicians. and are identifying which of these physicians are following IVIG patients. Pharmacies might be required to keep records of lot numbers. Manufacturers might package fractionated blood products with peel off labels that include lot numbers. The peel off label could be used in the patient record or chart and could be kept in a patient log book. Many patients who are infused in hospitals receive *mixed* product, the manufacturers' labels could be applied to the IV bag for transfer to patient records. All such suggestions need to be given careful scrutiny and be examined for feasibility as well as effectiveness.

We would like to offer the services of IDF in attaining these goals. IDF has strong credentials. We enjoy a positive working relationship with industry. IDF is well respected in the medical and scientific communities. IDF's Medical Advisory Committee is comprised of the leading clinical immunologists from throughout the United States. IDF has sponsored numerous symposia over the years at medical society meetings on the subject of IVIG therapy.

IDF is currently completing a contract for NIH for a patient registry on Chronic Granulomatous Disease. IDF has recently begun a second patient registry for Hyper IgM Syndrome. The National Patient Survey is putting IDF in routine contact with physicians and patients.

The Immune Deficiency Foundation requests that the FDA move immediately to open a dialogue with the Immune Deficiency Foundation at the committee and staff level. IDF is offering to assist the FDA to assure an effective recall and withdrawal process.

Thank you.

BLOOD PRODUCTS ADVISORY COMMITTEE MEETING
TESTIMONY PRESENTED BY
IMMUNE DEFICIENCY FOUNDATION
MARCH 13, 1997
PATIENT NOTIFICATION

Presented by John Boyle, Ph.D.

Good Afternoon. My name is John Boyle and I live in Columbia, Maryland. Nineteen years ago, my six month old son was diagnosed as having X-linked agammaglobulinemia, a primary immune deficiency disease. Although the condition is life-threatening, and we have six weeks in intensive care units to prove it, there is effective treatment.

In 1980, two years after our son was initially diagnosed as immune deficient, my wife and I with a handful of others formed a national organization, the Immune Deficiency Foundation, to support advances in the care and treatment of these diseases. I am here today both as parent of an immune deficient patient and as a trustee of an organization dedicated to the well-being of all patients with primary immune deficiency disease.

The term "primary immune deficiency disease" is an umbrella covering approximately 70 specific diseases. Collectively, NIH estimates that primary immune deficiency diseases affect 500,000 Americans. However, most of these individuals have never been diagnosed as immune deficient. Many of these are asymptomatic. Others have symptoms, but the underlying condition of immune deficiency has not been diagnosed.

How many diagnosed cases are there? No one knows for certain. IDF has recently taken steps towards the first population estimates of these diseases. As the first step towards a national patient survey, IDF identified medical societies most likely to represent physicians who treat patients with primary immune deficiency diseases. We mailed physician screeners to approximately 17,500 specialists asking for the number of patients with primary immune deficiency diseases that they currently follow by diagnostic category. **To date, the survey has identified over 1,200 specialists who follow approximately 17,000 patients with primary immune deficiency diseases.**

This represents only a fraction of diagnosed patients. Only 15% of the specialists survey completed and returned the forms. A comparison of physicians known to treat large numbers of immune deficient patients indicates that less than half of specialists with patients are included in this estimate. We are currently conducting a second wave mailing to improve our coverage. But in the interim, **we would consider an estimate of 35,000 patients** treated by these specialists (i.e., about twice the

number reported by the first 15%) **as a conservative estimate of the population.**

In addition, many patients with primary immune deficiency diseases may be treated exclusively by primary care physicians. This is particularly true for patients whose condition can be maintained by gammaglobulin and antibiotics. In an unrelated national survey of primary care physicians, 12% of a national sample of primary care physicians reported seeing patients with a family history of primary immune deficiency diseases. This translates into a population projection of approximately 25,200 primary care physicians who follow patients with primary immune deficiency (or have a family history of the condition).

In total, several thousand specialists and tens of thousands primary care physicians are treating patients with primary immune deficiency diseases.

The vast majority of these patients receive intravenous gammaglobulin (IVIG) as treatment for their disorder. In an ongoing national survey of patients with primary immune deficiency diseases, IDF **found that over 70% had been treated with IVIG** for their condition. If we make a conservative assumption that the total number of patients with primary immune deficiency diseases is in the range of 50,000, then approximately **35,000 are IVIG users.** This makes treatment of patients with primary immune deficiency disease the **primary FDA approved application of IVIG.**

In addition to the number of immune deficient patients using IVIG, there are three other characteristics of this patient population that bear directly on your considerations. First, although immune deficiency may be a life threatening condition when untreated, as a result of treatment with gammaglobulin this is a relative healthy population. **Nearly seven out of ten (68%) patients with primary immune deficiency disease classified their current health as good, very good or excellent. Only a quarter have spent a night in the hospital in the past year.**

In many ways, this is a model population whose members, despite a serious health condition, have a good chance to live normal, healthy lives if they have access to safe treatment.

Access to treatment, as well as safety of treatment, has to be considered. The cost of treatment is high. **Nearly half of this population (48%) have encountered health insurance limitations or discrimination because of their condition.** Over half have had to sell cars, homes, stocks, use their savings or borrow to pay for their treatment. **As a result of the cost or lack of insurance coverage, we find non-compliance with medically indicated treatment, including failure to take IVIG in the amounts and frequency prescribed, to quite high in this population.** This, of course, is a tragedy because it is the medical treatment that can keep this a healthy population.

Now, against this backdrop, let us consider patient notification of withdrawals and recalls. The present system depends entirely on pharmacies to remove recalled products from the system in a timely fashion. We have a lot of anecdotal evidence that this does not always occur. We know that in at least some instances, major medical centers did not receive recall notices for the recalled products. Moreover, lot numbers were not being properly recorded to permit patient identification. Unfortunately, we do not know whether these reports reflect isolated problems or systemic problems for the current product recall system. To the best of our knowledge, there is no evidence about how

well the current system, upon which the safety of tens of thousands of patients depends, is working. If the current recall system is to be preserved, we urgently need an independent test of the speed and completeness of the recall system. Such a test would identify weaknesses in the current system that might be remedied. It would also answer very legitimate patient concerns about the effectiveness of the system in protecting the health of patients.

No patient will accept having received an unsafe product after it has been recalled. If the current system does not assure virtually immediate and universal patient protection from recalled products, then it must be supplemented or replaced. A supplemental system would emphasize prescribing physicians as the second line of defense, and infusing patients as the last line of defense, against unsafe products. The total number of patients and physicians involved in IVIG, in addition to the absence of any enumeration of these populations, makes universal direct notification impractical at the present time.

Nonetheless, an improved physician and patient notification system is possible and potentially very beneficial. As indicated earlier, the Immune Deficiency Foundation has already identified 1,200 physicians who treat nearly 17,000 immune deficient patients. We are continuing our efforts to identify the vast majority of specialists who treat these patients. A supplemental notification system based on the 2,000-3,000 specialists who see the largest number of IVIG patients would provide a significant improvement over the present system in which prescribing physicians are not necessarily notified by pharmacies of recalls affecting their patients. The notified physician provides a check on pharmacy notification and action on the product recall.

The Immune Deficiency Foundation has already created several disease registries for immune deficient patients. As a result of its current patient survey, IDF is developing a voluntary listing of thousands of immune deficient patients. We do not expect our patient listings to cover the entire patient population. Nonetheless, a large but incomplete listing for patient notification could provide some immediate benefits for product safety. Prescribing physicians frequently do not dispense the product, which may be administered by a nurse, home health care technician, or the patient. If patients are informed of product recalls, and if patients can check these lot numbers against the products they are receiving, then failures in product recall can be identified and stopped before they hurt the patient. Moreover, if patients can record lot numbers, then we can identify who received tainted products distributed before the recall notice. This will facilitate early testing and treatment for affected patients and peace of mind for unaffected patients. In addition, patient monitoring provides an ongoing system of quality control over the pharmacy based recall system.

The success of a supplemental system of patient notification of product recall requires more than making recall information available to patients. First, product information needs to be displayed in a uniform fashion on bottles and bags that patients see so that they can record the lot numbers and compare them to current recalls. It is not sufficient to put them on boxes that are discarded before they reach the patient. Second, health professionals would have to accept patient review of the product before infusion as a necessary and appropriate behavior. Third, patients would have to be trained how to check their product against current recalls and record product information for future recalls. Finally, a means to communicate recall information to patients in a timely fashion would have to be established.

These steps in improving patient notification of product recalls could safe lives and reduce unnecessary product related injuries. It would also help to reassure a patient population whose faith in the safety of their product and the government regulation of product safety has been shaken. As we presented earlier, immune deficient patients represent a potentially healthy population if they can be assured access to an adequate supply of a safe product. It is essential that efforts be redoubled to avert avoidable tragedies in the future.

The Immune Deficiency Foundation, which represents the tens of thousands of patients with primary immune deficiency diseases, would be happy to work with this committee, the FDA and any other appropriate organizations to achieve this goal.

June 1, 1997

Chairman Christopher Shays Subcommittee on
Human Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington, D.C. 20515
Attn: Ms. Ann Marie Finley

Dear Chairman Shays:

I want to thank you for your support and concern for the need of greater involvement by the government regarding the area of blood safety. As a hemophiliac, and therefore, very dependant on blood products, it is of great concern to both me and my family that the blood pools be carefully analyzed to make every effort to prevent repeating the devastating HIV tragedy of the 1980's.

I am all to frequently advised through newsletters from concerned groups regarding another recall of product, or product being held for further testing due to believed contamination during the manufacturing process of the clotting factor concentrates used by me. I was very recently informed that a lot of factor was infected with Creutzfeldt-Jakob disease. This lot was held for review but never specifically identified. It was determined that the consumer did not need to be made aware of this potential risk and was released to the general population. This is an outrage considering the past performance contaminated product has had on people with hemophilia.

There will be will be new threats to the country's blood supply every day. There will continue to be errors made in the processing and handling of blood and blood products. The FDA must do all that it can to insure that the handling and processing of blood and blood products be as safe as possible. If a potential contamination occurs, it must notify all potential user groups and remove the product from the market as soon as possible. A clear recall and notification system must be created.

Please do all that you can so history cannot repeat itself.

Than you,

Barbara & Carl Piercey

Mr. and Mrs. Sidney F. Lessner
861 Knollwood Terrace
Westfield, New Jersey 07090
(908) 233-0865

June 1, 1997

Chairman Christopher Shays
Attn: Anne Marie Finley
Subcommittee on Human Resources
& International Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Shays:

My wife and I would like to thank you for all of your efforts through the Government Reform and Oversight Committee in helping with the need to provide a more stringent and responsive blood safety system.

As grandparents of an 18 month old grandson with hemophilia, the importance of blood safety cannot be minimized and is of utmost concern for our family. As the events of the 1980s have demonstrated together with the extremely high frequency of recent incidents of blood contamination, we cannot stress the importance of clear guidelines to direct FDA enforcement of blood product withdrawals and recalls and for the establishment of TIMELY patient notification system.

The safety of the blood supply is of paramount importance as emerging threats (such as Creutzfeldt-Jakob disease (CJD)) and new strains of hepatitis continue to afflict the hemophilia community and other users of blood and blood products.

In closing, enhanced enforcement, prompt patient notification, enforced recall procedures and intensified safety practice are all obligations to protect the safety of the blood supply for all Americans.

Thank you again for all your endeavors.

Sincerely,

Sidney F. Lessner

Faxed 6/2/97 (202-225-2382)
cc: Ms. Elena Bostick
Executive Director, HANJ

Mr. and Mrs. Thomas Brennan
43 Brandywine Drive
Florham Park, New Jersey
(201) 765-0335

June 1, 1997

Chairman Christopher Shays
Attn: Anne Marie Finley
Subcommittee on Human Resources
& International Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Shays:

My husband and I would like to thank you for all of your efforts through the Government Reform and Oversight Committee in helping with the need to provide a more stringent and responsive blood safety system.

As relatives of two 18 month old nephews with hemophilia, the importance of blood safety cannot be minimized and is of utmost concern for our family. As the events of the 1980s have demonstrated together with the extremely high frequency of recent incidents of blood contamination, we cannot stress the importance of clear guidelines to direct FDA enforcement of blood product withdrawals and recalls and for the establishment of TIMELY patient notification system.

The safety of the blood supply is of paramount importance as emerging threats (such as Creutzfeldt-Jakob disease (CJD)) and new strains of hepatitis continue to afflict the hemophilia community and other users of blood and blood products.

In closing, enhanced enforcement, prompt patient notification, enforced recall procedures and intensified safety practice are all obligations to protect the safety of the blood supply for all Americans.

Thank you again for all your endeavors.

Sincerely,

Debra Brennan

Debra Brennan

Faxed 6/2/97 (202-225-2382)
cc: Ms. Elena Bostick
Executive Director, HANJ

Mr. and Mrs. Richard D. Lessner
43 Fair Hill Road
Westfield, New Jersey 07090
(908) 654-7849

June 1, 1997

Chairman Christopher Shays
Attn: Anne Marie Finley
Subcommittee on Human Resources
& International Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Shays:

My wife and I would like to thank you for all of your efforts through the Government Reform and Oversight Committee in helping with the need to provide a more stringent and responsive blood safety system.

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In closing, enhanced enforcement, prompt patient notification, enforced recall procedures and intensified safety practice are all obligations to protect the safety of the blood supply for all Americans.

Thank you again for all your endeavors.

Sincerely,

Richard D. Lessner

Faxed 6/2/97 (202-225-2382)
cc: Ms. Elena Bostick
Executive Director, HANJ

Mr. and Mrs. Robert W. Lessner
3 Radley Court
Westfield, New Jersey 07090
(908) 233-0157

June 1, 1997

Chairman Christopher Shays
Attn: Anne Marie Finley
Subcommittee on Human Resources
& International Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Shays:

We would like to thank you for all of your efforts through the Government Reform and Oversight Committee in helping with the need to provide a more stringent and responsive blood safety system.

As parents of an 18 month old son with hemophilia, the importance of blood safety cannot be minimized and is of utmost concern for us. As the events of the 1980s have demonstrated together with the extremely high frequency of recent incidents of blood contamination, we cannot stress the importance of clear guidelines to direct FDA enforcement of blood product withdrawals and recalls and for the establishment of TIMELY patient notification system.

The safety of the blood supply is of paramount importance as emerging threats (such as Creutzfeldt-Jakob disease (CJD)) and new strains of hepatitis continue to afflict the hemophilia community and other users of blood and blood products.

In closing, enhanced enforcement, prompt patient notification, enforced recall procedures and intensified safety practice are all obligations to protect the safety of the blood supply for all Americans.

Thank you again for all your endeavors.

Sincerely,

Robert W. Lessner

Michelle M. Lessner

Faxed 6/2/97 (202-225-2382)
cc: Ms. Elena Bostick
Executive Director, HANJ

Mrs. Mildred Bradley
91 Hillyer Streeet
Orange, New Jersey 07050
(201) 414-9868

June 1, 1997

Chairman Christopher Shays
Attn: Anne Marie Finley
Subcommittee on Human Resources
& International Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Shays:

I would like to thank you for all of your efforts through the Government Reform and Oversight Committee in helping with the need to provide a more stringent and responsive blood safety system.

As the grandmother of two 18 month old grandsons with hemophilia, the importance of blood safety cannot be minimized and is of utmost concern for our family. As the events of the 1980s have demonstrated together with the extremely high frequency of recent incidents of blood contamination, we cannot stress the importance of clear guidelines to direct FDA enforcement of blood product withdrawals and recalls and for the establishment of TIMELY patient notification system.

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In closing, enhanced enforcement, prompt patient notification, enforced recall procedures and intensified safety practice are all obligations to protect the safety of the blood supply for all Americans.

Thank you again for all your endeavors.

Sincerely,

Mildred Bradley

Mildred Bradley

Faxed 6/2/97 (202-225-2382)
cc: Ms. Elena Bostick
Executive Director, HANJ

Finley, Anne Marie

From: Noreen Benson[SMTP:NoreenB@msn.com]
Sent: Sunday, June 01, 1997 11:21 PM
To: Finley, Anne Marie
Subject: Blood Safety Concerns

Chairman Christopher Shays
Subcommittee On Human resources
& International Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Shays:

Thank you for your efforts through the government reform and oversight committee to bring greater attention to the need for a more responsive blood safety system.

Blood safety and a strong FDA are of great importance to my family. The FDA's development of guidelines concerning timely patient notification and enforceable verifiable recall procedures are critical to anyone in need of a blood product or blood transfusion. I understand that this will directly affect two out three people at some point in their lives. It affects my family daily because three of my sons were born with hemophilia. Two years ago my son, Patrick, died from hemophilia-related AIDS. Please help protect my two remaining sons and the thousands of people with hemophilia. Please help protect every hospital patient and caregiver exposed to blood and blood products.

We are looking to you for enhanced enforcement of FDA regulations, a more responsive, timely and required patient notification system, and development of better viral inactivation methods for recombinant factors to prevent the recurrence of the HIV tragedy of the 1980's and to protect the safety of this country's blood supply.

Thank you again for your help with this issue.

Noreen Benson
117 Hickory Highlands Drive
Antioch, TN 37013
NoreenB@msn.com

Finley, Anne Marie

From: Noreen Benson[SMTP:NoreenB@msn.com]
Sent: Sunday, June 01, 1997 11:21 PM
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Thank you again for your help with this issue.

Noreen Benson
117 Hickory Highlands Drive
Antioch, TN 37013
NoreenB@msn.com

Michael J. Elhardt III
2827 W. Castle Road
Citrus Springs, Fl. 34433-3414
(352)465-1380
EndlsQuest@aol.com

fax (202-225-2382)
Attention of Anne Marie Finley

June 2, 1997

Chairman Christopher Shays
Subcommittee on Human Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Thank you for your efforts through the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system.

As a severe hemophiliac, I infuse blood products intravenously (Factor VIII concentrate) over 100 times a year. Injecting Factor every three days and having received HIV and Hepatitis C from those life-sustaining infusions, I cannot stress enough the importance of blood safety. Each dose is a constant reminder that the risks of using the product is uncertain at best.

The AIDS-tainted blood problems of the last decade and the repeated number of contaminated blood products (ranging from the emergence of new viruses to improperly heat-treated concentrate to cracked vials and poor manufacturing standards), make it frightenly clear that a strict guideline must be established to direct FDA enforcement of blood product withdrawal and recalls, as well as the implementation of a timely patient notification system.

As it stands now, there is no requirement that the Blood Fractionators inform blood product users that there is a problem or recall of their product. Only through the dedication of support organizations and treatment centers do the patients find out about these potentially deadly dangers. Case in point, I only found out that I had received vials of AIDS-contaminated Factor VIII from a NHF (National Hemophilia Foundation) bulletin -- months after I had injected the poisoned product into my body. No warning from the manufacturer. No word that there was even a threat. Had there been an FDA requirement to immediately

inform all blood product users, incidents of AIDS & Hepatitis could have been reduced.

While blood safety is a shared responsibility, the ultimate obligation for protecting America's blood supply should fall to the FDA -- just as all other food and drug products are. If a Tylenol product is found to be contaminated, the recall notification is immediate, highly publicized, and a serious threat. But when thousands of Factor VIII bottles contain AIDS, the news drips out, suppressed by the Fractionators who can conveniently claim no responsibility to inform their customers, finally arriving to a select few months too late.

And while the FDA relies on the Blood Product Advisory Committee in formulating blood safety policy, the Committee often continues to address blood safety issues using the same framework of product availability versus cost -- the poor policy that led to many of the disastrous decisions of the 1980s. To improve on this, one simple suggestion is to increase the number of blood product consumer members represented to help offset the powerful blood industry's stance.

Another problem with the current blood supply system is the large pools of plasma that are used to make blood products such as the Factor VIII concentrate that I use. One lot of Factor VIII could be made from the donated blood of thousands of people. Obviously, only one person with AIDS would be needed to infect the whole batch. Blood screening needs to be tighter, and the sources of donated blood must be carefully looked at as well. In the past, prisoners, drug addicts and anyone looking for a few bucks was allowed to donate blood. This intolerable type of action allowed by the FDA was, and continues to be a scary lack of judgment and policy that has caused disease transmissions and death for thousands of Americans.

With the onset of CDJ, new Hepatitis strains, and the potential of unknown or mutant viruses, the safety of the blood supply has to be one of our nation's biggest concerns. One bright spot has been the advancements in Recombinant Factors which has reduced the potential exposure, but still requires human albumin -- and should be no doubt that the possibility of a viral threat still exists.

Limitation of plasma pools, stricter procedural and manufacturing enforcement, a more responsive and direct patient notification system, greater incentives for the development of better viral inactivation methods, and the increased emphasis on safer products (such as recombinant factors) are needed to prevent another HIV tragedy and to protect the safety of the blood supply for all Americans.

Sincerely,

Michael J. Elhardt III

Finley, Anne Marie

From: yoda1@capecod.net[SMTP:yoda1@capecod.net]
Sent: Monday, June 02, 1997 10:58 PM
To: Finley, Anne Marie
Subject: Blood Safety

Chairman Christopher Shays
Subcommittee on human resources
& international relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Mr. Chairman

First of all, I know that I speak for the whole community when I say that we thank you for your efforts through the goverment reform and oversight committee to bring A greater attention to the need for A more responsive blood safety system.
As A hemophiliac ,I worry constantly every time I infuse because of what has happened to our community.
I infused with AHF today and as I did there was A recall brought forth telling me that there was A temp. deaviation of lot number of AHF that had been sent through an agent of baxter Hyland ,so if the agent had it, you can understand the amount of time it took for Baxter Hyland to notice this problem and react
to it.
Mr. Chairmen you and I know that the system is in place but it has to be enforced in A timely Manner.
patients and agents have to be responsible enough to prevent another virus out break such as the one that has devestated this community in the past.
Thanking you in advance for your support of this and I look forward to your response

Peter E. hussey
Post Office Box 95,
Buzzards Bay, Ma 02532

415 N. Cedar Street
Williamston, MI 48895
June 2, 1997

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources & Intergovernmental Relations
House Government Reform and Oversight Committee
U.S. House of Representatives
B372 Rayburn House Office Building
Washington, D.C. 20515

RE: Hearing on guidelines for recall procedures of contaminated blood products

Dear Representative Shays:

I am writing on behalf of approximately 1,600 persons in the State of Michigan with bleeding disorders, and their families, to request your continued vigilance in protecting the blood supply, upon which we depend for our lives and well-being. As a man with severe hemophilia, I can also personally speak to the problem, having been exposed to HIV, Hepatitis B and Hepatitis C through my prescribed Anti-Hemophilic Factor.

People with hemophilia and related disorders require intravenous adminstration of medicine derived from human blood to control life-threatening and crippling bleeding. When infectious agents enter the blood supply, as happened when HIV infected 80 percent of severe hemophiliacs in the 1980s, the results can obviously be catastrophic. AIDS has already killed several thousand American hemophiliacs--virtually an entire generation. Thousands more have been infected by hepatitis, often creating serious medical complications.

While better donor screening and viral inactivation processes have lessened the risk of AIDS to people with hemophilia over the past decade, several other serious contaminants continue to threaten the bleeding disorder community. Disease-causing entities, including several types of viral hepatitis, Parvovirus B19, and Creutzfeld-Jakob Disease (the human version of Mad Cow Disease), have been detected or suspected present in on-shelf and already-purchased Anti-Hemophilic Factor, prompting several recalls over the past several years. Other incidents such as the FDA's recent mandatory closure of a Anti-Hemophilic Factor manufacturing plant due to unsanitary conditions, make consumers justifiably nervous about the safety of the medications we must take to stay alive.

Unfortunately, the mechanism for reporting these problems to end-users, people with hemophilia, is notoriously slow and very inconsistent. The FDA does not adequately oversee the manufacture of blood-derived products in our opinion, nor does it mandate speedy recalls, relying on the corporations to self-police with potentially tragic consequences. The manufacturers do not notify consumers directly but rather send notices to the many retailers of their products, companies

that may delay consumer notification due to fear of customer panic and potential loss of sales. More ethical companies attempt to notify their customers by mail or phone, and/or notify prescribing physicians and non-profit advocacy groups so recall information can be passed along by them, but without any mechanism for reimbursing the costs of such an operation.

This practice of "passing the buck" places a tremendous burden on non-profit agencies such as the Hemophilia Foundation of Michigan. Given the high cost of staff time, telephone and mailing, many smaller chapters around the country simply cannot afford to provide this service for the profit-making companies. The Hemophilia Foundation of Michigan (HFM), a state-wide United Way agency which I serve as board president, is one of the most capable agencies serving hemophiliacs in our country. HFM has chosen to provide immediate notice by first class mail, on our World Wide Web page, and via an automated 800-number telephone recording to help prevent Michigan members from falling into harm's way. Unfortunately, given the urgency and unpredictability of notices, the process is often very disruptive and costly, but is essential with the potential cost of life or health if information is not quickly shared. We believe some of these costs should rightfully be borne by the groups who profit from sale of contaminated products, so that less well-funded groups can help with the notification process. Better yet, manufacture and sale of contaminated, life-threatening products should be prevented in the first place by even more careful donor screening, production methods that render all pathogens inactive, and development of technology that does not use pooled human plasma.

The lengthy delays or failure of notification created by the present cumbersome and slip-shod process could contribute to another catastrophic disease outbreak, such as the continuing AIDS tragedy. Obviously mechanisms for enforcing speedy notification of recalls and of better protecting the blood supply in general need to be set up, and we would encourage you not to depend on the industry to perform an adequate job given their track record.

I am grateful for the opportunity to advocate for persons with bleeding disorders and am pleased that your committee is presently working on this issue. Please feel free to contact me or the Hemophilia Foundation of Michigan if we can help your committee's decision-making or creation of blood safety policy.

Yours very truly,

Lynn R. Allen

Lynn R. Allen, MA, CSW
President, Board of Directors
Hemophilia Foundation of Michigan

Finley, Anne Marie

From: Michelle Bloodworth[SMTP:shelby@ethos.wustl.edu]
Sent: Monday, June 02, 1997 10:48 AM
To: Finley, Anne Marie
Subject: Blood Product Recalls

Chairman Christopher Shays
Subcommittee on Human Resources & Intergovernmental Relations B372
Rayburn House Office Building
Washington , D.C. 20515

Dear Chairman Shays,

Thank you for your efforts through the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system. As the mother of a 16 month old son with hemophilia who must regularly receive blood products, blood safety is of great importance to me and my family.

The events of the 1980s and the continued high frequency of recent incidents of blood products contamination demonstrate the urgency for clear guidelines to direct FDA enforcement of blood product withdrawal and recalls and for the establishment of a timely patient notification system.

While blood safety is a shared responsibility, FDA has the ultimate obligation for protecting our nation's blood supply to ensure its safety for all Americans. The FDA currently relies on an informal system in communicating with blood and blood product manufacturers about enforcement of its regulations.

The FDA also relies on the Blood Product Advisory Committee in formulating blood safety policy. While consumer representation on the committee has increased in the past few years, the Committee often continues to address blood safety issues using the same framework - product availability versus cost - used to make many of the detrimental decisions of the 1980s.

The safety of the blood supply is of paramount importance as emerging threats such as Creutzfeldt-Jakob disease and new strains of hepatitis continue to plague the hemophilia community and other users of blood and blood products.

Enhanced enforcement, a more responsive patient notification system, and greater incentives for the development of better viral inactivation methods as well as for recombinant factors are all needed to prevent the recurrence of the HIV tragedy of the 1980s and to protect the safety of the blood supply for all Americans.

Sincerely,

Michelle R. Bloodworth, M. A.
Project Coordinator
Collaborative Study On the Genetics of Alcoholism
Washington University School of Medicine
4625 Lindell, 2nd Floor
St. Louis, MO 63108
(314)454-3604
shelby@ethos.wustl.edu

Joseph C Caronna
623 Frederick Street
Ridgewood, NJ, 07460
(201) 251-7588

June 2, 1997

Chairman Shays Subcommittee on Human
Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington, D.C 20515

Dear Chairman Shays,

As a parent of a child with hemophilia, I would like to thank you for your efforts in bringing the much needed attention to the issue of establishing a more responsive blood safety system.

My son Alexander is a beautiful 2 ½ year old who was diagnosed with hemophilia a little over a year ago. Since that time, my wife and I have thrown ourselves into becoming as knowledgeable as possible in the area of hemophilia. We have read everything we could get our hands on relating to this issue, as well as met and communicated with other families who must also live with this disease daily. Among all of the critical hemophilia related issues, the single most concerning one to us would be the safety of the blood product.

As you are well aware, the history of a clean and safe blood supply has not been a good one. Even today, the continued high frequency of contaminated blood incidences clearly demonstrates the urgent need for clear and concise guidelines. These guidelines must direct the FDA enforcement of blood product withdrawals and recalls, as well as a need to establish a patient notification system in a timely manner. ***We must not forget that the ultimate responsibility of the FDA is to protecting the nation's blood supply.***

Yes there have been wonderful improvements made, but much work still needs to be done. When we, as parents, hear startling statistics like "according to the GAO, eight of every 10,000 units of blood pose a potentially serious health risk to the recipient, including allergic reaction, and bacterial or viral infection," we can clearly see the need for improvements in the inspection of blood facilities and methods used to notify the community of these potentially unsafe products.

Please, lets not repeat the catastrophic events of the early 1980's.

Sincerely,
Joseph C. Caronna

The Hemophilia Federation
918 Pennsylvania Avenue SE
Washington, D.C. 20003
202-547-9097 FAX 202-543-9056 1-800-230-9797
Advocacy for Persons with Clotting Disorders and their Families

June 2, 1997

Chairman Christopher Shays
Subcommittee on Human Resources &
Intergovernmental Relations
B372 Rayburn House Office Bldg.
Washington, D.C. 20515

Dear Chairman Shays:

Please accept our appreciation and thanks for your efforts and the work of the subcommittee members in bringing attention to the inadequacies of this nation's blood product withdrawal and recall policy. Equally important is the unsystematic and unpredictable policies that guide patient notification. Persons with hemophilia consume large quantities of blood products. And we have suffered irreparable harm as a result of their medical use with iatrogenic transmissions of HIV and hepatitis. It is clear that some degree of this harm was a result of this regulatory and industry failure to conduct effective blood product withdrawals, recalls, and nonexistent consumer notification procedures. Although guidelines and policies established on July 17, 1978 (21 FR 26202-26220) were promulgated to promote safe and effective blood product withdrawals and recalls and to require timely consumer notification, they were simply not enforced nor followed. Persons with hemophilia have suffered its aftermath. Even now some twenty-five years later we are still experiencing woefully inadequate and untimely recalls with little or no improvement in the procedures or regulatory requirements for systematic patient notification. It's shameful to have historically tolerated this degree of regulatory impotence but even more so to allow its continued practice as regulatory policy or "industry standard."

We concur with the FDA's position that it's the manufacturer's responsibility to finance and conduct product withdrawals and recalls but the FDA must not abdicate its regulatory enforcement responsibilities. It must remain accountable and vigilant to ensure industry compliance and to seek severe penalties against manufacturers who violate recall policies or do not adopt notification procedures that seek to maximize consumer safety. In order to accomplish this task the FDA must promulgate clear and unmistakable regulatory language such that blood products manufacturers cannot claim ambiguity in them and, as a result, invoke selective compliance. Accountability has been conspicuously missing from manufacturers' business practice and will not become part of it without strict regulation and

enforcement. For example, industry currently interprets the term consignee to mean only its direct customers, i.e., wholesalers, hospitals, pharmacies, and homecare companies, for purposes of product withdrawal, recall, and notification. But according to recall enforcement policy, 21 CFR Chap.1 Part 7, and Mary Pendergast, FDA Deputy Commissioner, they define consignees with respect to these issues as including all entities in the chain of distribution including the end user or consumer.

The safety of the blood supply must never again take a subordinate position to corporate profit or industry's self-interest to delay or prevent consumer notification for fear of potential litigation. Other blood safety issues such as pool size and continued plasma collection from paid donors will need to be discussed in the future and, if necessary, changes made in regulatory policies consistent with promoting the general public health and the health of regular users of this nation's blood and blood products supply. An example of the FDA moving in the right direction is the cleansing of its Blood Products Advisory Committee of members with clear conflict of interest and opening some seats to members of communities that regularly use blood and blood products. Consumers now have a seat at the table where important policy decisions are being made. This consumer influence will begin to realign the historic and prevailing framework of decision making from a function of cost versus product availability to one that values human life.

The regulation of the blood and blood products industry has historically relied on an informal cordial consensus building relationship. I am not aware of any other regulated industry where the FDA regulates by inference and as a result of that very industry's approval or consensus. It is clear from the continued frequency of blood product withdrawals and recalls that regulation of this industry must be more formal and demonstrable.

Enhanced enforcement and a more responsive patient notification system will help to save lives that were once lost in its absence. We support wholeheartedly the seriousness in which the subcommittee is taking this issue.

Respectfully yours,

Terry Rice,
Vice-president

June 2, 1997

Chairman Christopher Shays
Subcommittee on Human Resources &
Intergovernmental Relations
B372 Rayburn House Office Bldg.
Washington, D.C. 20515

Richard D. Darian II
6300 Lindenwood Ct, # 4
St. Louis, Missouri 63109

Dear Chairman Shays:

I would like to start by thanking you for your efforts in attaining a more responsive and responsible blood safety system.

As the sole surviving hemophiliac member in my family no one knows the importance of a safe blood supply more than I. As a result of inaction and a lack of safeguards (allowing the blood industry to self-regulate) I have watched 4 hemophiliac family members die of AIDs, received through tainted blood products. As well, I have watched all of my childhood hemophiliac friends die through the years-13 in all. Out of 18 hemophiliacs I am the sole survivor and one day AIDS will kill me too.

It is at the funerals of my friends and family were the real loss occurs. We can not allow the practice of product availability versus cost to determine the framework for blood safety. With so many hemophiliacs and even the nation as a whole dependant upon a safe blood supply the FDA must have clear and concise policy and procedures for ensuring a safe blood supply.

Thank you.

Sincerely,

Richard D. Darian II

June 2, 1997

Chairman Christopher Shays
Committee on Government Reform
Subcommittee on Human Resources
United States House of Representatives
Washington, D.C. 20516

Dear Congressman Shays;

Every week, on two different days, I open my refrigerator door and pause with greater purpose than any of the other several dozen times I may open it in any given week. My twelve year old son was not born in any given week or month. He was born the first week in March, 1985. Five months later he was diagnosed with severe factor eight deficiency following a traumatic hemorrhage in his arm. Immediately he received the first, of what is now over 1200, infusion of a blood product.

We currently infuse our son preventively, twice a week, with a recombinant derived factor product stored in our refrigerator. This prophylactic treatment regimen enables him to engage in the normal activity of an adolescent. I am grateful every time I remove the product from our refrigerator for science, for technology, for advocacy, and for his life.

In the early morning hours in the hospital after we were given our infant's diagnosis, we were told that he could not have been born at a better time. We have been painfully reminded of the significance of the March 1985 FDA mandate for heat treatment of all blood products over the twelve years since. I have now lost track of the numbers of funerals I have attended, embracing the mothers of young boys and men who happened to be born before March 1985. Each time I have found it incomprehensible to imagine *how* I would cope in their position.

The level of trust and confidence that we developed, early, in accessing the quality of care that our son requires was a direct result of my familiarity and professional training in health care. We developed similar confidence in the technology of the products we were giving our son through my husband's scientific background. When our son was diagnosed with chronic Hepatitis C at the age of eight, we were able to understand how the exposure occurred and resolved to stop using human blood derived products as soon as the FDA approved recombinant technology products.

My recent several months experience in communicating and advocating the needs of the bleeding disorders community on a national level, as the chair of the Advocacy Committee of the National Hemophilia Foundation, has afforded me knowledge, understanding and insight. It has never been more clear in my mind, both personally and professionally, of the role that the federal government must play through direct FDA enforcement and regulation of a blood safety system. For the welfare of all Americans, safety *must* be

June 2, 1997

Chairman Christopher Shays
Committee on Government Reform
Subcommittee on Human Resources
United States House of Representatives
Washington, D.C. 20516

Dear Congressman Shays;

Every week, on two different days, I open my refrigerator door and pause with greater purpose than any of the other several dozen times I may open it in any given week. My twelve year old son was not born in any given week or month. He was born the first week in March, 1985. Five months later he was diagnosed with severe factor eight deficiency following a traumatic hemorrhage in his arm. Immediately he received the first, of what is now over 1200, infusion of a blood product.

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emphasized first, over cost, in the complex monitoring of blood and blood products. Patients, in turn, must be notified as early as possible regarding potential adverse effects in order to make their own informed and responsible treatment decision. The right and responsibility to choose to temporarily set aside a product on our refrigerator shelf *must be ours.*

On behalf of the bleeding disorders community and the National Hemophilia Foundation, I would like to express my sincere appreciation of your long-standing interest and sensitivity of national blood safety issues and policy. The energy and dedication of your staff member, Anne Marie Finley, has provided our community great hope and opportunity. Please accept my best regards and support for the hearing on June 5th.

Sincerely Yours,

Katherine M. Muir

Katherine M. Muir
Westford, Massachusetts

100 Seventh Street
Harrison, NJ 07029
June 2, 1997

Chairman Christopher Shays
Subcommittee on Human Resources & Intergovernmental Relations
B 372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Shays:

Thank you for your efforts through the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system. As the widow of a hemophiliac who died at the age of 43 due to the infusion of contaminated blood products, blood safety is of great importance to me and my family.

My husband was a wonderful man, loved by everyone who met him. He was a dedicated Federal employee, who worked hard to improve the operations of the Division he worked for, even assisting his co-workers with automation problems from his death bed. He rarely gave in to the tremendous pain he suffered, but came in to work as often as possible. "Flexiplace" (work-at-home) was a thing of the future at that time, and the Agency was not willing to allow home access to it's automation systems as a Reasonable Accommodation for security reasons.

Mike suffered excruciating pain from the "normal" bleeding into the joints which causes arthritis in most hemophiliacs, as well as unfathomable pain from the fluid retention caused by the chronic liver disease resulting from the hepatitis (A, B, and C) which he was exposed to from the contaminated clotting factor he received.

But the worst pain of all, was the painful knowledge that we could never have children, that we wouldn't be together to enjoy our retirements, that he wouldn't see his darling little nephews grow up. Because, you see, the blood products were also contaminated with the HIV/AIDS virus. Mike and I knew, for six of the twelve years that we were married, that he was slowly, painfully, one infection at a time, dying. During the last two years of his life, Mike was hospitalized approximately 20 times for anywhere from 3 days to 5 weeks.

Can you even imagine the horror of watching the person you love die while you must keep up with his positive attitude, his cheerful smile, and his demand that the truth of his condition be kept secret from everyone, friend and family alike, for fear of being ostracized ? That was the life I led, but being with him was so much better, even under those circumstances, than being left without him. As horrific as that scenario is, there is one

even more agonizing - being a parent, going through the same situation with your child.

The events of the 1980s in the blood industry (and if you are not familiar with them, I highly recommend that you read Judith Reitman's book BAD BLOOD: The Crisis in the American Red Cross and Elaine DePrince's book Cry Bloody Murder) should have been enough to guarantee that the industry would take every conceivable precaution to ensure product safety in the 1990s. But it does not appear to be happening. The continued high frequency of incidents of blood product contamination and recall demonstrate the urgency for clear guidelines - no - **mandates** - to direct FDA enforcement of blood product withdrawal and for the establishment of a timely patient notification system.

I also remain concerned about the size of the plasma pools used to manufacture the clotting factor concentrates used by hemophiliacs. Recently, I sat at a table with four mothers of hemophiliacs. Three of them had already buried a total of five sons among them. One of those three has a teenage son who is being treated for AIDS related illnesses now (his 2 younger brothers have already died). The fourth was a "new mom". Her 16 month old son has been diagnosed with hemophilia. We learned that night of a decision by BAXTER not to recall, or issue an informational warning that clotting factor they had on the market had been exposed to Creutzfeld-Jakob Disease (CJD) in the manufacturing process. CJD is a rare, but deadly brain disease (similar to Mad Cow Disease) that can take up to 15 - 20 years to be detected after exposure. Inconceivably, the FDA **supported** BAXTER's decision!!!

All I could think of that night was "Don't they ever learn? When will they stop jeopardizing lives? Will this new mother have to live in fear that her son will meet the fate of these mother's sons?" I am incensed !! I am enraged !! **It can't happen again !!**

The safety of the blood supply is the most important protection the FDA can give to American consumers as emerging threats such as CJD and new strains of hepatitis continue to plague the hemophilia community and other users of blood and blood products. It is time for the country to adopt a zero-tolerance policy for any known or suspected contaminants in blood products. It is time to take the FDA's responsibility seriously and direct them to take enforcement action to the fullest extent. While blood safety is a shared responsibility, the FDA has the ultimate obligation for protecting our nation's blood supply to ensure its safety for all Americans. The FDA currently relies on an informal system in communicating with blood and blood product manufacturers about enforcement of its regulations. This must be changed.

One of the sources the FDA relies on to formulate blood safety policy is the Blood Product Advisory Committee. While this committee has increased its consumer representation in recent

years, it often continues to address blood safety issues within the old frame work of product availability versus cost. Even a casual reading of Reitman's BAD BLOOD will lead the most disinterested party to the belief that this frame work was responsible for many of the detrimental decisions of the 1980's.

When my late husband watched the game show "Wheel of Fortune", he frequently shook his head and said "Greed kills" to the contestant who knew the puzzle solution but decided to spin again for "Big money, big money". Most of the time that contestant would land on the "Bankrupt" spot. That phrase, "Greed Kills" would make a fitting epithet on the gravestones of thousands of hemophiliacs and transfusion AIDS victims in this country and throughout the world. Enhanced enforcement, a more responsive patient notification system, and greater incentives for the development of better viral inactivation methods as well as for recombinant factors are all needed to prevent the recurrence of the HIV tragedy of the 1980s and to protect the safety of the blood supply for all Americans.

Sincerely,

Therese B. Doran

Thesese B. Doran
(Mrs. Michael S. Rogers)

Judy Horn-McGinnis
811 Standish Rd.
Pacifica, CA 94044
(415) 355-9705

Chairman Christopher Shays
Subcommittee on Human Resources + Intergov. Relations
B372, Rayburn House Office Building
Washington DC 20515

Dear Chairman Shays,

I lost my husband, Sean McGinnis, in 1987 after he used Blood Product that was contaminated with the AIDS virus to treat his hemophilia condition. The product that was FDA approved and supposed to sustain and improve his health [his life] Killed him. It killed thousands of other American citizens of which many were our friends. Many were contributing members of our society, and our society has been wounded further with the loss of so many wonderful Dads, sons, brothers, uncles, and the women they passed the virus onto. I personally know of hemophiliacs whose doctors were not notified of the lot #'s suspected of viral contamination, who if they did that person would not of been treated + therefore not contaminated with it. We look to the FDA for the ultimate obligation for protecting our nations blood supply. The notification system now is not working! A more responsible system of blood user/buyer notification is imperative with strict enforcement. This travesty must not be repeated and Hepatitus C and other viruses are a future threat!

Protect our blood supplies!
Protect us from the bloodin[illegible]
Thankyou! Judy Horn-McGinnis

Olsten
Health Services
Infusion Therapy

Rep. Christopher Shays, Chairman
House Subcommittee on Human Resources
and Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515

June 3, 1997

Dear Chairman Shays:

I wish to express my appreciation for your efforts to ensure the future safety of our nation's blood supply through more stringent guidelines for blood product withdrawals and recalls and timely notification to blood product consumers.

As an attorney who has represented a number of persons with hemophilia on Social Security disability claims, I have seen the immense devastation endured by that community as the result of inadequate blood safety guidelines during the 1980s. Given the threat posed by other blood-borne illnesses, the need for reform of these guidelines is extremely important.

My fear is that without immediate action to strengthen the enforcement of blood safety guidelines by the FDA, we will confront tragedies of even greater magnitude in the future. I urge you and your committee to act now to prevent this threat to the health of all Americans who depend upon the safety of our blood supply.

Sincerely,

Wm. P. Leach

William P. Leach
Staff Attorney

4710 Eisenhower Boulevard, Building E, Suite 3, Tampa, Florida 33634 • 813-806-0800 Toll Free 888-700-7010 Fax 813-886-1324

Finley, Anne Marie

From: Joe Leverone[SMTP:levy@cq.cqi.com]
Sent: Tuesday, June 03, 1997 8:10 PM
To: Finley, Anne Marie
Subject: Re: Blood Safety letter

Chairman Christopher Shays
Subcommittee On Human resources
& International Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman and Committee Members:

Thank you for work and interest in investigating blood and frationated blood product safety. As a severe hemophiliac, this issue is very close to my heart. The fractionation industry has, quite literally, been getting away with murder for many years. The result of this lack of regulation and enforcement is already known to you. However, what everyone must realize is that it's not over. As the situation now stands, we hemophiliacs have to rely on what amounts to word of mouth to find out about recall notices - notices that are released months too late to prevent the use of the recalled product! This issue needs to be addressed if there is to be any hope of avoiding another "plague". Even when recombinate produced coagulant factor is a reality for all, this will still be an issue. Any product is going to have an occasional bad batch. A means must be found that will insure that recall notices get out in time to prevent the use of that batch.

Notification, regulation, and meaningful enforcement are needed to prevent a recurrance of tragedy. As Santayana said, " Those who do not remember history are condemned to repeat it". History has shown the results of an unregulated blood industry. Lets not repeat it.

Thank you again for your continuing efforts on our behalf!

Regards,

Joseph A. Leverone
levy@cq.cqi.com
726 Tiffany Court
Gaithersburg, Maryland
20878-1823

Michael W. Hylton
3498 Queens Court
Costa Mesa, CA 92626

June 3, 1997

The Honorable Christopher Shays
Chairman, Subcommittee on Human
Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515

Re: A Responsible and Accountable Blood Safety System

Dear Representative Shays:

I am writing to ask for your support for the development of an immediate **formal** consumer notification system concerning recall strategies of contaminated blood products. Additionally, I am asking you to consider legislating a reduction in the size of plasma pools used to manufacture the hemophilia clotting factor concentrates I use.

Ten thousand (10,000) of us in the hemophilia community were infected with the AIDS virus through medically prescribed, FDA approved, contaminated blood products. Due to this **preventable** tragedy, blood safety is of great importance to my wife of 28 years, my three children, and to me. Our families have been devastated physically, emotionally, and economically.

The urgency for clear and comprehensive procedures is here and now. FDA enforcement of blood product withdrawal and recalls and the establishment of timely patient notification systems is a no-brainer.

Representative Shays, The United States needs enhanced enforcement of blood safety, reduced donor size for pooled plasma products, a more responsive patient notification system, and development of superior viral inactivation methods of blood products. A more responsible and accountable blood safety system to protect America's blood supply is a must!

Sincerely,

Michael W. Hylton

Dolores Crooker
579 Ridgedale
Woodbridge NJ
07095

Congressman Christopher Shays
Commitee on Government
Subcommitee on Human Resources
2157 Rayburn House Office Building
Washington DC 20515-6143

Dear Congressman Shays:

As a grandmother of a Hemophiliac,who lost his life to Hiv,one month short of his 12th birthday.He became infected through the use of contaminated blood products.

I am sure you are aware of the devastation this Community has suffered,though the use of the contaminated blood products.Not only has over 50% of the people with Hemophilia become Hiv positive through product usage,but a higher number has been infected with Hepatitis.

In the early 80's we waited long periods of time,for answers on Hiv/Aids and blood product transference.The answer was positive and the devastation took a great toll on this Community.This must not happen again.

This Community and others,who use blood and blood products.Cannot afford more wasted years with possible contamination through this product.The new generation needs to be completely informed about the hidden perils lurking in a product they use.

THANK YOU,

Dolores Crooker

Dolores Crooker

Congreeman Christopher Shays
Commitee on Government
Reform and Oversight
Subcommitee on Human Resources
2157 Rayburn House Office Building
Washington DC 20515-6143

Denise Schworn
8 Nielson Street
Woodbridge NJ
07095

Dear Congressman Shays:

I'm writing you today,of a matter that concerns a whole Community of people.This Community of people are the Hemophiliacs and other blood product users.As I know you are aware of our tainted blood supplty,And the devastation it has caused to all of us.I have suffered a very big loss,so have many others.I have lost my oldest son who was 11 years old,because of Hiv/Aids that he recieved from our tainted factor.My concerns are of this,many more people are still having children that are Hemophiliacs.What are we going to do about our blood supply.I have two daughters,which could one day have childern of their own.That could be born with Hemophilia.So I'm very concerned about our tainted blood supply.What are we going to do? The same we are doing now!WHEN IN DOUBT GIVE!!!!! NO!!!WHEN IN DOUBT PULL!!!!

THANK YOU,

DENISE SCHWORN

June 3, 1997

Chairman Christopher Shays Subcommittee on Human Resources & Intergovernmental Relations
ATTN: Anne Marie Finley
B372 Rayburn House Office Bldg..
Washington, DC 20515

RE: Government Reform and Oversight Committee

Dear Chairman Shays:

I am a wife of a person with Classic, Type A, Severe Factor VIII Hemophilia. Like 10,000 other Hemophiliacs, he also contracted HIV and Hepatitis Infection transmitted through tainted blood products. As a blood product consumer, blood safety is of great importance to me and my husband. We have lived a major part of our life already with a disease that could have been avoided if the nations blood supply were better regulated. This not only concerns our family, but also future generations of all non-infected persons with hemophilia.

While blood safety is a shared responsibility, FDA has the ultimate obligation for protecting our nation's blood supply to ensure safety for all "Americans". The FDA currently relies on an informal system in communicating with blood and blood product manufacturers about enforcement of its regulations. The safety of the blood supply is of paramount importance as threats of new strains of hepatitis and who knows what other "Aids" like virus continue to plague the hemophilia community and other users of blood and blood products.

Enhanced enforcement, a more responsive patient notification system, and greater incentives for the development of better trial inactivation methods as well as for recombinant factors are all needed to prevent the recurrence of the HIV tragedy of the 1980's and to protect the safety of the blood supply for all Americans.

Thank you for your efforts through the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system.

Sincerely,

Diane C. Greer

Diane C. Greer
1538 Nordic Court
Medford, OR 97504
541-773-4728

Please help us pass Ricky Ray!

SUBCOMMITTEE ON HUMAN RESOURCES
& INTERGOVERNMENTAL RELATION

7/7/

DEAR CHAIRMAN SHAY:

I AM A 48 YEAR OLD PERSON WHO HAS CLASSIC, TYPE A, SEVERE, FACTOR VIII DEFICIENT HEMOPHILIA. YOU HAVE UNDOUBTEDLY RECEIVE HUNDREDS OF LETTERS FROM PERSONS IN THE BLEEDING DISORDER COMMUNITY RELATING THE TERRIBLY OF HIV AND HEPATITIS INFECTION TRANSMITTED THROUGH TAINTED BLOOD PRODUCT. I WILL THEREFORE SPARE YOU ANOTHER SUCH TALE OF WOE.

WHAT I WOULD LIKE TO BRING TO YOUR ATTENTION WHILE YOU AND YOUR COMMITTEE CONTEMPLATE PROCESSES OF INSURING BLOOD SAFETY IS THE GENERATIONS OF YOUNG PERSONS WITH HEMOPHILIA WHO HAVE BEEN BORN SINCE THE ORIGINAL INFECTION OF THE BLEEDING DISORDER COMMUNITY. THESE YOUNG PEOPLE HAVE A CHANCE AT A RELATIVELY NORMAL LIFE. THEY WILL ONLY HAVE THAT CHANCE IF YOUR COMMITTEE ACTS TO INSURE THE SAFETY OF THE NATIONS BLOOD SUPPLY. PLEASE ISSUE GUIDELINES TO DIRECT THE FDA TO ENFORCE BLOOD PRODUCT WITHDRAWAL AND RECALLS AND ESTABLISHMENT OF A TIMELY PATIENT NOTIFICATION SYSTEM. THE CURRENT INFORMAL SYSTEM DOES NOT WORK. THE F.D.A.'S RESISTANCE AN MANUFACTURES NOTIFICATION MUST BE STOPPED. THE SIZE OF PLASMA POOLS MUST BE REDUCED TO MANAGEABLE NUMBERS AND THE BLOOD PRODUCTS ADVISORY COMMITTEES SHOULD INCREASE ITS NUMBER OF MEMBERS WHO ARE END USERS. PLEASE DO NOT ALLOW THE MANUFACTURES TEETH TO GROW. YOU AND YOUR COMMITTEE MAY INSURE THAT YOUNG PERSONS WITH HEMOPHILIA NEVER HAVE TO WONT BACK

AND EVERY DAY FOR A FATAL VIRUS INTRODUCED THROUGH USE OF CONTAMINATED BLOOD PRODUCTS TO TAKE IT'S DEADLY TOLL. YOU CAN ACT TO ENSURE THAT THOSE WHO ARE UNINFECTED REMAIN SO. PLEASE DO NOT ALLOW THE MANUFACTURERS TO PERPETUATE A SYSTEM THAT EVENTUALLY WILL RESULT IN MORE TRAGEDY AND DEATH TO THOSE ALREADY BURDENED WITH THE DEBILITATING OF A BLEEDING DISORDER. PLEASE ACT TO ENSURE THE SAFETY OF THIS NATION BLOOD SUPPLY.

GOD BLESS YOU
AND THANK YOU.

WITH THE DEEPEST RESPECT
I AM,
Elwin L. Greer
ELWIN L. GREER
1538 NARDIC COURT
MEDFORD, OREGON 97504
(541) 773-4728

P.S. PLEASE HELP US PASS RICKY RAY!

Finley, Anne Marie

From: JB&EB[SMTP:jbon@softcom.net]
Sent: Tuesday, June 03, 1997 1:29 PM
To: Finley, Anne Marie
Subject: Blood Safety Notification System

June 3, 1997

Chairman Christopher Shays
Subcommittee on Human Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Shays:

I would like to thank you for your efforts via the Government Reform and Oversight Committee to bring greater attention to the need for a more responsive blood safety system. As a hemophiliac and consumer of blood products, blood safety is of great importance to me and the bleeding disorders community.

The catastrophe during the 1980s led to my being infected with HIV due to contaminated blood products. Here it is fifteen years later and there is still a high frequency of contaminated blood products, including new emerging threats such as Creutzfeldt-Jakob disease and hepatitis strains. We urgently need clear guidelines to direct FDA enforcement of blood product withdrawal and recalls and for the establishment of a timely patient notification system.

While blood safety is a shared responsibility, the FDA has the ultimate obligation for protecting our nation's blood supply. The FDA currently relies on an informal system in communicating with blood product manufacturers about enforcement of its regulations. But by the time the patient is notified of a recall by his treatment center, it is usually too late, as the product has already been used.

The blood product industry needs enhanced enforcement by the FDA, a more responsive patient notification system, and greater incentives for the development of better viral inactivation methods and recombinant factors.

Please consider these issues when your committee discusses the need for a more responsive blood safety system.

Thank you for your time and consideration in this urgent matter.

Sincerely,

Jeff Bonney

1511 Christopher Way
Sacramento, CA 95819

Finley, Anne Marie

From: scarlisle@net-ex.com[SMTP:scarlisle@net-ex.com]
Sent: Tuesday, June 03, 1997 11:10 AM
To: Finley, Anne Marie
Subject: BLOOD SAFETY

Chairman Christopher Shays
Subcommittee On Human resources
& Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman and Committee Members:

I would like to take this opportunity and thank you for your efforts through the government reform and oversight committee to bring greater attention to the need for a more responsive blood safety system. While the efforts so far have been great, much more needs be done!
As a Parent of a hemophiliac and constant blood product consumer, safety of the blood supply is of great importance to me and my family. To that end, the FDA's development of guidelines concerning timely patient notification and enforceable, verifiable recall procedures is an issue of serious consequences and of highest import.
A more responsive patient notification system and a better incentive for the development of better viral inactivation methods as well as for recombinant factors are all needed to prevent the recurrence of the HIV tragedy of the 1980's and to protect the safety of the blood supply for all.
All regulations are of course important, the critical element however, is enforcement. In the case of all blood supply tragedies in the past, the enforcement of regulations was not followed. The reason? Industry was asked to police itself. They have failed miserably! Time and time again. They cannot be trusted with the enforcement function - they have proved that themselves!
It is necessary that their be government mandated enforcement.
Please help your family with this as well as every other American family, we all deserve this.
Thank you for your time and I look forward to hearing from you on this matter.

Sincerely

SHIRLEY CARLISLE ~~ scarlisle@net-ex.com
23418 Chapman
Macomb MI 48042

Finley, Anne Marie

From: linlew5@juno.com[SMTP:linlew5@juno.com]
Sent: Tuesday, June 03, 1997 1:17 PM
To: Finley, Anne Marie
Subject: Patient Notification & Recall Procedures

June 3, 1997

Chairman, Christopher Shays
Subcommittee on Human Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Shays,

Thank you for your efforts through the Government Reform and Oversight Committee to bring the much needed attention for a more responsive, responsible blood safety system. As a parent, a sister and aunt of persons with hemophilia, blood safety is of great importance to me and my family.

The events of the 1980's and the continuing high frequency of recent incidents of blood product contamination demonstrates the urgency for clear, precise guidelines to allow FDA more aggressive enforcement of blood product withdrawal and recalls and to establish a TIMELY patient notification system.

Although it is shared, FDA has the main responsibility for protecting all Americans with a safe blood supply. The current mode of communication between FDA and blood and blood product manufacturers is lack in enforcement regulations. While FDA relies on the Blood Products Advisory Committee for blood safety policies, many of the same issues used in the 1980's such as product availability and cost are still used to make life saving decisions.
These decisions are what cost my brother his life and is slowly taking away that of my 17 year old son. They are what has deterred my nephew from ever using blood products to treat his hemophilia. I do not want these same issues to affect my daughter's future with her children.

The safety of the blood supply is extremely important with the emerging new threats such as Creutzfeldt-Jakob disease, new strains of hepatitis, parvovirus and many other diseases that plague the hemophilia community and users of blood and blood products. I pray each and every time I stick a needle into my already HIV infected son's body that he will not get another disease.

Please enforce a more timely, responsive notification system and work for the development of better viral inactivation methods including recombinant factors, to prevent the past HIV tragedy of the 1980's and protect our nation's blood supply to make it safe for all Americans.

Respectfully,

Linda Lewis
12494 Kitchem DR
Licking, MO 65542
(573) 674-3985
email: linlew5@juno.com

Finley, Anne Marie

From: FVIIIMan@aol.com[SMTP:FVIIIMan@aol.com]
Sent: Tuesday, June 03, 1997 12:31 PM
To: Finley, Anne Marie
Subject: Blood Safety

Chairman Christopher Shays
Subcommittee On Human resources
& International Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman and Committee Members:

I would like to take this opportunity and thank you for your efforts through the government reform and oversight committee to bring greater attention to the need for a more responsive blood safety system. While the efforts so far have been laudible, much more must be done!

As a hemophiliac and constant blood product consumer, safety of the blood supply is of great importance to me and my family. To that end, the FDA's development of guidelines concerning timely patient notification and enforceable, verifiable recall procedures is an issue of serious consequences and of highest import.

A more responsive patient notification system and a better incentive for the development of better viral inactivation methods as well as for recombinant factors are all needed to prevent the recurrence of the HIV tragedy of the 1980's and to protect the safety of the blood supply for all.

All regulations are of course important, the critical element however, is enforsement. In the case of all blood supply tragedies in the past, the enforcement of regulations was not followed. The reason? Industry was asked to police itself. They have failed miserably! Time and time again. They cannot be trusted with the enforcement function - they have proved that themselves! Please make an emphasis that with any new and necessary regulation, there be government mandated enforcement.

The American People and your constituents deserve that much!

Thank you for your time and I look forward to seeing you at the meeting on June 5th in the Rayburn building.

Regards,

Axel Freese
3828 Monte Vista Place
Alexandria, Virginia 22309

June 4, 1991

Dear Chairman Shays,

We are writing to you because we are very concerned about blood safety, the size of plasma pools and a timely patient notification system.

We lost our beloved son, who had hemophilia, four years ago to Aids. We have two other family members who have hemophilia and our daughter may be a carrier of hemophilia.

We are aware that some improvements have been made by the FDA, and for these, we are thankful. But it's not enough! Last week there was another recall of hemophilia factor. Since we are fortunate enough to have a computer, we found out about the recall within a short period of time – but it wasn't fast enough to keep my nephew from using some of the recalled factor. Now we play the waiting game. Will he too become infected with Aids and die a horrible death? What about the hundreds of hemophiliacs who don't even know about this bad blood? How much of this diseased product are they pumping into their arms as I write this letter because <u>no one has notified</u> them?

Someone must be strong enough and compassionate enough to help our community be safe from these problems. The blood industry must become more aware of their responsibility to the consumers. Unfortunately, we, the consumers, can't seem to get through to these people.

page 2

But you and your committee can make a difference. You have the power and the influence to make things happen. And by helping our community you will be helping everyone in the country who needs or uses blood products.

Please, help us help America. If we have a better and safer blood product, everyone in America who needs or requires blood will have a better and safer product.

Thanks for your help and support.

Karen Cross

Karen Cross

18473 Hope Villa Drive
Prairieville, La. 70769
504-673-3660

Finley, Anne Marie

From: Anthony & Phoenix Lindgren[SMTP:lindgren@cts.com]
Sent: Wednesday, June 04, 1997 6:28 PM
To: Finley, Anne Marie
Subject: Blood Product Safety

Dear Chairman Shays:

Thank you for your efforts to bring greater attention to the need for a more responsive blood safety system.

As the wife of a man with hemophilia, AIDS and HCV, blood safety is of great importance to me and my family.

The events of the 1980s and the continued high frequency of recent incidents of blood products contamination demonstrate the urgency for clear guidelines to direct FDA enforcement of blood product withdrawal and recalls and for the establishment of a timely patient notification system.

I also remain concerned about the size of the plasma pools used to manufacture the clotting factor concentrates used by my husband.

While blood safety is a shared responsibility, FDA has the ultimate obligation for protecting our nation's blood supply to ensure its safety for all Americans. The FDA currently relies on an informal system in communicating with blood and blood product manufacturers about enforcement of its regulations.

The FDA also relies on the Blood Product Advisory Committee in formulating blood safety policy. While consumer representation on the committee has increased in the past few years, the Committee often continues to address blood safety issues using the same framework - product availability versus cost - used to make many of the detrimental decisions of the 1980s.

The safety of the blood supply is of paramount importance as emerging threats such as Creutzfeldt-Jakob disease and new strains of hepatitis continue to plague the hemophilia community and other users of blood and blood products.

Enhanced enforcement, a more responsive patient notification system, and greater incentives for the development of better viral inactivation methods as well as for recombinant factors are all needed to prevent the recurrence of the HIV tragedy of the 1980s and to protect the safety of the blood supply for all Americans.

Thank you,

Phoenix N. Lindgren
1032 Tabby Lane
Escondido, CA 92026-3187

Finley, Anne Marie

From: Joe Leverone[SMTP:levy@cq.cqi.com]
Sent: Wednesday, June 04, 1997 5:57 PM
To: Finley, Anne Marie
Subject: Re: Blood Safety letter

Chairman Christopher Shays
Subcommittee On Human resources
& International Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman and Committee Members:

Thank you for work and interest in investigating blood and frationated blood product safety. As a severe hemophiliac, this issue is very close to my heart. The fractionation industry has, quite literally, been getting away with murder for many years. The result of this lack of regulation and enforcement is already known to you. However, what everyone must realize is that it's not over. As the situation now stands, we hemophiliacs have to rely on what amounts to word of mouth to find out about recall notices - notices that are released months too late to prevent the use of the recalled product! This issue needs to be addressed if there is to be any hope of avoiding another "plague". Even when recombinate produced coagulant factor is a reality for all, this will still be an issue. Any product is going to have an occasional bad batch. A means must be found that will insure that recall notices get out in time to prevent the use of that batch.

Notification, regulation, and meaningful enforcement are needed to prevent a recurrance of tragedy. As Santayana said, " Those who do not remember history are condemned to repeat it". History has shown the results of an unregulated blood industry. Lets not repeat it.

Thank you again for your continuing efforts on our behalf!

Regards,

Joseph A. Leverone
levy@cq.cqi.com
726 Tiffany Court
Gaithersburg, Maryland
20878-1823

Tiffany Althouse
3122 Juniper Ct. N.E.
Grand Rapids, MI 49505

June 4, 1997

Chairman Christopher Shays
Subcommittee on Human Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington D.C. 20515

Attention: Anne Marie Finley

Dear Representative Shays,

As the time approaches for your committee on Government Reform and Oversight to meet concerning matters related to the safety of our nations blood supply, I wanted to take the time to share a few thoughts with you. I am so appreciative of your efforts to address this matter as it effects my family very deeply. Any progress you are able to make will go a long way toward saving my son's life. There really are not words to tell you how much I have riding on this.

Our family has been affected by matters relating to the safety of the blood supply since my brother was born 30 years ago with severe hemophilia. I know you are aware of the devastation that has befallen thousands of people and their families with hemophilia due to the HIV infection of our nations blood supply during the tragic events of the 1980's. As my brother's wife, our mother and father, his sisters and friends circled around him in his bed, we each reached out to touch and comfort him one last time as my brother drew his last breath and died of AIDS at the very young age of 24. And in my arms I held my then ten month old son, also born with hemophilia. Despite the hopelessness and the helplessness that I felt, I also felt a determination to do whatever would be necessary to protect him from the same fate.

Today there is little doubt about what caused the tragedy that lead to my brothers death. A pharmaceutical industry that was singularly focused on their bottom line, who was allowed to be self regulated, who actively sought out blood donors from the absolutely highest risk categories possible and who continues to this day to practice the not so safe policy of pooling plasma from an extremely high number of donors. And while I fully recognize that nothing will bring my brother back, I feel very strongly that our nation needs to learn a very hard earned lesson from this tragedy and see to it that this type of devastation is never allowed to happen again. After his captivity in Lebanon, Terry Waite said, "I have been determined in captivity, and still am determined, to convert this experience into something that will be useful and good for other people. I think that's the way to approach suffering." We need to take this same approach with our nations blood supply, and turn the suffering into a strong regulatory mandate that will serve as a memorial to those who have suffered.

What can we do to protect my son from my brother's fate? We can start with very clear guidelines concerning timely notification and enforcement of blood product recalls and withdrawals. Furthermore we need to establish a timely system in which patients themselves can be notified. My family to this day is yet to be notified that my brothers product was contaminated. It is the FDA's duty and obligation to protect our nation's blood supply for all Americans. They need to

use their authority and be made to enforce strict regulations that will safeguard all people from being the next victim of the pharmaceutical industry's bottom line. I would also like to suggest that to allow blood and blood product manufacturers to regulate themselves is inherently wrought with a conflict of interest. Any information forthcoming from this industry needs to be closely scrutinized for their hidden agenda. Furthermore their common practice of exercising an "acceptable level of risk" should be prohibited. When lives are at stake, there is no acceptable level of risk. There are times when cost can not be a mitigating factor in decision making.

On almost a daily basis there is concern about a new contaminant in the blood supply. Hepatitis is on a mission to span the entire alphabet, and the incredible eerie presence of Creutzfeldt-Jakob disease clearly illustrates the utmost urgency of addressing this issue post haste. There should be incentives for this industry to continue to develop better technologies and products that will be safer than those containing human plasma. Then, maybe we will stand a chance of not reliving the tragedy of the AIDS epidemic.

Finally, while it often occurs to me that my focus too, may seem very narrow, I recently received a very personal reminder that every single person in our country needs the reliability of a safe blood supply. When my two year old daughter was diagnosed with lenkemia and needed to receive multiple blood transfusions, this realization hit me like a ton of bricks. There was no way to prepare for the situation we found ourselves in. Like many Americans at one point or another in their lives, we needed to rely on the gift of life from a total stranger and then pray that what was dripping into our daughters veins would indeed save her life as it was intended to do. When most people stop to think about it they realize that at any time someone we love or maybe even ourselves may need to rely on this nations blood supply due to an illness, a surgery or perhaps even an accident.

I know that the task before your committee is a large one and I want to assure you that your efforts do not go unappreciated. I am very thankful that you are addressing this matter and will be grateful for any amount of peace of mind that you may have to offer me. Like most people, all I want is long and happy futures for my children.

Sincerely,

Tiffany Althouse

Tiffany Althouse

Reperesentative Shay:

I am writing to you to request your help on the blood safety issues that will be address on 6/5/97. I am a hemophilia with severe factor 9 defiency and contracted HIV thru the use of factor. We need a system that will not allow such a problem to ever happen again. We need a system that will notify people of recalls in a matter that is as fast as humanly possible to stop use of unsafe products. Please we all need your help not only hemophilic's but anyone that may use anything involving blood or blood products. The 1980's cannot be repeated and we must learn from history or it will be repeated.

Thank You

Michael D Huggler
2445 Mt Hope Rd.
Okemos, MI 48864
517-347-8309
Fax 517-347-9812

National Hemophilia Foundation
Since 1948

110 Greene Street, Suite 303
New York, New York 10012-3832
(212) 219-8180 or (888) INFO-NHF
Fax (212) 966-9247
Web Site: www.infonhf.org

CFC #0543

June 4, 1997

The Honorable Christopher Shays
Chairman, Government Reform and Oversight Committee
Subcommittee on Human Resources
United States House of Representatives
Washington, D.C. 20515

Dear Chairman Shays:

Thank you for your continued efforts to bring greater attention to the critical need for a safer blood supply. The National Hemophilia Foundation appreciates the opportunity to work with you and your staff on this important issue and commends the Government Reform and Oversight Committee for holding a hearing on the enforcement and regulation practices of the Food and Drug Administration in the areas of blood collection, processing, and distribution.

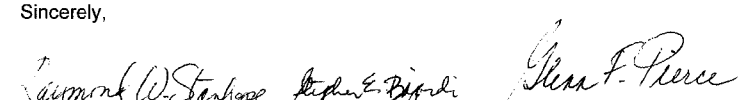
As the hemophilia community has worked to overcome the devastation of HIV, NHF has continuously looked for ways to improve the safety of our nation's blood and blood products. We are supportive of the recommendations included in last year's Committee report on emerging threats to the blood supply and have worked diligently, through our own interactions with the FDA, to encourage their implementation.

Our efforts, and those of the Committee, are making a difference. Communication with FDA has improved, and we are beginning to see a greater responsiveness to the occurrence of adverse incidents in blood and blood products. During the latest blood product recall, occurring just last week, FDA ordered a prompt recall and notified NHF early, allowing us to more quickly notify the bleeding disorder community and treating physicians of the recalled lots of product.

However, much remains to be done. For example, FDA recently has clarified the responsibility of manufacturers to notify patients and their providers of product withdrawals and recalls. An increased role for manufacturers in the notification process has been long sought by NHF, and we are supportive of this move by FDA. Unfortunately, without clear guidelines from FDA, manufacturers remain unsure of the actions FDA is encouraging them to perform, and, in fact, have argued against FDA on this issue. Although FDA has mandated the responsibility of end-user and treating physician notification to manufacturers, the agency has done little to facilitate achievement of this objective.

While blood safety is a shared public-private responsibility, FDA has the ultimate obligation for protecting our nation's blood supply. NHF and the hemophilia community remain concerned about the lack of clear regulations for manufacturers and of internal standard operating procedures for adverse event investigations, the need to establish a prompt end-user and physician notification system, the size of plasma pools, and FDA's inconsistent enforcement record. The events of the 1980s and the continued high frequency of adverse blood product incidents demonstrate the urgent need to take steps to prevent the recurrence of the HIV tragedy and to ensure safe blood products for the hemophilia community and a safer blood supply for all Americans. We look forward to continuing to work with you, the Committee, and FDA to achieve this mutual goal.

Sincerely,



Raymond W. Stanhope	Stephen E. Bajardi	Glenn F. Pierce, M.D., Ph.D
President	Executive Director	Chair, Blood Safety Working Group

cc: NHF Blood Safety Working Group
NHF Medical and Scientific Advisory Council

Jacquilyn Otto
750 Lake Shore Dr
Escanaba, Mi 49829
1-906-789

The Honorable Christopher Shay
B372 Rayburn Office Building
Washington, DC 20515

Dear Representative Shay,

It is my understanding that the Government Reform and Oversight Committee is meeting to discuss the progress of F.D.A and industry in developing guidelines concerning timely patient notification and enforceable recall procedures, concerning the biological products my family uses for Hemophilia.

I am pleased to see our Government taking an active role to assure that the Hemophilia Holocaust of the 1980's is not repeated in the future.

My son Patrick used H.I.V tainted products in the early, thru mid 1980's. Became ill with Aids symptoms in 1988 and died with full blown Aids in 1991. Where are the FDA warnings? We are still waiting. Where are the recall notifications? We are still waiting. Why where these products never recalled? Why after 1985 where these companys allowed to sell probable H.I.V tainted

products in other countries like Japan and Costa Rica?

Because my 6 year old grandson Patrick has hemophilia, we continue to be aware of current problems with blood safety. I feel the FDA needs to have the power and be held accountable for the collection of safe blood. There should be no close ties between FDA and industry to prevent proper and regular monitoring of biological products.

I would like to see more random checks of blood collecting and manufacturing procedures. There needs to be strong measures that can be enforced if regulations are not met.

Mandatory recalls of suspected tainted products is a must!

Early notification may have saved my son's life. We could very well need it save my grandsons life!

Thank you again for being apart of this important decision making process.

Yours,
Jacquelyn Otts

Finley, Anne Marie

From: jvin2611@uriacc.uri.edu[SMTP:jvin2611@uriacc.uri.edu]
Sent: Wednesday, June 04, 1997 6:15 AM
To: Finley, Anne Marie
Subject: Blood Safety Notification Hearings

June 4, 1997

Chairman Christopher Shays
Subcommittee On Human Resources
& Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Shays,

Please excuse the untimeley nature of this letter but I was just recently informed of your committees scheduled hearings. As you know you will be discussing the accountability of blood product manufacturers and consumer notification. Please allow me to tell you why I feel this is an important measure.

As recently as last week, I had the misfortune of having a bleed into the right calf muscle in my right leg. As a Severe, Factor VIII Deficient Hemophiliac, I had to infuse large numbers of Factor VIII derivative. In the middle of the week, a recall was posted on the internet for products made by the Baxter/Hyland label. To my relief I was lucky and did not have these tainted Lot. numbers. If I had, I would have possibly been exposed to the HIV virus, yet again. How many dead Hemophiliacs does there have to be before the Pharmaceutical companaies, such as Baxter, will be held accountable for their gross negligence. Please force them to notify each person that is using their products so that the tragedy of the 1980's does not happen today!

Respectfully,

James Viner
70 John Potter Road
West Greenwich, RI 02817

Rich Vogel

12 Fifth Avenue
Suite 41
New York, New York 10011
212.677.6528

Chairman Christopher Shays
Subcommittee on Human Resources
& Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515
Attn: Ms Anne Marie Finley

Chairman Shays,

First, I'd like to thank you for your efforts in bringing attention for the need of a more responsive blood safety system through the Government Reform & Oversight Committee. I am a forty-one (41) year old hemophiliac who depends on blood products to lead a somewhat "normal" life. Therefore a safe product is essential to my well being. I am sure you are aware of the devastation of lives and families due to the contamination of the blood supply in the late 1970's and early 1980's with the AIDS virus. If you are not aware of how a whole **INNOCENT** and **NAIVE** community became infected, let me tell you a quick story. Being diagnosed with hemophilia at 9 months old I was immediately dependent on blood products. First it was whole blood, then plasma, cryopercipatate and finally Factor VIII concentrate-all manufactured from human blood. This is a story of trust and faith, not only in our doctors and health care providers but also in our government. The story goes bad in the early 1970's when a method of eliminating most viruses was discovered by pharmaceutical companies but it would cut into there profits so therefore nothing was done. Unfortunately and unknowingly to the hemophiliac community our lives and those of our families and friends was changed forever by being infected with a deadly and devastating disease that took a great many lives to date and left the rest of us with a feeling of isolation, hopelessness and loss of faith. We had trusted these people to help us live our lives "normally" and with dignity and because of greed and profit, they took that away from us.

photography

Rich Vogel

12 Fifth Avenue
Suite 41
New York, New York 10011
212.677.6528

Now it seems it is happening again. With the high frequency of recent blood product recalls, it is clear that the FDA needs guidelines to enforce product recall and timely patient notification, not 3-4 months after product is released. Severe hemophiliacs use product 3-4 times per week, therefor product would have been used months before notification, thereby making notification months later useless to a severe hemophiliac. While blood safety is a shared responsibility between government and fractionators(blood product manufacturers) we have seen what kind of communication there has been in the past. Delaying tactics by manufacturers has resulted in a community devastated by loss to a community fueled by profit. With the emerging threat of Creutzfeldt-Jacob Disease(human "MAD COW") and newer and stronger hepatitis strains, the safety of the American blood supply is at a great risk. I therefore implore you to enhance enforcement of FDA regulations, enlist a more responsive & timely patient notification system and greater incentives for the development of better viral inactivation methods as well as for recombinant factors. Please don't make the tragedy of the 1980's become the standard for blood safety-that was NO accident--NO act of God---it was pure greed for profit, where human life took a back seat to MONEY, where compassion was spelled MONEY.

I'd be happy to tell my whole story any time you find the need or are interested in hearing what its like to grow up being a hemophiliac-before and after AIDS.

Adress:207 Copeley Way
North Brunswick,NJ 08902
Phone :908/821-5460

photography

Linda Leigh Sulser
14032 Dallas Street
Chantilly, VA 20151
(703) 817-0657

FAX TO: Anne Marie Finley (202) 225-2382

DATE: June 4, 1997

FOR: Chairman Christopher Shays
Subcommittee on Human Resources & Intergovernmental Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Shays,

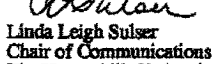
I am the wife of a person with Hemophilia, Hepatitis-C, HIV disease and Diabetes. It is a constant struggle to keep him healthy and active. He infuses Antihemophilic Factor VIII three to four times per week to prevent and treat bleeding episodes. While we realize that the absence of FDA regulations protecting the blood supply from a suspected virus, such as Hepatitis and HIV, in the 1970's and 1980's have altered our lives forever, we are actively advocating for the safety of our blood supply for all Americans and people in other countries who benefit from American processed blood products.

- We contend that all available screening tests for viral contamination should be used, no matter what the costs, and those methods must be monitored by specific guidelines determined by the Blood Product Advisory Committee and the FDA.
- We also believe a limit must be placed on the number of donors to plasma pools used by fractionators to manufacture clotting factor.
- We desire the adherence of clear-cut guidelines to direct FDA enforcement of blood product withdrawal and recalls. We would like to see attention given to a responsive patient notification system, should a recall become necessary.

It is great to see your efforts in the Government Reform and Oversight Committee for review of blood safety that affects us and many others every day. We are anxious for the day that virtually all risks of viral contamination through the blood supply will be a sad tragedy of the past. The passage of the Ricky Ray Hemophilia Relief Fund Act - HR1023 would be a welcome consolation for past FDA decisions that allowed my husband and so many of our community to become infected with Hepatitis and HIV.

A response outlining the outcome of the Committee's recommendations would be greatly appreciated.

Sincerely,



Linda Leigh Sulser
Chair of Communications Committee,
The Hemophilia Federation

Finley, Anne Marie

From: Michael Leslie Johnson[SMTP:mjohnson@mis.net]
Sent: Thursday, June 05, 1997 9:46 AM
To: Finley, Anne Marie
Subject: Blood safety

Chairman Christopher Shays
Subcommittee On Human resources
& International Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman and Committee Members:

Thank you for investigating blood and frationated blood product safety. As the parent of severe hemophiliac, this topic is of great interest to me. The fractionation industry has not been kind to their customers. My son was lucky enough to have missed the HIV/AIDS that infected many hemophiliacs via blood products, but not HCV.

I've seen many recalls of blood products since my son was born. NONE of them timely enough to prevent the products from being used. In fact by the time a recall notice filters down through the national, state and local hemophilia community chapters, most of these products have already been used. Imagine the terror of knowing you've injected yourself or a loved one something that could possible result in their death. What if a timely recall notice could have prevented this injection from ever haven taken place.

The fractionater's claim it's not their responsiblity to notify the individuals of a recall of product. They state it's up to the party that sold the product to the individual to notify them. The automotive industry does not work this way. If you have a defective automoble the manufacture will notify you by letter. They may ask you to return the car to the dealership for repair, but the manufacturer will notify you. Now, I ask you which is more important a defective fan belt or the substance we inject into our veins. The car dealer will replace my fan belt, who's going to replace my son's liver.

Michael L. Johnson
3358 Tisdale Drive
Lexington, Ky. 40503

Michael L. Johnson
mjohnson@mis.net

Finley, Anne Marie

From: Dmoongo@aol.com[SMTP:Dmoongo@aol.com]
Sent: Thursday, June 05, 1997 11:13 AM
To: Finley, Anne Marie
Subject: Blood Safety

Chairman Christopher Shays
Subcommittee on Human Resources &
International Relations
B372 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman and Committee Members:

As an HIV infected hemophiliac, I have seen dozens of my hemophiliac friends die in the past fifteen years as a result of being infected by impure clotting substances.

I urge you to continue your fight for speedy notification of recalls to the hemophiliac community, as well as stringent regulation and strict enforcement of all blood and fractionated components of blood used in this country.

Too many have died. Too many more are lingering--praying for a cure which may not come in our lifetimes. Please see that future generations of Americans are not faced with the tragedy our community has endured.

Sincerely,

Danny M. Moon
6405 Wildwood Circle N. # 102
Fort Worth, TX 76132
817-292-2327

COMMITTEE OF TEN THOUSAND
918 PENNSYLVANIA AVE. SE
WASHINGTON D.C. 20003
(202) 543-0988 FAX (202) 543-6270
ADVOCATES FOR PERSONS WITH HIV/AIDS

SUBCOMMITTEE ON HUMAN RESOURCES
&
INTERGOVERNMENTAL RELATIONS

TESTIMONY OF COREY S. DUBIN
PRESIDENT COMMITTEE OF TEN THOUSAND
MEMBER-FDA BLOOD PRODUCTS
ADVISORY COMMITTEE

THURSDAY JUNE 5, 1997

RECALL, NOTIFICATION & LOOK-BACK WHERE DO WE STAND TODAY

Chairman Shays, gentleman and gentlewoman of the Subcommittee, I am Corey S. Dubin, the President of The Committee Of Ten Thousand. We represent the roughly ten thousand persons with hemophilia infected with the AIDS virus through tainted blood products during the 1980's. I am also a member of the Food & Drug Administration's, Blood Products Advisory Committee, the BPAC. Being both a consumer of blood products and a member of the BPAC has given me a very informed and experience based analysis of the nation's blood supply and the problems that continue to plague its operation.

As we have previously testified to this Subcommittee, the hemophilia/HIV holocaust did not begin in the 1980's and sadly it appears to have not ended in that decade either. While there is no doubt that the blood supply is significantly safer today than it was in the 1980's, troubling and potentially dangerous problems exist apparently unabated, even as we speak today. Recently we have seem two large scale recalls that have raised serious questions about the entire structure for recall and end-user notification. As a consumer, I was deeply troubled in both instances at my inability to ascertain "where the buck stops" and who is

advising whether a product should or should not be infused. Is it the FDA or the manufacturers or some player still unknown to me who wields the authority. This remains a mystery to myself and others in the consumer community who are directly involved in the regulatory loop. However this is just one small part of what we, the end-users are most concerned about.

When looking at the question of recall, notification and look-back, one cannot gain a clear picture of the current situation without understanding the history of what occurred during the 1980's with HIV/AIDS and to a lesser degree Hepatitis C. Let us understand very clearly that the statutory requirements for recall, look-back and notification were never met vis-a-vi persons with hemophilia and HIV tainted Factor VIII products. Let me restate that with emphasis, an entire community of end-users infused products that it became known, in many instances by lot numbers, were tainted with HIV and those individuals were never notified by the FDA or the manufacturers. Even when this information was known by individual lot numbers consumers where never officially notified by any entity. It is also clear to anyone who cares to read the 1978 regulations regarding recall, look-back and notification that there was a statutory responsibility to notify the consumers who infused these AIDS tainted products. We, The Committee Of Ten Thousand have placed the question of why this never occurred before the deputy commissioner of the FDA and we are currently still awaiting an answer.

I think it is also very interesting to note that as of March of this year I was the only member of the BPAC who had read or was in possession of the 1978 regulations concerning recall, look-back and notification. I find this very troubling and have yet to ascertain why the most important FDA advisory committee concerning blood/blood products is generally ignorant of the very regulations governing a key component of the blood/blood products equation. Clearly, this does not leave one with a very positive view of the current situation.

It is our contention that there does not exist an efficient, effective or far reaching structure of end-user notification. The system remains grossly inadequate and faced with a new and deadly agent we will again be looking at a disaster as the down time for notification remains far too

long for an acceptable margin of safety.

From our perspective, we have yet to begin designing the necessary system for notification because we are still too busy debating who is ultimately responsible for this notification. Clearly the manufacturers of blood products do not want to be saddled with the entire bill. They are convinced the taxpayers must also weigh in financially. Our position remains that between government and industry, all sectors of the blood/blood products industry, there must be a concerted and immediate effort to design and implement a notification system that reaches the end-user in a reasonable time frame thereby strengthening the overall margin of safety.

At the March BPAC meeting the IPPA, the plasma products producers made it patently clear that they were not and should not be solely responsible for designing and establishing, but most important paying for, a national notification system. It still remains unclear to us where the buck stops on this issue and who is exercising the authority necessary to protect the users of blood /blood products. It is high time the bickering stop and we get down to the business of creating the highest margin of safety possible and without an effective notification system this clearly will not be attained. We are tired of watching this debate go on while clearly understanding that given a new deadly blood borne pathogen we do not currently have an effective national notification system in place that would reach the end-user fast enough to prevent another disaster. From our perspective, it is just that simple and we must act with all deliberate speed and diligence to correct this unacceptable situation. Do we have to again use the hemophilia/AIDS holocaust to remind people what it is that is at stake here. Again, clearly stated it is human life and the potential devastation of many lives if we do not get this problem solved expeditiously.

Unfortunately we are still laboring under a situation of competing interpretations of what constitutes recall, look-back and notification. FDA seems unable to clearly interpret and enforce the, what we believe are very clear, 1978 regulations governing recall and notification. We find the regulations very clear and to the point, yet, this seems not to be the case at FDA where the difference between market withdrawal and

recall is

still open to debate. Are there really question of regulatory interpretation or are they questions of a critical federal regulatory agency unwilling or unable to exercise the power invested in it by the Congress. It is high time we answer this question and create the conditions whereby FDA clearly interprets and enforces regulations regarding blood and blood products.

Recall and notification are at the heart of consumer confidence in the system and what we are seeing today leaves a great deal of room for continued distrust of the situation. These are problems of regulatory interpretation and implementation and we are tired of waiting for the buck to stop somewhere.

A good example of this is the recent recall of Baxter and American Red Cross monocional factor VIII. The product was recalled by Baxter, yet FDA would not advise consumers whether or not the product should be infused. We asked, who's responsibility is it to make that distinction and I was told that COTT should make an independent medical determination about the safety of infusing this recalled product. We find this situation mind boggling and unacceptable. This is not our role and our position is that if a product is recalled then it should never be infused if the highest margin of safety is to be attained. Again we were faced with where does the buck stop and with whom?

We need an independent FDA, capable of clearly interpreting and implementing the regulations and developing the structures necessary to meet the goal creating the highest margin of safety for the end-users of blood/blood products. This is what we are really addressing here, where does the buck stop and who is ultimately responsible for what occurs. We never want to again here as we have in the 1990's that. "we are sorry, but, we dropped the ball and you guys got seriously harmed". That is not acceptable and will never be acceptable to human beings who are wholly dependent on federal regulators to ensure that the priority is always the health and well being of the consumers of blood/blood products. It is time for Congress to provide leadship here and require that establishment of an operating blood policy that creates the highest margin of safety possible for the American people who depend on the safety of our nation's blood supply.

Finley, Anne Marie

From: Lee Harder[SMTP:charder@hevanet.com]
Sent: Friday, June 06, 1997 2:16 PM
To: Finley, Anne Marie
Subject: safe blood for us all

Dear Chairman Shays,

As a sister of two brothers born with Hemophilia, who became infected in the 1980's as a result of tainted blood products, I want to thank you for your time and the effort of you and your staff to bring attention to the very important subject of a better blood safety system. I realize that it is too late for my brothers, but if there is any chance that we can help to protect other families from this heartache and injustice we urge you to press on.

We pray that you will continue to put pressure on the F.D.A. who has the ultimate obligation of protecting our nations blood supply to insure safety to all. Once again thank you for your efforts and may God be with you.

Teresa Harder
Hillsboro, Oregon

Mr. SHAYS. Today we have two panels. The first panel will be testimony from Bernice Steinhardt, Director, Health Services Quality and Public Health Issues, U.S. General Accounting Office, accompanied by Marcia Crosse and Thomas Roslewicz——

Mr. ROSLEWICZ. Roslewicz.

Mr. SHAYS. Roslewicz?

Mr. ROSLEWICZ. Yes, sir.

Mr. SHAYS. Sir, it's nice to have you here.

Mr. ROSLEWICZ. Thank you.

Mr. SHAYS. And accompanied by Thomas Robertson. And as is the practice we swear in our witnesses, even Members of Congress.

[Witnesses sworn.]

Mr. SHAYS. For the record, all four of our witnesses have responded in the affirmative. And we will begin, I guess, with the testimony from you, Ms. Steinhardt.

Ms. STEINHARDT. Yes. Thanks very much.

STATEMENTS OF BERNICE STEINHARDT, DIRECTOR, HEALTH SERVICES QUALITY AND PUBLIC HEALTH ISSUES, U.S. GENERAL ACCOUNTING OFFICE, ACCOMPANIED BY MARCIA CROSSE, ASSISTANT DIRECTOR, HEALTH SERVICE QUALITY AND PUBLIC HEALTH ISSUES, U.S. GENERAL ACCOUNTING OFFICE; AND THOMAS D. ROSLEWICZ, DEPUTY INSPECTOR GENERAL FOR AUDIT SERVICES, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY THOMAS J. ROBERTSON, REGION III INSPECTOR GENERAL FOR AUDIT SERVICES, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Ms. STEINHARDT. Before I begin I'd like also to introduce some other members of the team who contributed substantially to our blood study. I have Kurt Kroemer and Jacqui D'Alessio and Dr. Kwai-Cheung Chan also with me.

Mr. SHAYS. Let me ask. Is it likely that any of those who are accompanying you might respond to testimony?

Ms. STEINHARDT. It's possible. Yes.

Mr. SHAYS. OK. I would just ask—even it's possible you won't, but if it's possible you might, I'd like you to stand now and swear in anyone who is accompanying. Do you have anyone that would be accompanying?

Mr. ROSLEWICZ. Yes, sir, I have.

Mr. SHAYS. If you would invite them to stand, as well.

Mr. ROSLEWICZ. I will. It's Carol Lessans, Steve Virbitskby, Joe Green, and Frank Zuraf.

Mr. SHAYS. All right. Thank you. For the sake of our transcriber, if they do come and testify, we'll make sure you have their full name. But if you'd raise your right hands.

[Witnesses sworn.]

Mr. SHAYS. For the record, all seven have responded in the affirmative. Sorry. Thank you.

Ms. STEINHARDT. OK. Thanks very much. We appreciate the opportunity to be here today to talk about our two recent reports on the safety of the blood supply. Let me begin by saying, as the subcommittee did in its report last year, that the blood supply in the United States is safer than it has ever been. Since HIV was intro-

duced into the blood supply in the early 1980's we've taken important steps to improve the way blood is collected, processed——

Mr. SHAYS. I'm just going to stop you a second. I'm sorry, Ms. Steinhardt. We've getting a little bit of an echo. And this is one of the fascinations that I have, is figuring out why. If you could just turn your mic away a bit and if you'd lower your mic and just put it a little away from you. Let's see if that makes a difference.

Ms. STEINHARDT. OK.

Mr. SHAYS. OK. All right.

Ms. STEINHARDT. We'll try this.

Mr. SHAYS. No, it's not good.

Ms. STEINHARDT. No. That's worse. Let me see if——

Mr. SHAYS. OK. Yes. Why don't we do that?

Ms. STEINHARDT. Putting it over to the side.

Mr. SHAYS. Do you have a way of turning it down a little bit or is it just one level? Yes. OK. Why don't we try again here?

Ms. STEINHARDT. OK. I simply wanted to turn to the graphic that we've provided which shows the five layers of safety that FDA and the blood industry now have in place as a quality assurance system to help ensure the safety of the blood supply. I want to emphasize that even if this quality assurance system were working perfectly there would still be risks associated with transfusion. Blood is a biological product—it comes from humans—not a synthetic process.

In one of the reports we did we set out to calculate the risks associated with transfusion. And we estimate that for people receiving the average transfusion of five units of blood, the risk of receiving a contaminated unit of blood is 1 in 250, or 4 out of every 1,000 patients. Ultimately, roughly 1,500 of the 4 million patients who receive transfusions each year are likely to die or develop a chronic disease as a direct result of a blood transfusion.

On the other hand, as many as half of the patients receiving transfusions—that's about 2 million of the 4 million—would be at serious risk of dying if they didn't receive transfusions. Many of them, in fact, do die even after transfusion. So the risks from contaminated blood are considerably smaller than the risks of dying as a result of surgery or the risk of developing an infection from a stay in intensive care.

Having said this, let me reiterate my earlier point. These are the risks that we calculate from transfusion if the quality assurance system—the five layers of safety—are working perfectly. The second major part of our work revealed that, in fact, the system is not working perfectly. I'd like to spend the remainder of my testimony focusing on some of the more significant problems that we found and the actions we think FDA can take so that it can better vouch for the safety of the blood supply.

The first area I want to talk about this morning has to do with notification. Blood facilities have an opportunity to notify both donors and recipients of indications of infection. But these are not standard nor required practices. Let me speak first about donors. While some facilities may notify donors that they've tested positive on a viral screening test and that they are deferred from donating again, not all do.

FDA recommends that facilities notify donors who test positive for HIV, but it doesn't require facilities to do so nor does it even

recommend this practice for other types of viral infection, like hepatitis. Although the blood in those cases wouldn't be used for transfusion, donors can still attempt to donate at another site. And, of course, they don't have the information that might prompt them to seek treatment or change their behavior.

Facilities also vary in how they handle notifying recipients of infected blood. FDA now requires that patients be notified if they've been transfused with blood that came from a donor who has since been confirmed as HIV-infected, but the agency doesn't require that patients be notified if they've received blood from donors who were later found to be infected with other viruses. We think this kind of notification is important both from an ethical as well as from a public health perspective.

Hepatitis C, for example, can be treated, even if medical therapies aren't yet 100 percent effective. And while the mechanisms of transmission are not well established, CDC has issued guidance on measures that people infected with hepatitis C can take to avoid transmitting it to others.

I'd like to turn now to the issue of recalls and the problems we found in the last layer of safety. If an error or accident occurs that results in a potentially contaminated unit of blood being made available for distribution, licensed facilities have to report the incident to FDA. A reportable error or accident could involve the release of blood that was repeatedly reactive to tests or blood where mistakes were made in testing or that came from donors that should have been deferred or a number of other conditions.

If a facility hasn't already taken steps to recall the blood products, FDA may recommend that it be recalled. This system of required error and accident reports is by and large the basis for recalls. About two-thirds of recalls in 1994 were preceded by error and accident reports. Yet these reports are only required of licensed blood facilities. Those facilities that are not licensed are only asked to submit error and accident reports.

Let me try and put this into some sort of perspective. Of the roughly 3,000 blood facilities in the United States, about 770 engage in interstate commerce and are therefore required to obtain licenses from FDA. The remaining 2,300 or so, many of them hospital-based blood banks, for example, are intrastate facilities, and therefore don't require licenses to operate, although they are required to register with FDA and they are subject to many of the same regulations.

In this case FDA requires that both licensed and unlicensed facilities maintain records of errors and accidents, but only licensed facilities are required to notify FDA when blood safety is affected. Unlicensed facilities are asked to do this on a voluntary basis. The resulting differences in reporting rates is quite striking. I have a graphic here that I would like to refer to. Looking at this in terms of how much blood they are collecting, the licensed facilities, which make up the large bar on the left, are submitting 82 error and accident reports for every 100,000 units of blood they collect. For unlicensed facilities, the comparable number is 12.

Thus, even though unlicensed facilities account for 10 percent of the blood supply, they are submitting only 1 percent of the reports.

Mr. SHAYS. So, 2,300 out of the 3,000 are 10 percent?

Ms. STEINHARDT. They make up 10 percent of the blood supply. They make up far more in terms of the total number of facilities. But in terms of the volume of blood they collect they account for 10 percent.

Mr. SHAYS. Ten percent of the patients?

Ms. STEINHARDT. Ten percent of the blood, of the actual volume of blood collected.

Mr. SHAYS. Right. But I just wanted to have an idea of the number of patients that would be affected in either case. Can I draw a parallel that if it's 10 percent of the blood supply it's potentially approximately 10 percent of the patients, give or take?

Ms. STEINHARDT. Probably. Sure.

Mr. SHAYS. Nodding of heads behind you. Does that give you——

Ms. STEINHARDT. As long as we're all moving in the same direction.

Mr. SHAYS. And they're under oath. So, my gosh, even nodding of heads has got to be acknowledged as—OK.

Ms. STEINHARDT. In addition to these overall error and accident reports, unlicensed facilities also underreport errors that end in product recalls. Out of the hundreds of error and accident reports that preceded a recall in 1994, only six came from unlicensed facilities. And while more than 70 percent of licensed facilities submitted a report before recall, only 17 percent of the unlicensed facilities did this.

Given that these reports are one way of alerting FDA of the need for an immediate recall, we feel that the underreporting by unlicensed facilities is a serious problem. We're also concerned about the amount of time that's taken in responding to error and accident reports leading up to a recall. The longer it takes to initiate a recall, the more likely it is that all the product will have already been transfused.

But as you can see from the pie chart—and I'll refer you to the sum of the green and blue wedges—we found that in 70 percent of the approximately 300 recall cases in 1994, FDA took more than 7 months to confirm a recall from the time it got the error and accident report to review. The total time ranged from a little over a month to 2½ years, with an average of nearly 9½ months. And we couldn't find any significant difficulties in these times based on the severity of the cases. That is, more serious cases were not processed any faster than less serious ones.

Now, typically, a facility will initiate a recall without waiting for FDA to give the go-ahead. But 25 percent of recalls are not undertaken until the agency recommends it. So the agency's timeliness can have very important safety implications.

Finally, I want to highlight some concerns that we have about FDA's standard setting and inspection processes—in point of fact, the underpinning of the entire safety system. FDA now communicates the requirements of this system through a complex of regulations, manuals, guidance documents and recommendations that is often confusing and ambiguous to those facilities who are supposed to implement the system.

Many of the blood facilities we surveyed didn't know which of FDA's various statements were recommended and which were required. With regard to inspections, we found problems in several

areas. FDA policy calls for inspecting facilities every 2 years, unless there have been problems, in which case they could be inspected annually. At the end of the inspection the inspector prepares a report and lists his or her observations. One of the problems we found is that the agency is not performing any sort of systematic statistical analysis of these reports or these observations to try to understand more about problem areas within and among facilities and to make sure that the inspection process itself is working well, that inspections have a certain consistency and rigor.

Second, we found that inspections are not always timely. Twelve percent of the blood facilities nation-wide, according to our projections, may not have been inspected in the past 2 years, as FDA regulations require. And when inspections are conducted, it's not clear that they're complete. In looking through a sample of reports, we could find no indication that about a third of the areas that should have been covered in the inspection—like screening, deferral and testing—had, in fact, been covered at all by the inspector.

FDA's current policy is for inspectors to list on the reports only those areas that were not covered during the inspection. We think this policy is not reliable.

Let me sum up and review what actions we think FDA ought to take in light of our findings. As I indicated at the outset, we think the blood supply is safe, but that it can be safer still.

To start with, we believe that FDA ought to require blood facilities to notify all donors who are permanently deferred, not just those who test positive for HIV, that they have been deferred, and the medical reasons for their deferral. These people should not be attempting to continue donating blood. And they should be given the opportunity to seek further medical care if they choose.

Next, we require that FDA ought to require blood facilities to notify patients when they have been transfused with blood from a donor whose subsequent donations were found to be positive, here too, not just for HIV, but for all viruses for which a confirmatory test is available. Likewise in these cases, we believe facilities ought to be conducting a look back, to identify and remove from their inventories any implicated blood units.

FDA should also be requiring unlicensed as well as licensed facilities to report all errors and accidents. To improve its own enforcement efforts, we believe that FDA ought to clarify what facilities have to do to remain in compliance by determining which guidelines or recommendations are essential for ensuring blood safety, and publishing these in the form of regulations.

And finally, FDA should improve its inspection processes by doing statistical analyses of its reports, making sure that its inspections are more timely, and having inspectors indicate in reports the activities they've actually observed. With that, I'll conclude my remarks and look forward to your questions.

[The prepared statement of Ms. Steinhardt follows:]

Mr. Chairman and Members of the Subcommittee:

It is a pleasure to be here this morning to discuss our examination of the safety of the nation's blood supply. Donors give approximately 14 million units of whole blood and 12 million units of plasma annually. As many as 4 million patients receive transfusions of whole blood components and millions more receive plasma products each year. Since the human immunodeficiency virus (HIV) was introduced into the U.S. blood supply in the early 1980s, the benefits of a potentially life-saving transfusion have had to be weighed against the risks of acquiring this deadly disease through blood transfusion.

Widespread concern about the safety of the blood supply has led to many positive changes in the way blood is collected, processed, and transfused. In testimony on July 28, 1993, before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, the Commissioner of the Food and Drug Administration (FDA) outlined five overlapping "layers of safety" that provided a framework for regulating and monitoring the blood supply industry: (1) donor screening, (2) donor deferral registries to list unsuitable donors, (3) viral testing, (4) quarantining blood until tests and control procedures have established its safety, and (5) monitoring facilities and investigating adverse incidents to ensure that deficiencies are corrected.

While the blood supply is very safe, no amount of federal regulation can entirely eliminate blood transfusion risks because of the biological nature of the product itself. Increasingly sophisticated tests are shortening the time between infection and detectability of infection in the blood. Blood donated during this interval, known as the window period, is the leading cause of infected blood remaining in the blood supply.[1] Improved viral tests will continue to close this gap, but the window period is not likely to disappear completely.

My statement today is based on our two reports on the blood supply issued in February 1997.[2] In these reports, we assessed the current risks of transfusion, evaluating the content and quality of data collected to assess these risks. We also evaluated the FDA's layers of safety and their ability to ensure the safety of the nation's blood supply.

In summary, our analysis of current risks from transfusion showed that, while the nation's blood supply is safer today than at any time in recent history, some risk remains, even if all the safeguards available work perfectly. We also found several vulnerabilities

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[1]The window period is the time from infection to the point at which currently licensed test kits can ascertain antibodies or antigens to certain viruses tested for by blood facilities.

[2]Blood Supply: Transfusion-Associated Risks (GAO/PEMD-97-2, Feb. 25, 1997) and Blood Supply: FDA Oversight and Remaining Issues of Safety (GAO/PEMD-97-1, Feb 25, 1997).

and gaps in current procedures which, if eliminated, would provide greater assurance of safety for the nation's blood supply. The most serious of these problems follow:

- Not all donors who test positive for certain viruses are notified, which means that they can attempt to donate again and also may go without treatment.

- Similarly, not all recipients of virally contaminated blood are notified, which may keep them from seeking treatment and also allow them to transmit the disease.

- Blood facilities are not required to remove from their inventory blood from donors who have subsequently tested positive for viral infections.

- Unlicensed blood facilities that, together, produce 10 percent of the nation's blood do not have to submit to FDA error and accident reports that may signal the need to recall potentially contaminated units of blood.

- FDA's investigations of error and accident reports that warrant a recall take a long time and increase the risk that units will have been transfused before a recall is accomplished.

- Finally, FDA's inspections of blood facilities are inconsistent in focus, scope, and documentation.

Our reports contained a number of recommendations to the Secretary of Health and Human Services to eliminate these weaknesses in the quality assurance system for the blood supply.

TRANSFUSION-ASSOCIATED RISKS

At this time, I would like to tell you more about our analysis of the current risks of transfusion-associated complications from blood, assuming all layers of safety are working properly–that is, blood from donors who were properly screened, whose names were checked against a deferral registry, whose viral test results were negative, and so on.

In conducting our analysis, we reviewed current data and the scientific literature as well as interviewed government and industry epidemiologists. We then compared our final estimates on risks from blood transfusions with data on risks from other health-related causes. We included risks from eight viruses, various bacteria, one parasite, and

four complications of transfusion itself.[3] When we encountered differing estimates of risks from research that we considered equally valid, we chose the higher estimate.

We found that the blood supply is safer today than at any time in recent history. Nevertheless, blood is a biological product, and some risk remains. Eight of every 10,000 donated units carry some kind of potentially serious risk to the recipient, including allergic reactions, bacteria, reactions to incompatible blood, and viruses. We calculated that 4 of every 1,000 patients who receive the average transfusion of 5 units of blood are at risk of receiving a contaminated unit and thus may be exposed to conditions with the potential for the development of serious (that is, chronic, disabling, or fatal) outcomes at some point in the future. We believe this risk is small considering that as many as 50 percent, or 500, of the 1,000 recipients would be at serious risk of dying immediately if they did not receive transfusions.

Moreover, not all recipients of a contaminated unit acquire the disease it contains. And, many recipients die soon after transfusion from the underlying condition for which the blood was prescribed. Finally, the likelihood that a patient will develop chronic disease or die is small for some diseases that are transmitted by transfusion. We determined that the overall risk of developing chronic disease or dying as a direct result of a blood transfusion is about 4 in 10,000, which translates into about 1,525 of the 4 million patients who receive transfusions each year. Thus, if all the safeguards are working properly, the risks are relatively small and are certainly far outweighed by the benefits.

Because risks should never be discussed out of context, we sought to determine whether these transfusion risks were small or large by comparing them with other known health-related risks. The risks to blood transfusion recipients are considerably smaller than the risk of dying as a direct result of surgery, the risk that a hospital stay will result in death or chronic disability, the risk of suffering a serious injury from hospital drug therapy, and the risk of developing an infection of unknown cause in intensive care.

Risks From Plasma Products

The risk estimates I have just presented are for whole blood products from unpaid donors, which account for about half of all donations. The remaining blood products are plasma products, such as immune globulins or clotting factors, which are usually obtained by commercial facilities from paid donors. Because only limited data are available concerning the risks posed by plasma products, we were unable to include plasma

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[3]The viruses included were hepatitis A, hepatitis B, hepatitis C, HIV-1 and HIV-2, human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II), and non-ABC hepatitis. The parasite-transmitted disease included was Chagas', and the transfusion complications were ABO incompatibility, acute lung injury, allergic reaction, and circulatory overload.

derivatives in our analysis of risks. However, because the ways in which plasma products are manufactured differ from the way whole blood products are prepared, and because these products are used differently, it may be worth highlighting some of these features to try to understand the nature, if not the full extent, of risks associated with this sector of the blood supply.

More than 40 million hospital patients use plasma products each year. Plasma is the liquid portion of blood, containing nutrients, electrolytes (dissolved salts), gases, albumin, clotting factors, hormones, and wastes. Many different components of plasma are used for purposes that range from treating the trauma of burns and surgery to replacing blood elements that are lacking as a result of a disease such as hemophilia.

In the 1980s, before the etiology of HIV transmission was understood, many hemophilia patients used plasma products infected with HIV, and 63 percent of all hemophilia patients in the United States became infected as a result. Many more contracted hepatitis B and hepatitis C. Since the introduction of antibody tests and heat treatments and solvent-detergent washing processes for inactivating and removing viruses, however, the transmission of disease has been considerably reduced.

Current techniques appear effective for protecting against the transmission of HIV, hepatitis C, and hepatitis B. But certain viruses that are not surrounded by a fatty envelope–such as hepatitis A and parvovirus–are not inactivated by current techniques. Moreover, different manufacturers producing similar products may or may not use these techniques.[4] The extent to which current manufacturing techniques will be effective against unknown pathogens that could enter the blood supply is not known.

Despite the evidence that viral inactivation and removal processes improve the safety of plasma products, the fact remains that the paid plasma donor pool has higher rates of viral infectivity than the volunteer whole blood donor pool. Unlike whole blood,

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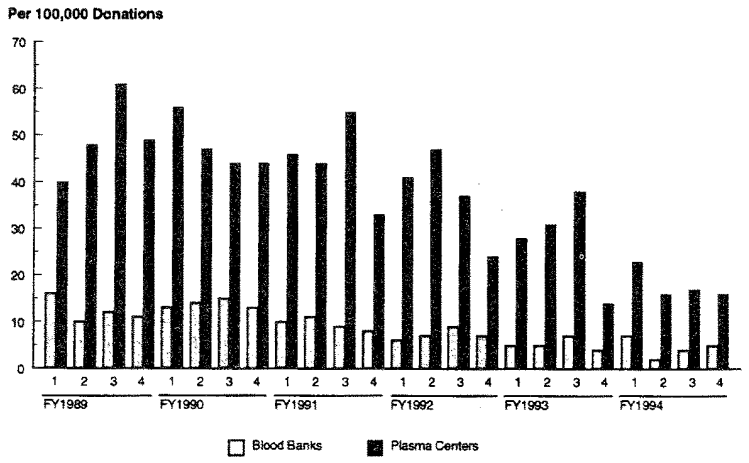
[4]In December 1994, FDA notified manufacturers of immune globulin products that it would begin testing for hepatitis C in all products that had not undergone a validated virus inactivation or removal process. The products affected by this policy include Rho(D) immune globulin for Rh-negative pregnant women and specific immune globulins for hepatitis B; tetanus; and varicella-zoster, the agent that causes chicken pox. No new cases of hepatitis C transmission by these intravenous products have been reported to date. A similar product, immune globulin for intramuscular administration, is not virally inactivated. Although no cases of hepatitis C transmission by intramuscular administration of immune globulin have ever been reported, concerns have been raised about this product, and FDA allows only the manufacturing lots that have been tested for hepatitis C to be distributed. HIV is a delicate virus that is readily inactivated. No cases of HIV transmission by plasma products inactivated according to current standards have been reported.

plasma is typically collected from paid donors in a commercial setting. In 1978, FDA required that each blood unit be labeled as either volunteer or paid. In the regulations, FDA concluded that paid blood donors were more likely to transmit hepatitis to recipients than were volunteer donors. FDA's conclusions were based on research evidence showing higher rates of hepatitis in commercial donors and in recipients of paid donor blood as well as evidence showing that the elimination of commercial blood resulted in substantially fewer cases of posttransfusion hepatitis. While the commercial donor pool for whole blood is all but nonexistent in the United States today, the plasma industry continues to rely on paid donors to supply the raw plasma for further manufacturing into plasma derivatives.

We were unable to obtain national data on the viral test positivity rates among paid plasma donors compared with those of volunteer blood donors. We did, however, find several sources of information pertaining to this issue. First, we found that California requires the reporting of initial and confirmed HIV prevalence rates for both blood banks and plasma collection centers. Figure 1 shows that the confirmed HIV prevalence rates per 100,000 commercial plasma donations in California have decreased in recent years but remain substantially higher than those same rates for volunteer whole blood donations.

Figure 1: Quarterly Confirmed HIV Prevalence Rates for Donations in California, Fiscal Years 1989-94



Note: These rates are reported Western Blot confirmed HIV prevalence rates per 100,000 commercial plasma donations and volunteer whole blood donations.

Source: California Department of Health Services, Office of AIDS, HIV/AIDS Epidemiology Branch, Sacramento, California, August 1995.

Unlike whole blood donors, who cannot donate blood more often than once every 8 weeks, plasma donors can donate twice a week. As a result, fewer plasma donors are needed to collect 100,000 units. Moreover, several plasma units could be donated during a window period, whereas it is unlikely that more than one whole blood unit could be donated in a window period.

We also analyzed the clinical data that plasma manufacturers submitted to FDA during the approval process for several viral tests. The test-positive rates for commercial

plasma donors were substantially higher than those of volunteer whole blood donors, ranging from about 2 to 20 times higher on the different tests.

While most commercial plasma donors are healthy and free of disease, monetary incentives such as those offered by commercial plasma-collection centers may be tantalizing to some of those who are known to be at risk for infectious diseases, such as intravenous drug users and prostitutes. Screening questions address these risk behaviors, but there is no definitive way to screen out all risky donors, and current tests may not be sufficient to catch all infected units.

Newly emerging and yet unknown viruses often enter the population through high-risk individuals. Viral antibody tests may not yet exist for these new viruses, and current viral inactivation and removal techniques may be ineffective for them. Moreover, one infectious donation can contaminate an entire pool of as many as 60,000 units. Without national data on the differences in prevalence and incidence rates between paid and volunteer donors, it is not possible to draw firm conclusions about potential risks posed by plasma derivatives. Such data would be valuable because they could be used to monitor the blood industry in its entirety.

FDA OVERSIGHT AND REMAINING ISSUES OF SAFETY

To test whether blood supply safeguards are working, we examined FDA's layers of safety and found vulnerabilities throughout, including problems in the areas of donor screening, notification, postdonation information, recalls, and FDA standards and inspections.[5] These vulnerabilities are summarized in the appendix.

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[5]We limited the scope of our investigation to policies and procedures that were current in 1994. Thus, we did not examine problems and consequent policy changes of the mid-1980s as a result of the discovery that HIV can be transmitted via blood transfusion. Nor did we examine the patterns of violations by individual facilities. The focus of our work was the general policies and procedures in place to help ensure the safety of the blood supply.

Donor Screening

Donor screening, the first layer of safety, is designed to prevent the donation of blood by people who have known risk factors for disease transmission or are not in good health. High-risk donors, those whose blood may pose a health hazard, are encouraged to exclude themselves. All potential blood donors must answer a series of behavioral and medical questions. If any one answer indicates high risk, the prospective donor is not allowed to donate. If the questions are answered truthfully, they isolate about 90 percent of people whose risk of having HIV is too recent for their bodies to have produced sufficient antigen or antibodies that would be detected by viral screening tests.[6]

We found two potential vulnerabilities in the area of donor screening. First, while questioning and screening donors about their behaviors and medical history is important in maintaining a safe blood supply, studies have shown that the style and content of history taking may influence the accuracy and completeness of donor's answers. The American Association of Blood Banks has a comprehensive and readily available uniform donor history questionnaire that, if adopted by more facilities, could strengthen donor screening procedures. Second, the amount of privacy for screening donors varies across blood facilities. A lack of privacy during donor screening inhibits forthright communication.

The importance of screening donors with validated questionnaires in a private environment is underscored by a study published after our reports were issued of 35,000 blood donors who completed a mail survey 4 to 8 weeks after their most recent blood donation.[7] A total of 186 per 10,000 donors (1.9 percent) reported a deferrable risk that was present at the time of their donation, and 39 per 10,000 donors (0.4 percent) reported having engaged in behaviors that should have resulted in deferral within the 3 months prior to donation. Further refinement of the donor qualification process could help deter these potentially risky donors from donating blood.

Notification

At both the deferral and testing layers, blood facilities have an opportunity, and sometimes a requirement, to notify donors as well as recipients of indications of disease. We found two areas of concern related to notification. Not all blood facilities notify donors that they have tested positive on a viral screening test and that they are deferred

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[6]Antibody tests detect antibodies that the human body produces in its immune response to a virus, whereas antigen tests detect a component of the actual virus. Because it takes time to develop antibodies, antigen tests detect infection earlier than antibody tests.

[7]Alan E. Williams and others, "Estimates of Infectious Disease Risk Factors in U.S. Blood Donors," Journal of the American Medical Association, 277:12 (1997), pp. 967-72.

from donating again.[8] FDA recommends notification of donors deferred for HIV only. While the blood is not used in cases in which test results are positive, this does not ensure that these donors will not attempt to donate at another site; neither does it prompt them to change behaviors or seek treatment so that they do not transmit the disease to family members or others.

Also contributing to this problem is the fact that facilities vary in the extent to which they perform confirmatory or supplementary tests on blood that has repeatedly tested reactive on initial screening assays. FDA only requires confirmatory testing of HIV-positive units. Units repeatedly reactive for other viruses do not always have confirmatory tests performed on them, and confirmatory tests for some viruses have not been developed or licensed by FDA. Thus, facilities that do not perform such tests cannot adequately inform donors about their disease status, even if they notify donors that they are deferred.

Facilities also vary in their policies for notifying recipients who have received blood from donors who later test positive for viruses and for conducting lookback, that is, tracing and removing units from implicated donors that remain in inventory. FDA requires these practices for HIV and recommends--but does not require--quarantine and destruction of units in inventory from donors who subsequently have repeatedly reactive tests for hepatitis B, hepatitis C, and HTLV. FDA has made no recommendations about notifying recipients who may have received blood infected with these other viruses.

Not notifying these recipients poses a potential public health problem. Using hepatitis C as an example, we found that, although the mechanisms of secondary transmission are not well established, some secondary transmission of hepatitis C does occur. The Centers for Disease Control and Prevention has issued guidance for infected people that includes recommending protected sex for individuals with multiple partners and the avoidance of sharing common household articles, such as razors and toothbrushes. Furthermore, abstinence from alcohol is strongly recommended for infected people because alcohol intake results in more liver disease and increases the risk of liver cancer. Although medical therapies are not yet 100-percent effective, clinical trials for alpha interferon therapy show that 23 percent of patients achieved a long-term remission at the end of treatment. We believe recipients of hepatitis C-infected blood

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[8]Screening tests are conducted for hepatitis B by testing for surface antigen (an indication of active virus) and antibody to core (an indication of resolving or past infection and a surrogate marker for high-risk behavior, such as intravenous drug use); for hepatitis C by antibody test; for HIV by antibody and antigen tests; for HTLV-I by antibody test; and for syphilis by serological test. Increasingly sophisticated tests are closing the time between infection and detectability of infection in the blood.

should have the right to decide with their physicians whether medical therapy is indicated for their disease. Moreover, should a more effective therapy arrive in the future, recipients who are not notified today would likely be lost to follow-up.

Postdonation Information

Another critical layer of safety is the quarantining of blood for a period of time following donation during which additional information and test results may lead to the decision that the blood is unsuitable for use. For example, donors may provide information after donating that would have excluded them from donating had it been known at the time of donation. Sometimes donors call to report relatively minor issues such as having developed a cold; other times, donors call to say that they engage in behaviors (such as intravenous drug use) that put them at serious risk of disease; still other times, donors report at a subsequent donation attempt that they engage in behaviors that put them at serious risk of disease. If such postdonation information is received after a unit is made available for distribution, the blood facility must submit this information as an error and accident report–a type of report that a facility must file with FDA whenever it discovers a mistake that affects the safety, purity, or potency of blood products. Postdonation information accounted for about 3,800, or more than one-third, of all error and accident reports in fiscal year 1994.

The preponderance of errors and accidents related to postdonation information is a concern. It could indicate that the system is working properly or that FDA should more clearly define what is to be reported. The large proportion of errors and accidents discovered as a result of postdonation information also calls into question the adequacy of screening processes. For example, 65 percent of the error and accident reports related to postdonation information stemmed from information obtained at a subsequent donation.

While we cannot explain the differences, we found far fewer postdonation error reports from plasma centers than from licensed whole blood facilities: Whole blood facilities' reporting rate was 135 times higher, although both collect approximately the same number of units each year. Since data show higher prevalence rates of HIV and perhaps other diseases at plasma centers, as we pointed out earlier, this appears to be an area where more information is warranted.

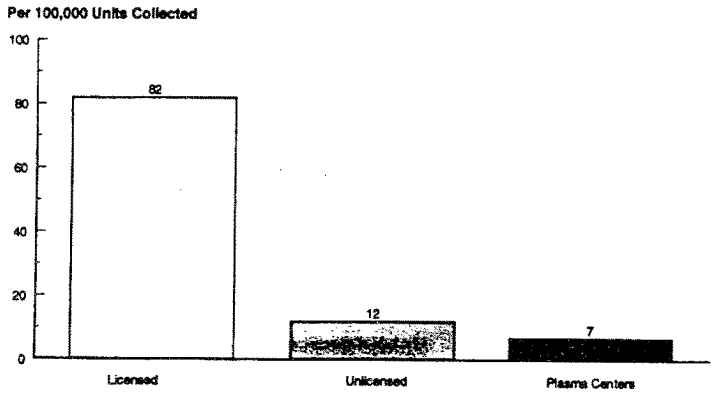
Recalls

As the final layer of safety, blood facilities are obligated to monitor and investigate errors and accidents in their procedures, to audit their systems, and to correct deficiencies. As explained earlier, if an error or accident results in a potentially contaminated unit of blood being made available for distribution, licensed facilities (both whole blood and plasma) are required to report the incident to FDA. Unlicensed facilities are requested to voluntarily report such incidents.

Once a facility reports an error or accident to FDA's Center for Biologics Evaluation and Research (CBER), depending on the severity of the incident, FDA's district field office located nearest the facility evaluates it and may recommend a recall. Most recalls are initiated by the responsible establishment and often are completed before FDA learns of them. Recalls are voluntary; while FDA may prompt a firm to initiate a recall, this occurs in only 25 percent of recalls. In egregious cases, such as those posing an imminent threat to the public where the blood establishment resists initiating a recall, FDA has the authority to initiate product recalls but has never done so for blood products. CBER's role is to determine that an unsuitable product should be recalled if the establishment has not already done so and to classify the recall based on a health hazard evaluation to establish the level of FDA follow-up required to ensure that the public is protected.

Only licensed facilities are required to submit error and accident reports to FDA. Although unlicensed facilities are asked to voluntarily submit their reports, FDA's annual summaries suggest that unlicensed facilities may be underreporting. Our analysis of FDA's summary for fiscal year 1994 found that unlicensed facilities submit only 12 reports for every 100,000 units of blood they collect, compared with 82 reports per 100,000 units for whole blood facilities (see fig. 2). This means that unlicensed facilities submit only about 1 percent of the reports, although they account for 10 percent of the blood supply. While plasma centers are required to submit error and accident reports, they also report at rates much lower than licensed whole blood facilities, despite collecting equivalent amounts of blood products. Moreover, 39 percent of the error and accident reports that CBER received from plasma centers were sent forward to the districts to be reviewed for potential product recalls, as compared with only 5 percent of reports submitted by licensed whole blood facilities.

Figure 2: Total Error and Accident Reports by Facility Type, Fiscal Year 1994



Source: GAO's analysis of FDA's Annual Summary for fiscal year 1994.

Unlicensed facilities also submit fewer error and accident reports in situations that end in product recalls. In roughly two-thirds of the recalls in 1994, a report was submitted before the district office's recommendation for recall: Nearly all of these reports came from licensed facilities, including plasma centers.[9] More than 70 percent of licensed facilities submitted a report before recall, but only 17 percent of unlicensed facilities did this. Given that these reports are one way of alerting FDA to the need for an immediate recall, we believe that underreporting by unlicensed facilities is a serious problem.

In those cases in which facilities are reporting, the Department of Health and Human Services' (HHS) Inspector General's Office has found that timeliness is a problem.[10] For a random sample of 163 reports from October 1992 to April 1993, the time

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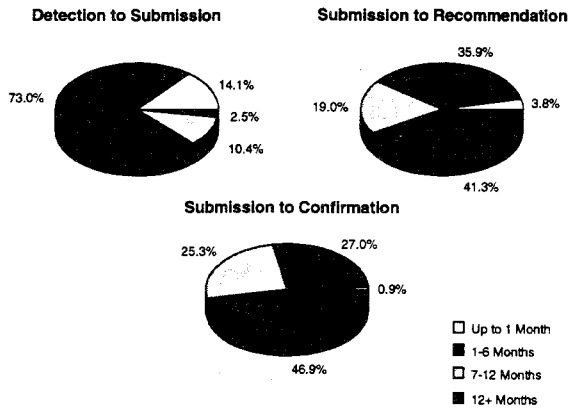
[9]Our statistical analysis determine that this difference between licensed and unlicensed facilities was highly significant (t= -8.96, p <.0001).

[10]Office of Inspector General, HHS, Reporting Process for Blood Establishments to Notify the Food and Drug Administration of Errors and Accidents Affecting Blood, A-03-93-00352 (Washington, D.C.: HHS, May 1995).

between the date when a blood facility detected an error or accident and the date when this information was submitted to FDA ranged from less than 1 month to more than 1 year, the average being a little over 4 months. While 14 percent of reports were submitted within 1 month, 13 percent were reported 6 months or more after the error was detected.

Further, we found that timeliness of FDA actions in response to reports is also a problem. Our analysis of FDA's recall database showed that in 60 percent of cases, 7 months or more elapsed between the time of report submission and the district office's recommendation to CBER that a recall should be considered. The average time for CBER review was 9 weeks, but reviews sometimes took as long as a year. The total time from report submission to recall confirmation and public announcement ranged from a little over 1 month to 2-1/2 years, with an average of nearly 9-1/2 months; in 70 percent of cases, the time was 7 months or more (see fig. 3).

Figure 3: Time Elapsed From Error and Accident Detection to Recall Confirmation, October 1992-April 1993



Note: Numbers may not sum to 100 percent because of rounding.

Source: GAO's analysis of FDA Recall Action Database.

We found no significant differences in FDA's processing time based on the severity of the case. That is, more serious cases were not processed faster than less serious ones. Given the long time FDA takes to go through its formal recall process, blood product safety could be compromised. Clearly, the longer it takes to initiate a recall, the more likely it is that all the product will have already been transfused.

FDA Standards and Guidelines

FDA communicates its requirements through the Code of Federal Regulations (CFR) and its policies and recommendations through memorandums and letters, compliance manuals and the compliance program, compliance policy guides, and a guide for blood facility inspections. The requirements in the Public Health Service Act; the Food, Drug, and Cosmetic Act; and the C.F.R. are the only mandatory requirements.

We found substantial confusion in the industry on the distinction between FDA regulations and guidance, potentially leading to different interpretations and applications of FDA's requirements and recommendations. As part of our review, we conducted a survey of 45 full-service blood facilities.[11] Many of our survey respondents told us they were unclear about which statements had to be followed and which were only FDA recommendations. Respondents also noted that FDA inspectors sometimes filed reports on significant infractions--forms 483--on the basis of FDA recommendations, that the regulations should be updated to incorporate current memorandums, and that the language in the memorandums should be clarified to indicate which actions are required and which are recommended.[12]

A 1995 Institute of Medicine study on blood safety issues recommended that "when issuing instructions to regulated entities, FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration."

The issue has practical implications. The law explicitly requires FDA to prescribe standards for insuring purity, potency, and safety of blood products. However, regarding HTLV testing, FDA has issued memorandums on such procedures; its regulations do not refer to HTLV testing at all. Thus, a facility could be licensed and yet view testing for HTLV as only a recommendation and not a requirement. Nevertheless, not testing for HTLV could directly affect the safety of blood products.

To its credit, FDA has historically issued memorandums to give the industry immediate feedback on its positions on new issues. However, guidelines and memorandums issued for expedience appear to rarely move into the formal regulatory process. While blood facilities often incorporate recommendations into standard operating procedures, the lack of a public comment period--as is required in the formal rulemaking process involved in setting regulations--gives blood facilities no opportunity to address important implementation issues and could lead to inconsistent policies in the industry.

FDA Inspections

We found several problems in FDA's inspection process in four broad categories: the use of inspection reports, the timing of inspections, the completeness of inspection

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[11]By "full-service," we mean those facilities that conduct the full range of blood collection, processing, and distribution (including viral testing). The response rate to our survey was 100 percent.

[12]An FDA inspector who identifies significant infractions that could affect blood safety files a form 483, noting the objectionable conditions.

reports, and the consistency of inspection reporting. FDA inspects blood facilities every 2 years. Facilities that have received a warning letter or have been found deficient in inspections within the past 2 years may be inspected annually until they pass two consecutive inspections without significant observations. Inspectors file an establishment inspection report with FDA at the close of the inspection, which descriptively narrates the activities covered in the inspection and any problems identified. Observations of potentially unsafe conditions are filed on a form 483 and discussed with management of the facility.

We were told by FDA that it reviews all inspection reports. However, we found that FDA conducts no systematic statistical analyses of inspection reports or forms 483. Without collating, synthesizing, analyzing, and evaluating these data, FDA has no means of assessing overall national compliance, assessing trends by type of facility, identifying the problems of different types of blood facilities, or evaluating the effects of policy changes on implementation rates. By performing these types of statistical analyses, FDA could obtain information on different rates of form 483 observations among district offices, rates of observations by type of activity (for example, donor screening, donor deferral, and viral testing), and rates among types of facilities. We conducted such an analysis, discussed below, which illustrates the feasibility and importance of this task.

We obtained inspection reports and form 483 reports of inspection observations on a nationally representative sample of blood facilities. FDA's own requirement is to inspect blood facilities every 2 years, or more often if significant violations have been detected. However, of the 373 blood facilities in our sample, 45 (12 percent) had not been inspected in more than 2 years. Because our sample represented all blood facilities in the nation, we could project that 348 of the 2,900 registered blood facilities (12 percent) may not have been inspected within the past 2 years.

We also found problems with the completeness of inspection reports. We examined each facility in our sample for whether the inspection report indicated that a particular function (such as viral testing) had been examined. For the purpose of our analysis, if it was mentioned at all in the report, we considered it to have been examined. If it was not mentioned anywhere in any way, we considered that one could not determine whether the area had been examined.

For the time period when checklists were required, we found that 40 of 224 inspections (18 percent) that should have included an inspection checklist did not have one.[13] In many instances, we were unable to determine whether procedures relating to donor screening, deferral, collection, routine testing, viral testing, postdonation information, labeling, quarantining, storage, and "machines" were examined at all in the individual inspections. In fact, for all the areas in our analysis that FDA should have

[13]In September 1994, FDA replaced the checklist with a systems-based guide.

inspected, we could not find indications that it did so in 33 percent (963 of 2,957 areas). Further, we were able to determine in only half of all reviewed reports that inspections covered all activities necessary to ensure compliance.

FDA's current policy is for the inspectors to list on the inspection report only areas that were not covered. That is, when an inspector notes on the report that the inspection was undertaken within a specific compliance program, this means that all blood banking practices covered in the compliance program have been examined. We found that this policy is unreliable in ensuring that activities not covered during the inspection are, in fact, noted on the report. Moreover, without detailed information, FDA supervisors or subsequent inspectors cannot determine what blood banking processes have been examined in an inspection.

For example, at a blood facility inspected in 1994, an inspector found that no lookback procedures had been followed in several cases of reported HIV-positive donors identified since 1990. When we examined the inspection report for this facility for the inspection that took place in 1993, we found no indication that lookback procedures were not being followed. This means either that the 1993 inspection examined lookback procedures and did not find that they had not been carried out since 1992 (according to the 1994 inspection) or that lookback procedures were not observed in the 1993 inspection and this was not noted on the inspection report, which is FDA's stated policy.

As a further measure of the comprehensiveness of inspections, we asked the 45 full-service blood facilities in our survey to what extent FDA examined standard operating procedures in 12 separate areas in their last inspection. In every area except deferral, more than half the respondents indicated that FDA examined standard operating procedures only to a moderate extent or less. Similarly, the respondents reported that FDA does not observe or otherwise examine firsthand major activities in many areas. More than 20 percent reported little or no FDA observation of six different areas. Furthermore, 35 percent of the respondents indicated that FDA evaluated the existence and suitability of only half or fewer of the critical control points their facilities had in place to ensure safety, purity, and potency.

Finally, we have concerns relating to the consistency of inspection reporting. We found significant disparities in inspection reporting across the eight FDA districts we examined. For example, more than 21 percent of form 483 observations related to labeling in one district but only 2 percent in another. We also found statistically significant differences between districts in the issuance of forms 483. In particular, one district issued forms 483 to only 20 percent of inspected facilities, compared with a range of 42 to 52 percent among the districts most likely to issue a form 483. Districts differed in the types of activities that warranted forms 483. Why observations are issued inconsistently is not clear. Either different districts have different problems, or different districts interpret FDA policy differently. Neither we nor FDA can say which is the case. Yet 27 percent of our survey respondents reported that they do not know what to expect

from one inspection to the next; what is acceptable to one inspector, they say, may be an unsafe condition to another. And while respondents reported that their most recent inspection team was knowledgeable about blood banking terminology and technology, 45 percent reported a wide variation among inspectors.

CONCLUSIONS AND RECOMMENDATIONS

While FDA, together with industry, has made great strides in improving the nation's blood supply since the recognition of the risks posed by HIV, we believe that eliminating the vulnerabilities we identified would enhance the safety of blood products.

Therefore we have recommended that the Secretary of Health and Human Services take the following actions:

- Require that blood facilities notify all donors who are permanently deferred (not just those who test positive for HIV) that they have been deferred and the medical reasons for their deferral, so that they do not attempt further donation and can seek further medical care if they desire.

- Require confirmatory testing of all repeatedly reactive viral test results for which there is a licensed confirmatory test, in order for blood facilities to be able to properly counsel donors as to their disease status.

- Require that patients be notified when they have been transfused with blood from a donor whose subsequent donations were found to be positive by confirmatory testing for any virus for which a confirmatory test is available, not just for HIV. We note that the reasonable time period for tracing back units to recipients varies with each virus, and decisions should be made in consultation with the blood industry.

- Require lookback to identify and remove units from implicated donors that remain in inventory in situations in which those donors' subsequent donations are found to be positive by confirmatory testing (for any virus for which a confirmatory test is available, not just for HIV).

- Require unlicensed facilities to report all errors and accidents.

We have recommended that the Secretary take the following additional actions:

- Publish in the form of regulations the guidelines that FDA deems essential to ensure the safety of the blood supply and require that FDA clarify its position on the extent to which facilities must adopt guidelines and memorandums in order to remain in compliance.

- Correct problems that we have identified in FDA inspection processes. FDA should perform statistical analyses of inspection reports, ensure that all blood facilities are inspected in a timely fashion, develop policies for the inspectors to list on inspection reports the activities they observe, and publish better guidance to inspectors on the types of activities that warrant reports on deviations and warning letters.

FDA has been aware of a number of these problems for several years and has initiated some actions to address them. In other cases, the agency has said that our recommendations would be too costly or unnecessary.

We remain convinced, however, that if all the improvements we identified are made, the American public will be better assured that the blood supply is as safe as possible given the current state of technology and medical knowledge. Continued safety depends on the scientific and medical communities' vigilance in detecting and identifying any new threats to the supply.

This concludes my prepared statement, Mr. Chairman. I will be happy to respond to any questions that you or Members of the Subcommittee may have.

REMAINING VULNERABILITIES IN THE LAYERS OF BLOOD SAFETY

Donor screening	– The style and content of history-taking questionnaires may influence the accuracy and completeness of donors' answers. – Lack of privacy at some facilities may inhibit forthright communication.
Notification	– Lack of universal donor deferral notification could create public health problems. – Lack of universal confirmatory testing of donors testing repeatedly reactive on initial screening assays precludes facilities from having complete information on disease status to use in notifying donors and recipients. – Except for HIV, recipients who have received potentially infectious blood do not have to be notified, and blood facilities do not have to trace and remove units that remain in inventory.
Postdonation information	– Many errors and accidents are discovered as a result of postdonation information that would have excluded the donor had it been known at donation. – Plasma centers report proportionately fewer postdonation errors and accidents than licensed whole blood facilities, despite being subject to the same reporting requirement and collecting equivalent amounts of blood.
Recalls	– Only licensed facilities are required to report. – Plasma centers report proportionately fewer errors and accidents in all areas, despite being subject to the same reporting requirement and collecting equivalent amounts of blood. – Report submissions and subsequent FDA investigations are not always timely.
FDA standards and inspections	– FDA guidance to blood facilities is often ambiguous. – FDA does not perform statistical analyses on inspection reports and forms 483 and therefore cannot assess compliance trends. – Some facilities are not inspected within FDA-established timeframes. – Inspection reports are often incomplete. – Differences exist in form 483 observations among FDA districts, including disparities in what actions constitute need for further action.

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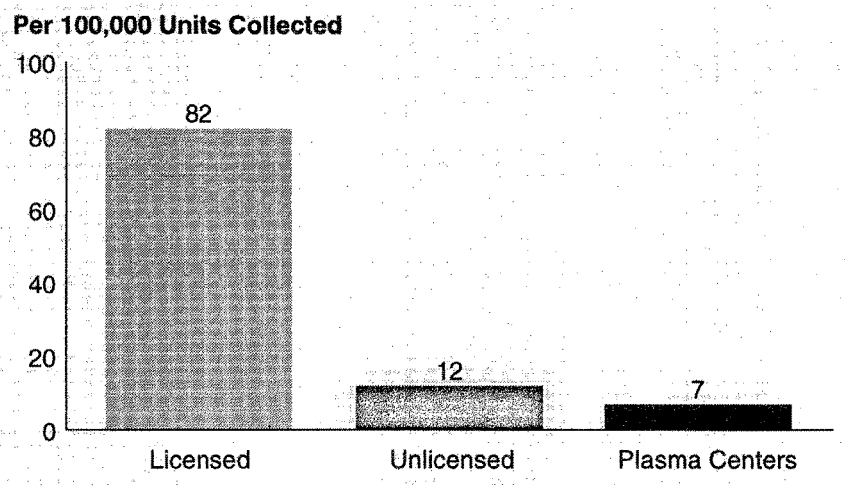
Total Error and Accident Reports by Facility Type



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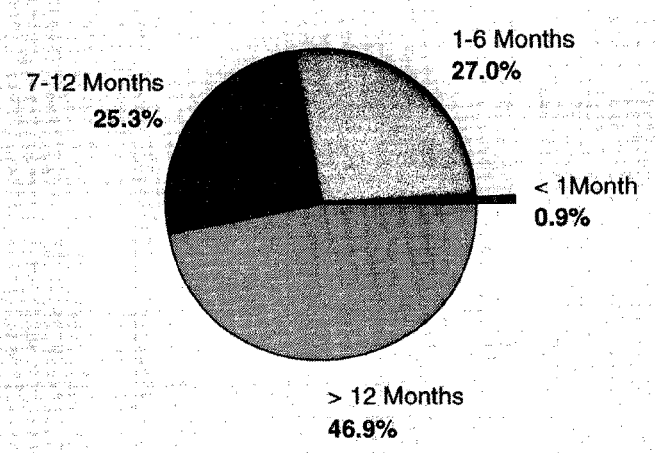
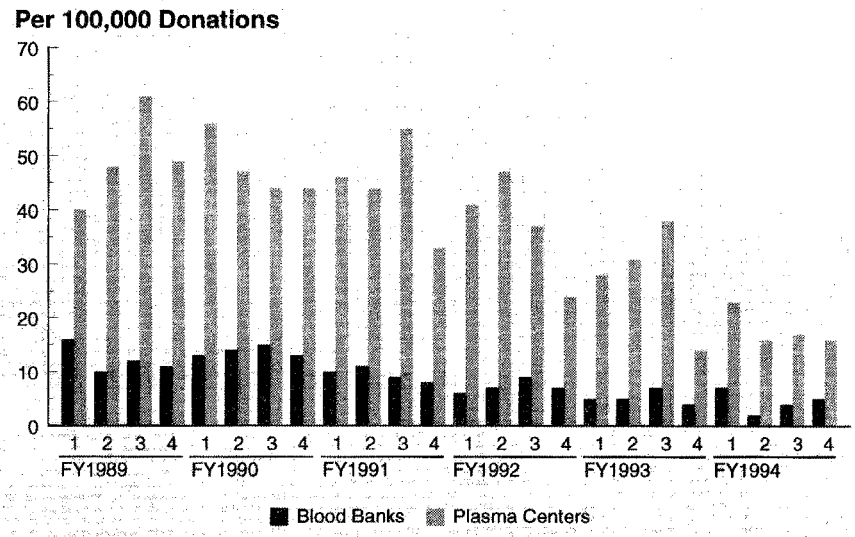
Time from Error and Accident Report Submission to Recall Confirmation



GAO

Quarterly Confirmed HIV Prevalence Rates Among Donations in California, FY1989-94



Mr. SHAYS. Thank you. Mr. Roslewicz, I forgot to introduce your title. You're Deputy Inspector General for Audit Services, Office of the Inspector General, U.S. Department of Health and Human Services. And it's nice to have you here. It's very helpful to our committee to have both the GAO and the Inspector General participate in these hearings. You do a lot of the work for our committee, and we appreciate it. You may begin.

Mr. ROSLEWICZ. Thank you, Mr. Chairman. I also have with me Mr. Tom Robertson, who is the Regional Inspector General for Audit in our Philadelphia regional office. It was his staff that did the review of the audit. I'm pleased to discuss the results of our work which you requested concerning the Food and Drug Administration's inspection process for the plasma fractionator industry.

The Center for Biologics Evaluation and Research [CBER] is the FDA component responsible for regulating blood products, vaccines, serums and toxins. The Office of Regulatory Affairs [ORA] directs the agency's field staff which performs inspections of FDA-regulated establishments. Our work focused on FDA's role of regulating the industry that fractionates, or chemically breaks down, blood plasma into other useful components.

Products made from plasma are essential in treating serious health conditions such as hemophilia, shock, trauma, and burns. The FDA has licensed 26 sites worldwide to fractionate plasma and manufacture plasma derivatives that are used in the United States. The Food and Drug Administration is responsible for inspecting licensed plasma fractionators to ensure that the products are safe, effective, properly labelled and contain the quality and purity that they purport to possess.

Inspections where problems are identified can result in FDA issuing regulatory actions. Prior to 1992, CBER staff performed inspections of plasma fractionators and initiated regulatory action stemming from such inspections. From 1992 through 1996 ORA was phased into the inspections of fractionators, with CBER retaining the lead role in the inspections. That CBER performed these inspections was unique because ORA's field staff conducted inspections of all other FDA regulated firms including manufacturers of drugs, devices and foods.

Prompted by a variety of factors including the subcommittee's concern about this unique inspection situation, FDA has begun to change how it inspects plasma fractionators. Beginning in fiscal year 1997, except for prelicensing inspections, ORA assumed lead responsibility for inspecting plasma fractionators.

Mr. Chairman, the FDA is moving in the right direction to ensure that plasma fractionators and other biologics manufacturers are properly inspected and held accountable for regulatory violations. However, we do believe that the agency can do more to improve the inspection process.

We reviewed 63 plasma fractionator inspections conducted between 1992 and 1997 which accounted for 25 of the 25 fractionators. Of the 63 inspections, 33 were conducted by CBER staff only and 30 were conducted jointly by CBER and ORA staff. Our review revealed two key areas where ORA's involvement appeared to bolster the plasma fractionator inspection and the enforcement processes.

By comparing the inspections conducted solely by CBER, the joint inspections resulted in, first of all, more reported problems being identified and, second, more enforcement actions. If I may call everybody's attention to the chart on the wall here, the blue represents the joint inspections by ORA and CBER, the red represents the inspections that were done by CBER only. As you can see, the CBER only——

Mr. SHAYS. Do you have fun using that little thing?

Mr. ROSLEWICZ. Oh, I love it.

Mr. SHAYS. My staff moved back, thinking it was going to kill him here.

Mr. ROSLEWICZ. I love it. It helps me to focus on the chart.

Mr. SHAYS. OK. The FDA—do you regulate this? OK. It's a safe product. And effective.

Mr. ROSLEWICZ. As long as I don't point it in somebody's eyes it's safe.

Mr. SHAYS. I would like to be able to use that, and I could just point to each one as I wanted them to speak. OK. Sorry.

Mr. ROSLEWICZ. What we're showing on this chart is that the average problem reported where CBER only did the review was six. However, when they did joint review, the average problems reported on the inspection were 26. Now, of course, the more observations or problems that are reported result in more advisory actions and more other regulatory actions being taken. As you can see, again, the red bar shows that with CBER only, there were two regulatory actions taken. When the joint review started, it increased to 11, adding the 9 here plus the 2 over there.

So, while CBER brings scientific expertise to the inspection process, ORA offers the following. The ORA staff are full-time inspectors, compared to the CBER staff, who are part-time inspectors. Further, the ORA staff have expertise in conducting good manufacturing practices. We also noted that when ORA was involved, the joint ORA/CBER inspections had more staff and lasted longer than the CBER only inspections.

Our work also revealed continuing problems in two other areas: prenotification and documentation. Although CBER's policy is not to prenotify plasma fractionators of upcoming inspections, we have found that CBER has not followed its own procedures on requiring production schedules. The subcommittee expressed concern that CBER's practice of required production schedules resulted in de facto prenotification, which could permit out of compliance firms to clean up their facilities prior to FDA's appearance.

In November 1996, CBER developed new procedures designed to ensure that prenotification would not occur. The procedures state that CBER is to simultaneously request, by letter, every 6 months, production schedules from all licensed manufacturers of biological products, which number about 150. However, instead of sending these letters, CBER opted in making telephone calls, resulting in only 23 firms submitting their production information.

Contacting all manufacturers ensures that those to be inspected are not tipped off to FDA's appearance onsite. As a result of not following its procedures, CBER cannot provide definitive assurance that all manufacturers were contacted and that all manufacturers were contacted at the same time. A second continuing problem we

noted with plasma fractionator inspections is the absence of documentation in the files to show the inspection was classified.

The classification occurs when CBER reviews the inspection report. It indicates the seriousness of the problems observed, and determines whether some form of corrective action or sanction is appropriate. Of the 63 inspection files we reviewed, 15 did not contain documentation to show that the inspection was classified. CBER informed us that six of these inspections were never classified.

Without a timely classification, any appropriate corrective action or sanction is unlikely. We were encouraged to learn that FDA has plans for ORA to take the lead for all biological inspections now being conducted by CBER. An April 1997 draft plan proposed a core team of ORA and CBER investigators, and allows the agency to focus highly skilled resources on violative situations and to expedite their correction.

We recommend that FDA implement this plan and ensure that appropriate milestones are included for transferring all biological inspections to ORA.

Finally, at the subcommittee's request, we reviewed FDA's handling of two plasma problem cases. In the first case, involving a fractionator called Centeon, a plasma product recall was effectively communicated to the affected parties. However, FDA ineffectively handled the initial report of the problem related to the Centeon product and had not previously inspected the production of the plasma product, albumin.

The second case study involved an industry-wide saline contamination problem associated with the collection of plasma. Such contamination could result in a viral test showing false negatives. We found that FDA's involvement with an industry-sponsored work group formed to solve the problem was neither illegal or unethical. We noted, however, that FDA did not provide equal regulatory oversight to the two device manufacturers involved. They did not inspect the viral inactivation procedures at a manufacturers plant and were not aware of saline contamination problem for 5 years because they had not required the industry to report it.

With regard to the inspection, we subsequently learned that the manufacturer initiated a class 3—the least serious—recall of a plasma product on May 24, 1997, due to the firm not maintaining the specified temperature for the viral inactivation process.

Mr. Chairman, we believe that FDA's actions to increase ORA's role in the inspection and enforcement of plasma fractionators have improved the process, as evidenced by the increased number of problems identified and enforcement actions taken. Our report, which we submit today for the record, contains recommendations that should further strengthen FDA's role in preventing, detecting and handling plasma related problems.

As indicated in the report, FDA generally agrees with our recommendations and is taking action to correct them.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Roslewicz follows:]

INTRODUCTION

Mr. Chairman and members of the Subcommittee, I am Thomas D. Roslewicz, Deputy Inspector General for Audit Services of the Department of Health and Human Services. I am pleased to discuss the results of our work concerning the Food and Drug Administration's (FDA) regulation of the plasma fractionator industry. This is the third review that we have conducted in the blood safety area--our previous work addressed FDA's handling of error and accident reports submitted by blood establishments and the blood product recall classification process.

The Subcommittee asked us to review certain aspects of FDA's oversight of the plasma fractionator industry, most notably the agency's effectiveness in conducting inspections of such firms. During my testimony, I will briefly describe the FDA regulatory oversight program for plasma fractionators; discuss findings from our analysis of over 60 previous plasma fractionator inspections and the agency's plans to improve the inspection process; address the issue of FDA pre-notifying the plasma industry of impending inspections; and respond to your concerns regarding specific plasma product problems.

BACKGROUND

The Food and Drug Administration (FDA) is the Federal agency responsible for regulating the blood industry by licensing products, and issuing and enforcing safety rules. The

Center for Biologics Evaluation and Research (CBER) is the FDA component responsible for regulating products used for the prevention, treatment or cure of diseases and injuries, including blood products, vaccines, serums, and toxins. The Office of Regulatory Affairs (ORA) directs the agency's field force, which performs inspections of FDA-regulated establishments.

Plasma Fractionation

Our work focused on FDA's role in regulating the industry that "fractionates," or chemically breaks down blood plasma into other useful components. Certain blood products are made from plasma, which is the portion of blood containing nutrients, electrolytes (dissolved salts), gasses, albumin, clotting factors, hormones, and wastes. Plasma-based products are essential in treating serious health conditions such as hemophilia, shock, trauma, and burns. They are also used to prevent certain infectious diseases. The FDA has licensed 26 sites worldwide to fractionate plasma and manufacture plasma derivatives that are used in the U.S.

The FDA is responsible for inspecting licensed plasma fractionators every 2 years. The purpose of the inspection is to ensure that the products are safe, effective, properly labeled, and contain the quality and purity they purport to possess.

Inspections with objectionable conditions can result in FDA initiating regulatory action including, for example, issuing warning letters and revoking establishment licenses.

Product recalls may be undertaken at any time on the initiative of manufacturers and distributors, and FDA can request a firm to initiate a recall when the firm has not already done so and the action is needed to protect the public health.

CBER vs. ORA Inspections

The Subcommittee has been concerned about a long-standing situation regarding CBER's involvement in plasma fractionator inspections. Prior to 1992, CBER headquarters staff--mostly part-time inspectors--performed inspections of plasma fractionators and initiated regulatory actions stemming from such inspections. From 1992 through 1996, ORA was phased into the inspections of fractionators, with CBER retaining the "lead" role. That CBER performed these inspections was unique because ORA's field staff conducted inspections of all other FDA-regulated firms, including manufacturers of drugs, devices, and foods.

Prompted by a variety of factors, including the Subcommittee's concern about this unique inspection situation, FDA has begun to change how it inspects plasma fractionators. Beginning in Fiscal Year 1997, except for pre-licensing inspections, ORA assumed "lead" responsibility for inspecting plasma fractionators.

THE PLASMA INSPECTION PROCESS HAS IMPROVED BUT MORE CAN BE DONE

The Subcommittee conveyed to the Office of Inspector General (OIG) its serious concern

that CBER was not as effective as ORA in carrying out inspections of the plasma industry, and that such a difference could have implications on public health issues. Mr. Chairman, we are pleased to report to you that FDA is moving in the right direction to ensure that plasma fractionator facilities and other biologics manufacturers are properly inspected and held accountable for regulatory violations. However, we believe the agency can do more to improve the inspection process.

ORA Involvement Has Bolstered Plasma Fractionator Inspections

We reviewed 63 plasma fractionator inspections conducted between 1992 and 1997, accounting for 25 of the 26 fractionators. Of the 63 inspections, 33 were conducted by CBER staff only, and 30 were conducted jointly by CBER and ORA staff. Comparing the CBER-only inspections with those conducted jointly by CBER and ORA, we identified two key areas where ORA's involvement appeared to bolster the plasma fractionator inspection and enforcement processes (see attached chart):

(1) The joint inspections resulted in more reported problems--from an average of 6 per CBER-only inspection to an average of 26 for those conducted jointly.

(2) The joint inspections resulted in more enforcement actions--increasing from 2 for the CBER-only inspections for the 33 we reviewed to 11 for the 30 joint inspections we reviewed.

While CBER brings scientific expertise to the inspection process, ORA brings several qualities, which we believe help explain the increases in reported problems identified and enforcement actions. The ORA staff are full-time inspectors, compared to the CBER staff who are part-time inspectors. Further, the ORA staff have expertise in conducting Good Manufacturing Practices reviews, which focus on such areas as organization and personnel, building and facilities, equipment, and records and reports. We also noted that the joint ORA and CBER inspections had more staff and lasted three times longer than the CBER-only inspections.

Problems Persist in the Inspection Process

While ORA involvement appears to have strengthened the inspection process for plasma fractionators, we noted continuing problems in two areas--pre-notification and documentation.

(1) *Pre-notification:* Although CBER's policy is to not pre-notify plasma fractionators of upcoming inspections, we found that CBER was inadvertently pre-notifying them. Pre-notification could theoretically permit out-of-compliance plasma manufacturers to clean up their facilities and records prior to FDA's appearance on-site.

An FDA document provided to the Subcommittee shows that from 1994 through 1996, CBER acknowledged requesting production schedules from biologic establishments in advance of 40 of 193 inspections scheduled, or almost 21 percent

of those scheduled. However, because FDA maintained no written records indicating the firms whose schedules were requested, it was not possible to assess the impact of such requests on the inspection process. Cognizant CBER officials assured us that it was standard operating procedure to not announce annual inspections, even though such pre-announcement is permitted under regulations and is practiced in some sectors of FDA, particularly for foreign inspections.

Recent procedures, dated November 21, 1996, state that CBER is to simultaneously request by letter, on a semiannual basis, production schedules from all licensed manufacturers of biological products, which number about 150. By requesting such schedules at one time from all manufacturers, there would still be an element of surprise as to when each inspection would occur. Instead of sending out letters, however, CBER told us it made telephone calls to manufacturers between November 1996 and January 1997, resulting in only 22 firms submitting their production information. Without the documentation that letters can provide, we are concerned that CBER does not have definitive assurance that all manufacturers were contacted and that all manufacturers were contacted at the same time.

(2) *Documentation:* For one-quarter (15 of 63) of the inspection files we reviewed, there was no documentation to show that the inspection was classified. Of the 15 missing classifications, 11 were associated with CBER inspections and 4 were with CBER/ORA inspections.

The inspection classification, which occurs when CBER reviews the inspection report, indicates the seriousness of the problems and determines whether some form of corrective action or sanction is appropriate. Without documentation indicating the inspection classification, appropriate corrective action or sanction is unlikely.

At our request, CBER has provided us some classification documentation for the 15 inspections. However, at least 6 of these inspections have yet to be classified. In one of these cases, involving 21 problems, CBER told us that it would have issued the firm a warning letter had the inspection report been prepared on a more timely basis and then classified.

CBER/ORA Proposals Should Be Implemented

We are also pleased to report that ORA, in April 1997, in consultation with CBER, developed a draft plan that provides a comprehensive ORA/CBER partnership for regulating not only the plasma fractionator industry, but also the remaining establishments in the biologics sector. The proposal, now under review at FDA, is designed to address the inconsistencies in the inspection and enforcement process between CBER and ORA and among the district offices. By proposing a core team of ORA and CBER investigators, the agency can focus highly skilled resources on violative situations and expedite their correction. It is envisioned that the plan would begin with plasma fractionators and be expanded to other CBER product areas, such as biotechnology, allergens, and vaccines. In light of our finding that ORA has indeed strengthened the inspection process, we believe

the proposal represents a major improvement and should be expedited for other biological products.

OIG Recommendations for Further Improving the Inspection Process

While we support these recent efforts by CBER, Mr. Chairman, we believe that additional measures should be considered by FDA. As a result, we have made the following recommendations to the Commissioner of Food and Drugs:

(1) Review the ORA/CBER partnership plan and ensure that appropriate milestones are included for transferring all biological inspections to ORA.

(2) Ensure that staff are provided instructions on the importance of completing the classification of inspections, and classify the inspections identified during our review as lacking documentation.

(3) Require CBER to comply strictly with its procedures on requesting production schedules from biological establishments.

FDA'S HANDLING OF TWO PLASMA PRODUCT-RELATED PROBLEMS

The Subcommittee brought to our attention concerns related to FDA's handling of two plasma product issues--one involving the recall of plasma products, mainly albumin,

manufactured by Centeon L.L.C. (Centeon); and the other involving an "industry-wide" problem of saline contamination. Both of these case studies point to areas where FDA could further improve its regulatory oversight of the plasma industry. I will briefly discuss our findings with respect to each of the issues.

Centeon's Plasma Product Recall

The Subcommittee raised concerns that FDA issued a Talk Paper rather than a Press Release to communicate to the public the September and October 1996 recall of Centeon products associated with possible bacterial contamination. The FDA and Centeon are continuing to monitor this Class I (most serious) recall. To date, according to the Centers for Disease Control and Prevention, no deaths have been linked to the Centeon products.

We found that the FDA's issuance of a Talk Paper had no adverse impact on the recall of Centeon's plasma product, albumin. We are concerned, however, about the findings of an internal Department of Health and Human Services' (HHS) review, which disclosed serious problems with the recall process.

Talk Paper

Although FDA did not develop a Press Release on the plasma product albumin, it developed three Talk Papers for use outside the agency. Further, FDA initiated a meeting with the Associated Press, which represents about 6,000 newspapers, and made the information about the case available on the Internet. For its part, Centeon was active in

notifying distributors, hospitals and special interest groups.

Internal Review Highlights Problems with Recall

A December 1996 report, prepared by a member of HHS' Office of the Assistant Secretary for Legislation for the HHS Blood Safety Committee, highlighted significant problems with FDA's handling of the Centeon recall, including the ineffective use of adverse event reports and FDA's failure to perform inspections of the plasma product, albumin.

In the report, FDA is cited for its failure to respond to the first notification of a patient's adverse reaction after being administered Centeon's albumin product. The day after the incident, the hospital, where the patient was being treated, notified FDA's MedWatch system of bacterial contamination of the Centeon albumin product. MedWatch is FDA's voluntary system for professionals to report adverse reactions to drugs and biologics, of bacterial contamination of the Centeon albumin product. However, FDA did not treat the report as an emergency and thus was not prompted into further action until the hospital inquired 4 days later about the status of FDA's follow-up.

With respect to the inspection process, the internal report disclosed a troubling situation: FDA had not, until the possible contamination problem arose, inspected Centeon in connection with the production of albumin. This was because the agency considered albumin to be a safe product with a long history of low-risk use. The internal report states that "albumin was not on the compliance radar screen" prior to the contamination incident.

Responding in January 1997 to the critical internal HHS report, the Commissioner of Food and Drugs acknowledged that the Centeon recall could have been handled more effectively and pledged to take corrective action. FDA has established a task force to identify areas where improvement is needed in the handling of adverse event reports. Further, the Commissioner noted that ORA would take the lead for follow-up inspections.

In addition to the critical HHS review, our analysis of MedWatch adverse event reports submitted between 1991 and April 1997 showed that albumin was regularly in the top 5 of the 22 plasma products on which health professionals reported patient adverse reactions. Therefore, we recommended that the FDA task force, established in response to the internal report for the HHS Blood Safety Committee, determine if the intelligence gathered by the adverse event reports could be put to better use in the planning of inspections, particularly with regard to the targeting of fractionators and/or plasma products.

Saline Contamination In Plasma Collections

The second case study the Subcommittee asked us to examine involved FDA's handling of an industry-wide problem involving saline contamination of plasma samples used for viral testing. The issue involves the "backwash" of saline into the sample collection tube when saline is reinfused to the source plasma donor at the completion of product collection. When plasma is contaminated with saline, tests used to detect the presence of HIV and hepatitis could yield false negative results, and could result in the inadvertent use of potentially infectious units of source plasma in the manufacture of fractionated products.

One of the Subcommittee's chief concerns in this matter was CBER's involvement with an industry-sponsored group formed to develop corrective actions to the contamination problem. We found that CBER's involvement with the work group was neither illegal nor unethical.

We have concerns, however, about the agency's regulatory oversight of the firms involved and its policy for requiring the reporting of such contamination.

Saline Contamination Work Group

The FDA's identification of an industry-wide saline contamination problem led the agency to become involved with an industry-formed work group rather than taking regulatory action against the firms involved.

As a result of a March 1995 ORA Chicago District Office inspection, FDA became aware of saline contaminated samples at Baxter Screening Laboratory (BSL). The BSL tests over one million units of plasma a year from 39 plasma centers nationwide. The plasma centers were contracted to supply plasma used in the manufacture of several fractionated products at a Baxter manufacturing plant. The ORA inspection at BSL documented several samples that the laboratory had determined were saline contaminated. Fortunately, the plasma associated with those samples was discarded rather than used in the manufacture of fractionated products. However, the ORA inspection concluded that BSL's investigation into the cause of the saline contamination was deficient and that its procedures may be inadequate to identify other saline contaminated plasma samples. Consequently, ORA's

Chicago District Office recommended that CBER suspend Baxter's licenses for plasma products and inspect the viral inactivation (removal of viruses from the plasma) procedures at Baxter's manufacturing plant.

CBER, however, disagreed with both recommendations because it determined the situation did not involve a danger to health. Instead of singling out Baxter for regulatory action, CBER determined that its resources would be better used if it coordinated with the industry to correct the problem. A plasma industry trade group--the American Blood Resources Association--formed an ad-hoc work group representing source plasma collection facilities, testing laboratories, and collection device manufacturers to address the saline contamination problem. The CBER was invited to participate.

The work group's proposals to correct the problem were contained in a report prepared by CBER. The proposals included: 1) implementing design changes to the plasma collection devices by the two device manufacturers; 2) increasing training for operators of the collection devices; and 3) fostering communication between all parties when saline contamination is identified. The CBER also issued changes to its guide to inspections of viral testing labs designed to alert inspectors to the possibility of saline contaminated plasma. Although CBER made similar revisions to its guide to inspections of source plasma establishments, the revisions are in draft form and have not been cleared for final issuance.

Both HHS' Office of General Counsel and OIG believe CBER's involvement with the industry group was neither illegal or unethical. Further, we understand that FDA routinely cooperates with industry through such means as conferences and meetings to develop regulatory strategies.

OIG Identified Additional Concerns with the Saline Contamination Problem

Nevertheless, our review identified several issues that were not fully addressed during CBER's examination of the saline contamination problem and involvement with the industry-sponsored work group.

First, an ORA recommendation to conduct a follow-up inspection of viral inactivation procedures at Baxter's manufacturing plant was rejected by CBER. A regularly scheduled inspection conducted subsequently gave no indication that the viral inactivation procedures were reviewed. The FDA informed us that, as of May 12, 1997, it had underway an inspection of Baxter's manufacturing plant that included examining the viral inactivation procedures. We subsequently learned that Baxter initiated a Class III (the least serious) recall of a plasma product on May 24, 1997 due to the firm not maintaining the specified temperature for the viral inactivation process.

Second, the problem of saline contamination was traced to the operation of plasma collection devices, the majority of which are produced by two manufacturers--Baxter and Haemonetics. For Baxter's device, FDA issued a safety alert that required FDA follow-up

to ensure that the problems were corrected. For the Haemonetics's device, no safety alert was issued, and FDA follow-up was neither required nor made.

Third, CBER was unaware of a saline contamination problem for about 5 years because firms were not required to report problems if the plasma was not released. We believe this absence of reporting needs to be changed since saline contamination, according to CBER, could have affected the entire source plasma industry had the plasma been released.

OIG Recommendations

To address the problems we found with these issues, we have made the following recommendations to the Commissioner of Food and Drugs:

(1) Verify that the inspection of Baxter, ongoing as of May 1997, included a review of viral inactivation procedures. If the procedures were not included, require such an inspection.

(2) Review the changes made to the plasma collection devices to determine whether they meet the criteria for classification as medical device safety alerts.

(3) Consider requiring plasma collection and testing facilities to report all incidents involving saline contamination.

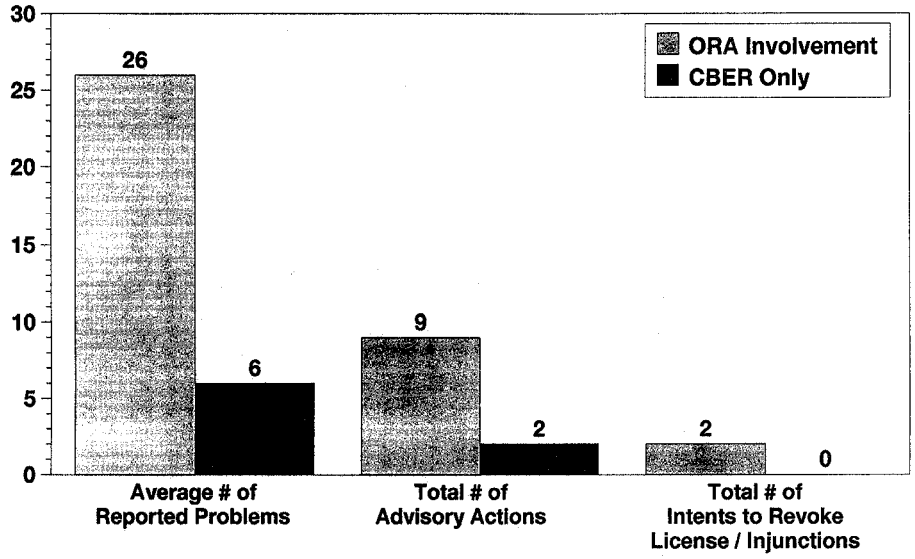
(4) Finalize and implement the draft changes to the inspection guide for source plasma establishments and the compliance program for plasma fractionators.

CONCLUSIONS

We believe that FDA's actions to expand ORA's role in the inspection and enforcement of plasma fractionators have improved the process, as evidenced by the increased number of problems identified and enforcement actions. We further support FDA's plan to transfer the lead inspection role to ORA for other products regulated by CBER. We have outlined additional recommendations that should further strengthen FDA's role in preventing, detecting, and handling plasma contamination problems. These recommendations, as well as a more detailed discussion of our findings, are contained in a report that we have submitted this morning, for the record. As indicated in the report, FDA generally agrees with our recommendations and is taking action to implement them.

This concludes my testimony, Mr. Chairman. Thank you for the opportunity to testify today. At this time I will be happy to answer any questions you may have.

Effect of ORA Involvement On Inspections of Plasma Manufacturers



Source: OIG Review of 63 FDA Inspection files representing inspections conducted between August 10, 1992 and March 21, 1997 of 25 of the 26 plasma manufacturers.

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S INSPECTION PROCESS OF PLASMA FRACTIONATORS

JUNE GIBBS BROWN
Inspector General

JUNE 1997
A-03-97-00350

EXECUTIVE SUMMARY

BACKGROUND

At the request of the Subcommittee on Human Resources, House Committee on Government Reform and Oversight, the Office of Inspector General (OIG) reviewed selected aspects of the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) and Office of Regulatory Affairs (ORA) regulation of blood plasma fractionator industry. The CBER is responsible for regulating products used for the prevention, treatment or cure of diseases and injuries including blood products, vaccines, serums, and toxins. The ORA directs the agency's field force, which performs inspections of FDA-regulated establishments.

Certain blood products are made from plasma, which is the portion of blood containing nutrients, electrolytes, gasses, albumin, clotting factors, and salts. Blood plasma fractionators, which number 26 worldwide, separate the various active components of plasma.

The FDA is responsible for inspecting licensed plasma fractionators every 2 years. The purpose of the inspection is to ensure that the products are safe, effective, and contain the quality and purity they purport to possess and are properly labeled.

CBER vs. ORA Inspections

Prior to 1996, CBER headquarters staff, located in Rockville, Maryland, performed inspections of plasma fractionators and initiated regulatory enforcement stemming from such inspections. That CBER performed these inspections was unique because FDA's field force, directed by ORA, conducted inspections of all other FDA-regulated products, including drugs, devices and foods. The ORA inspectors are generalists who have expertise in Good Manufacturing Practices (GMP). The CBER inspectors are scientific experts in the fractionation process. Beginning in Fiscal Year 1997, FDA authorized ORA to have "lead" responsibility for inspecting plasma fractionators, except pre-licensing inspections, and to assume the lead role for other biological products over a 3-year period.

Inspection reports are to be completed within 30 work days of completing a violative inspection, and within 45 work days of a non-violative inspection. Inspections with objectionable conditions can result in FDA initiating regulatory action including, for example, issuing warning letters and revoking establishment licenses.

Inspections Reviewed by OIG

We reviewed 63 inspection files for 25 of the 26 plasma fractionator inspections conducted between August 10, 1992 and March 21, 1997. During that period, several changes were made in the fractionator inspection process, leading to more ORA involvement in the process. Of the 63 GMP inspections, 33 were conducted by CBER staff only, while the remaining 30 were joint inspections conducted by CBER and ORA staff.

OBJECTIVE

The objective of our review was to respond to the Subcommittee's concerns in the following three areas:

(1) Plasma fractionator inspection process: The Subcommittee was concerned about CBER's effectiveness in conducting inspections of plasma fractionators when compared to inspections conducted by ORA. It was also concerned whether CBER routinely notified plasma fractionators in advance of upcoming inspections.

(2) FDA's handling of Centeon's albumin recall: The Subcommittee was concerned about the appropriateness of the agency issuing a talk paper rather than a press release to communicate a 1996 recall of plasma products made by Centeon, a plasma fractionator; and how this situation compared with a recall of a juice product.

(3) FDA's handling of an industry-wide plasma saline contamination problem: The Subcommittee was concerned that FDA, instead of taking enforcement action against a plasma fractionator, elected to participate with an industry-sponsored committee established to address the problem.

SUMMARY OF FINDINGS

Overall, we found that FDA was aware of the Subcommittee's concerns and, for this and other reasons, had begun taking steps to ensure that plasma fractionators and other biological manufacturers are properly inspected and held accountable for regulatory violations. The most significant improvement has been for ORA to assume the lead inspection role for plasma fractionators. However, as delineated below, we believe FDA can do more to strengthen its regulatory oversight of the plasma fractionator industry.

Regarding the specific Subcommittee concerns, we found that:

(1) Inspections of plasma fractionators in which ORA was involved resulted in more reported observations of objectionable conditions and more enforcement actions against plasma fractionators than inspections conducted solely by CBER.

- ✓ Inspections involving ORA staff (these inspections also involved CBER staff and are referred to in this report as joint inspections) resulted in four times as many observations being reported, and five times as many enforcement actions as inspections involving CBER staff only.

- ✓ Timeliness and documentation problems previously reported by internal FDA reviews continue. We noted delays in the preparation of Establishment Inspection Reports (EIRs) and warning letters. Most of the delays and missing documentation were associated with CBER inspections.

- ✓ CBER's policy was not and is not to pre-notify plasma fractionators located in the United States of upcoming inspections. To ensure that requests for production schedules are requested on a consistent basis and do not amount to a *de facto* prenotification of an inspection, CBER recently established new guidelines for requesting production schedules. These guidelines, however, were not being complied with, and there is no assurance that the intent of the guidelines are being met.

(2) The FDA's issuance of a talk paper in lieu of a press release was effective in communicating the recall of the plasma product albumin; however, an internal review disclosed serious problems with the recall.

- ✓ Although FDA did not issue a press release on the plasma product albumin, it issued a talk paper, which was distributed outside the agency. In addition, it initiated an interview by the Associated Press (which represents about 6,000 newspapers) with the appropriate CBER official.

- ✓ Significant problems surrounding the albumin recall were reported in an internal review made for the Department of Health and Human Services Blood Safety Committee. The focus of the problems dealt with the FDA's inadequate response to a MedWatch[1] adverse event report, and to previous inspection results.

- ✓ The Commissioner of Food and Drugs responded that corrective action was taken and planned. A task force was established to identify areas where improvement is needed in the handling of adverse event reports.

- ✓ Our review showed there is a need to ensure that adverse event reports are used to target plasma fractionators and/or products for inspection. Albumin

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1. MedWatch is a voluntary reporting system by health professionals of adverse events and problems. MedWatch is operated by a contractor and does not assess the reports. The FDA's Center For Drug Evaluation and Research evaluates and processes the adverse event reports on all drugs and biologics.

was regularly in the top five of all plasma products reported via adverse event reports, but inspections were not focused on the product until the Centeon recall.

(3) ***The CBER's participation with the plasma industry's work group established to study the problem of saline contamination was neither illegal nor unethical, but CBER was not consistent in its handling of devices found to be involved with the contamination.***

- ✓ The CBER chose not to implement the ORA's Chicago District Office recommendation to revoke the license of a plasma fractionator because a CBER Health Hazard Committee determined that a health hazard did not exist.

- ✓ In lieu of an enforcement action CBER chose to participate with an industry work group. According to the HHS Office of General Counsel and the OIG Office of Counsel, CBER's participation with the industry group was neither illegal nor unethical.

- ✓ An ORA recommendation to conduct a follow-up inspection of viral inactivation procedures at a plasma fractionator (Baxter's Hyland facility) was rejected by CBER. A regularly scheduled inspection conducted subsequently gave no indication that the viral inactivation procedures were reviewed.

- ✓ The problem of saline contamination was traced to a plasma collection device, the majority of which are produced by two manufacturers. For one device, FDA issued a safety alert thus requiring FDA follow-up to ensure that the problems were corrected. For the other device, no safety alert was issued, and FDA follow-up was not required, and not made.

- ✓ CBER was unaware of a saline contamination problem for about 5 years because firms are not required to report it if the product is not released. We believe this needs to be changed since saline contamination, according to CBER, has the potential to affect the entire source plasma industry.

RECOMMENDATIONS

We, therefore, recommend that FDA:

1. Review the proposal on the inspection process originally drafted by ORA's Biological Advisory Committee in April 1997 and implement it to the extent feasible.

2. Ensure that CBER has a viable plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biological products currently being inspected by CBER.

3. Adhere to time frames established for the preparation of EIRs and the issuance of warning letters.

4. Instruct employees of the importance of completing the classification of inspections; and require CBER to classify the inspections identified in this report as lacking documentation and take whatever enforcement actions that are appropriate based on the classifications.

5. Require CBER to comply strictly with the policy on requesting production schedules from biological establishments.

6. Require the FDA task force, established in response to the internal report for the Blood Safety Committee, to determine if the intelligence gathered by the adverse event reports could be put to better use in planning inspections, particularly with regard to the targeting of plasma fractionators and/or plasma products.

7. Verify that the inspection of Hyland, ongoing as of May 12, 1997, includes a review of viral inactivation procedures. If the procedures were not included, require such an inspection.

8. Review the changes made to the plasma collection devices to determine whether they meet the criteria for classification as medical device safety alerts.

9. Consider requiring plasma collection and testing facilities to report all incidents involving saline contamination.

10. Finalize and implement the draft changes to the inspection guide for source plasma establishments, and the compliance program for plasma fractionators.

On June 3, 1997, we received FDA's written response to the recommendations contained in a draft of this report. The comments consisted of editorial and factual comments and the status of implementation of our recommendations. We made those editorial and factual changes to this report that were appropriate and supported by documentation. We have summarized FDA's response regarding the implementation of our recommendations along with our comments on page 32. The FDA's written response is included in this report as Appendix F.

The FDA generally agreed with our recommendations and has begun implementing them. Most importantly, FDA has developed a plan for regulating all biologic products. The plan entitled, "Team Biologics--A Plan for Reinventing FDA's Ability to Optimize Compliance of Regulated Biologics Industries," is dated May 28, 1997. It redefines the working relationship between CBER and ORA. It also sets dates to transition lead inspection responsibilities for all biologic products currently being inspected by CBER to ORA. The FDA also noted that the ongoing inspection of Baxter's Hyland facility (OIG recommendation number 7) resulted in a Class III recall. Specifically, Baxter has recalled 9 lots of Antihemophilic Factor (Human). While FDA's response to our report was generally positive, we believe further actions are required for two of our recommendations dealing with the possible need for safety alerts (OIG recommendation number 8) and the mandatory reporting of saline contamination incidents (OIG recommendation number 9).

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INTRODUCTION

BACKGROUND

The Food and Drug Administration (FDA) receives its primary regulatory authority through the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. The FDA is responsible for helping to ensure the safety of blood and biological products, food, cosmetics, human and veterinary drugs, medical devices, and electronic products that emit radiation. The Office of the Commissioner (OC) is responsible for all FDA operations. Oversight responsibilities of FDA are divided among the following five centers.

- Center for Biologics Evaluation and Research (CBER) which regulates blood, blood products and biologics,
- Center for Food Safety and Applied Nutrition (CFSAN) which regulates all foods for human consumption, except meat and poultry products, and cosmetics,
- Center for Drug Evaluation and Research (CDER) which regulates human drugs,
- Center for Veterinary Medicine (CVM) which regulates animal drugs, animal feed, and drugs and chemical residues in foods derived from animals, and
- Center for Devices and Radiological Health (CDRH) which regulates medical devices and controls the unnecessary exposure to radiation from medical, occupational, and consumer products.

Also reporting to the OC is the Office of Regulatory Affairs (ORA). The ORA conducts inspections and investigations for the five FDA centers with oversight responsibilities, although its relationship with CBER is unique among the five centers. Prior to April 1992, CBER inspected some blood and biological establishments, including plasma fractionators and manufacturers of plasma derivatives (hereafter referred to in this report as plasma fractionators). Since then, ORA has been given an ever increasing role in the inspection process. In 1994, ORA was involved in the inspection of all plasma fractionators, with CBER taking the lead role. In 1997, lead responsibility in all biennial inspections of fractionators was transferred to ORA.

Blood and Blood Products

Blood and blood products have been licensed and inspected since 1946 under Section 351 of the Public Health Service Act (42 U.S.C. 262). In 1972, this statute was amended to

transfer regulation of biological products to FDA. The CBER is the Center within FDA that regulates blood, blood products and other biologics.

Blood is the tissue circulating through arteries and veins that contains the components needed to sustain bodily functions. Plasma is the liquid portion of blood containing nutrients, electrolytes (dissolved salts), gasses, albumin, clotting factors, hormones, and wastes. Plasma is a straw-colored, clear liquid that is 90 percent water.

Plasma is collected by plasmapheresis, a procedure that removes blood from a donor and separates plasma from the formed elements. Plasma may also be obtained by separation from collected whole blood. The formed elements of the blood include erythrocytes, leukocytes, and platelets. Some formed elements are returned to the donor. Once collected, plasma is shipped to pharmaceutical manufacturing sites. At each site, plasma is pooled into processing lots up to as many as 60,000 units.

The primary fractionation process chemically separates the various active components of plasma. Primary fractionation takes place on both human and animal plasma. Derivative therapeutic products are also manufactured from intermediate material obtained from primary fractionators. One component, albumin, is used to restore plasma volume in treatment of shock, trauma, surgery, and burns. Another component, antihemophilic factor concentrate, treats bleeding episodes in hemophiliacs.

There are 26 sites world-wide licensed by FDA to fractionate plasma and manufacture plasma derivatives. There are 13 primary fractionators of human plasma, 5 primary fractionators of animal plasma, and 8 manufacturers of plasma derivatives from intermediate material obtained from primary fractionators. Nine of the fractionators also manufacture products that are regulated by other FDA centers. These fractionators are termed dual processors. A listing of licensed fractionators can be found in Appendix A.

Biologics are defined under the Public Health Service Act section 351(a). Drugs are defined in section 201 (g)(1) of the Federal Food, Drug, and Cosmetic Act. Biologics, which are also drugs, are used for the prevention, treatment, or cure of diseases or injuries. Biologics include bacterial vaccines and antigens, viral and rickettsial vaccines, toxins and antitoxins, and therapeutic serums.

The Center for Biologics Evaluation and Research

Much of CBER's regulatory authority is found in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. It has focused on disease prevention and eradication through pre-market approvals. The CBER regulates about 150 establishments that produce vaccines, plasma and other biologics.

The CBER's Office of Compliance coordinates inspection activities through its Inspection Task Force (ITF). The ITF schedules and participates in the planning of establishment

inspections. Within CBER, blood and blood product inspections are conducted by the Office of Blood Research and Review (OBRR) and the Office of Establishment Licensing and Product Surveillance (OELPS). Members of OBRR have scientific expertise. Members of OELPS have expertise in current Good Manufacturing Practices (GMP) which cover such areas as organization and personnel; buildings and facilities; equipment; control of components, product containers and closures; production and process controls; packaging and labeling controls; holding and distribution; laboratory controls; records and reports; and licensing. The Office of Compliance is responsible for addressing enforcement action recommendations.

The Office of Regulatory Affairs

Much of ORA's regulatory authority is found in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Its focus has been on product adulteration and mislabeling through post-market controls. In addition, ORA conducts pre-approval inspections for drugs and devices. It is responsible for several thousand establishments which produce food, drugs, cosmetics, medical devices, and veterinary products.

The ORA's inspection activities are performed by a decentralized field organization of five regional offices. There are 3 to 5 district offices within each regional office for a total of 21 districts. Each district office is usually comprised of three to four branches, including a compliance branch or an enforcement branch which is the primary regulatory contact within a district office. Inspections are conducted by field investigators who are generalists, that is, trained to inspect more than one product area, i.e., foods, drugs and devices for GMP compliance. Supporting the field activities in headquarters is the Office of Regional Operations under the direction of an Associate Commissioner for Regulatory Affairs.

Other Agencies with Oversight Authority of Blood, Plasma, and Biologics

Other agencies within the Department of Health and Human Services (HHS) share with FDA the responsibility for safeguarding the nation's blood supply. These agencies include the Centers for Disease Control and Prevention (CDC), the Health Care Financing Administration (HCFA), and the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI).[2] In addition, the Blood Products Advisory Committee, composed of government, industry, and consumer representatives, provides scientific advice and expertise to FDA on blood issues.

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2. The HCFA inspects facilities that perform viral testing procedures and blood transfusion services that are reimbursed through Medicare and Medicaid. The CDC collects data on incidents of infectious disease, including blood borne ailments. The NHLBI sponsors blood-related research such as developing virus screening tests.

To further improve safeguards over the nation's blood supply, the HHS Secretary, in testimony before the Subcommittee on October 12, 1995, announced the appointments of a Blood Safety Director, a Blood Safety Committee, and an Advisory Committee on Blood Safety and Availability. The Assistant Secretary for Health was named Blood Safety Director and coordinates HHS blood safety programs. The Blood Safety Committee advises the Director. It includes the FDA Commissioner and Directors of the CDC and NIH. The Advisory Committee, whose members include representatives of industry, consumers, and scientific experts, provides advice to the Secretary and the Assistant Secretary. None of these functions supersede FDA's regulatory authority.

Prior OIG Reviews Concerning Blood Safety

This is the third review by the OIG concerning blood safety issues. The prior two reviews addressed CBER's processing of error and accident reports by blood establishments. The first review concluded that the reporting process used by blood establishments to notify CBER of errors and accidents is a valuable management tool but needed certain improvements. The second review, which was a follow-up to the previous review, noted that CBER did not properly process 5 of the 17 error and accident reports reviewed that were identified as potential blood recalls.

SCOPE OF REVIEW

Our review, which was conducted in accordance with generally accepted government auditing standards, was in response to a request from the Subcommittee on Human Resources, Committee on Government Reform and Oversight, United States House of Representatives (hereafter referred to as the Subcommittee). The Subcommittee was concerned about CBER's lead role in the inspection of plasma fractionators and requested that we review:

1. The CBER's effectiveness in conducting inspections of plasma fractionators when compared to inspections conducted by ORA; and whether CBER routinely notified plasma fractionators in advance of scheduled inspections.

2. The appropriateness of FDA issuing a talk paper for a recall of a plasma product versus the issuing of a press release in the recall of a juice product.

3. The appropriateness of FDA's role in participating with an industry work group established to study a saline contamination problem rather than taking enforcement action.

To achieve these objectives, we reviewed the provisions in statutes concerning blood and blood products found in the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. We reviewed FDA regulations, policies and procedures found in Section 21 of the Code of Federal Regulations (CFR), FDA's Regulatory Procedures Manual,

Compliance Policy Guide and Investigations Operations Manual, CBER's Inspection Manual, and ORA's Warning Letter Reference Guide. We also reviewed FDA training manuals, Standard Operating Procedures (SOPs) and internal memorandums concerning the inspection process of plasma fractionators.

We interviewed FDA officials in the Rockville, Maryland headquarters including those from CBER, ORA, and the Office of Public Affairs. We also interviewed ORA staff in the Chicago District Office who had participated in several inspections of plasma fractionators and a plasma testing facility. Some of these individuals were identified by the Subcommittee as being knowledgeable in the issues addressed by our review.

We reviewed 63 inspection files for 25 of the 26 plasma fractionators (the remaining fractionator was not identified by CBER until our review was near complete) representing inspections conducted between August 10, 1992 and March 21, 1997. During that period, several changes were made in the fractionator inspection process, leading to more ORA involvement in the process. Of the 63 GMP inspections, 33 were conducted by CBER staff only, while the remaining 30 were joint inspections conducted by CBER and ORA.

Of the 25 fractionators in our review, 17 underwent at least one inspection by CBER and one inspection by a joint CBER/ORA team. The 17 fractionators accounted for 50 of the 63 inspection files that we reviewed. The remaining eight fractionators were inspected at least once by either CBER or by a CBER/ORA team. The following table shows by fiscal year, the number of inspections of plasma fractionators that were conducted solely by CBER and the number conducted by a joint CBER/ORA team.

OIG REVIEW OF INSPECTIONS OF PLASMA FRACTIONATORS			
Fiscal Year	CBER Inspections	Joint Inspections	Total
1992	4	0	4
1993	11	1	12
1994	7	6	13
1995	8	3	11
1996	3	11	14
1997	0	9	9
Total	33	30	63

In reviewing the use of a talk paper versus a press release, we reviewed the files of the two specific recalls, the internal review that was conducted at the request of the HHS Blood Safety Committee, and FDA's response to the report. Our objective was not to determine the overall effectiveness of either recall, but to ascertain if the use of a talk

paper adversely affected the recall of the plasma product. We also reviewed reports of adverse events reported to FDA.

In reviewing the appropriateness of FDA's role with the industry work group, we consulted both the OIG Office of Counsel, and HHS Office of General Counsel. We also reviewed the inspection report which first alerted CBER to the saline contamination, interviewed the ORA inspector from the Chicago District Office, and reviewed subsequent inspection reports of other source plasma collection facilities. We also interviewed various CBER officials and reviewed the report prepared by these officials which summarized the industry's work group activities.

We conducted our audit field work from December 17, 1996 through May 28, 1997.

FINDINGS AND RECOMMENDATIONS

INSPECTIONS OF PLASMA FRACTIONATORS

Prior to December 1995, inspections of plasma fractionators were conducted primarily by CBER. Since then, ORA has gradually assumed a lead role in the inspection process. Additional changes have been proposed that will further strengthen the inspection and enforcement process not only for plasma fractionators, but for all biological establishments now being inspected by CBER. Also, CBER has issued a policy statement clarifying its policy for requesting production schedules so as to preclude inadvertent notification of scheduled inspections.

The CBER cited several factors that caused them to re-examine their role in GMP inspections. These include concerns of the CBER inspection process previously expressed by the Subcommittee, and FDA's efforts to downsize, streamline, improve consistency and eliminate redundancy. Another factor, in our opinion, is that CBER has been aware of weaknesses in its inspection process since at least 1992.

An internal review conducted by CBER in that year reported delays in the preparation of Establishment Inspection Reports (EIR). The internal reviewers also reported EIRs were not always completed and that Form FDA 483, Inspectional Observations (key to documenting observations of objectionable conditions and practices) were frequently incomplete, and not forwarded to the appropriate authorities. In 1993, the FDA's Office of Special Investigations (OSI) reported similar findings. Inspection files were missing or incomplete, there were significant delays in writing reports, and the average CBER inspection of biologics establishments was only 16 hours.

Our review has shown that the changes made in the inspection and enforcement process have resulted in more effective inspections, but that further actions need to be taken. Specifically, we found that:

- ✓ Past inspections of plasma fractionators conducted solely by CBER were not as effective as joint inspections involving ORA in reporting observations of objectionable conditions and practices, or in generating enforcement action. We were unable to determine the definitive cause for the apparent difference in inspection results since both CBER and ORA inspected the same establishments and used the same regulatory criteria when conducting the inspections. We noted, however, that joint inspections involving ORA generally involved more staff and took longer to conduct. Also, ORA is staffed with personnel whose primary function is conducting inspections while CBER is staffed with scientists whose involvement in inspections is essentially part-time.

- ✓ As previously reported in FDA internal reviews, past inspections have not met specific time frames established by FDA for completing EIRs and for issuing warning letters. Also, classifications were not completed for all inspections as required.

- ✓ Although CBER has recently clarified its policy of requiring production schedules from plasma fractionators, the policy was not being complied with.

- ✓ A plan of action to further improve the inspection and enforcement process proposed by ORA with some CBER input will, if implemented, further improve the overall process.

The gradual expansion of ORA's role in the inspection process has strengthened the overall inspection and enforcement process as it pertains to plasma fractionators. We believe, however, that the process can be further strengthened by timely implementation of an ORA proposed plan of action, and by expanding ORA's inspection role to biologic establishments that are currently being inspected by CBER, and by correcting the deficiencies included in this report.

FDA Inspection Process and Requirements

Federal regulations (21 CFR 600.21) require that, once licensed, a facility should be inspected at least once every 2 years. These are referred to as GMP inspections. Inspections may also be conducted if special circumstances warrant. These are referred to as directed inspections.

The purpose of an inspection is to ensure that biological products are safe, effective, contain the quality and purity they purport to possess, and are properly labeled. Facilities under inspection must conform to:

- o the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374(a)) and/or the Public Heath Service Act (42 U.S.C. 262-264), and

- o Good Manufacturing Practices as defined under 21 CFR Parts 210-211, 600-680, and, if a device, Part 820.

The official notice of inspection to a facility is made through a Form FDA 482 which must be signed by each inspector. Inspection warrants can be sought if an inspection request has been refused or significantly limited. Facilities and production methods are observed and reviewed. The inspectors report significant observations of objectionable conditions and practices on Form FDA 483, Inspectional Observations. The observations could relate to such areas as faulty manufacturing, processing and packaging; violations of the law or deviations from applicable standards, deviations from commitments included in

the approved license application or from written SOPs; unsanitary conditions or practices which may render the product injurious to health; and undesirable conditions or practices resulting in contamination with filth.

At the completion of the inspection process, the inspectors present their observations to the firm, and subsequently prepare the EIR to formally summarize their activities and findings. The EIR narrative includes the following: the reason for the inspection; a brief history of previous findings; refusals, voluntary corrections, and promises made by the firm's management; and a concise summary and evaluation of current findings. The EIR is required to be completed within 30 work days after completion of a violative inspection, and within 45 work days of a non-violative inspection.[3]

An endorsement of the EIR serves to classify an inspection's reported observations as follows:

- ✓ No Action Indicated. Indicates that no objectionable conditions or practices were found and that no further action is necessary.
- ✓ Voluntary Action Indicated. Indicates that objectionable conditions were found but none serious enough to warrant advisory, administrative, or judicial action. Corrective actions are voluntary.
- ✓ Official Action Indicated. Indicates that objectionable conditions of a serious nature were found and corrective measures must be taken. These include advisory, administrative, or judicial actions.

Advisory actions include a warning letter or an untitled letter. A warning letter notifies a firm that a product, process, or other activities violate government regulations but there is no imminent public safety threat. This should be done within 30 work days after completion of the inspection if the recommendation for the warning letter was initiated by ORA and approved by CBER. If the warning letter recommendation is generated by CBER, it must be issued within 15 work days after the inspection. An untitled letter notifies the firm of circumstances that do not violate government regulations. A written response from the firm is required for a warning letter and optional for an untitled letter.

Administrative actions include citations, and license revocation or suspension. A citation notifies the firm that a prosecution recommendation to the United States Attorney is being considered since there is evidence that a law has been violated. A license revocation, resulting from violations of the licensing standards or regulations, withdraws the firm's

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3. A violative inspection is one in which significant objectionable conditions or practices were observed and documented and for which an enforcement action is recommended. A non-violative inspection is one in which any objectionable conditions or practices observed do not warrant a recommendation for an enforcement action.

authority to ship interstate a biological product. A suspension also withdraws the firm's authority to ship interstate a biological product. A suspension is used when a danger to health exists. License revocation or suspension must be approved by CBER.

Judicial actions include seizures, injunctions, or prosecutions. Judicial actions are conducted through the United States Attorney's Office. Seizures remove adulterated or misbranded products from the market. An injunction is a civil process initiated to stop or prevent violation of the law, to prevent the flow of defective products through interstate commerce, or to correct the conditions that caused the violations to occur. Injunctions may be preliminary or permanent or simply a temporary restraining order. Prosecutions are sought for criminal violations. In most instances, referrals for criminal prosecutions proceed only after the firm has had an opportunity to address the charges.

Product recalls may be undertaken at any time on the initiative of manufacturers and distributors. The FDA may also request a firm to initiate a recall when the firm has not already done so and the action is needed to protect the public health and welfare. Section 351(d)(2)(A) of the Public Health Service Act authorizes FDA to order a biologic recall upon a determination that a batch lot or other quantity of product presents an imminent or substantial hazard to the public health.

Prior to April 1992, CBER inspected plasma fractionators. In April 1992, CBER and ORA formalized an agreement to conduct joint inspections of dual processors. A dual processor is a manufacturer of a biological and non-biological drug and/or device at a specific location. There must be shared pieces of manufacturing equipment and/or systems and includes personnel, storage area, and quality control. In August 1994, CBER and ORA conducted a Biologics Conference to update and enhance the joint inspection process agreed to in April 1992. Inspections of fractionators, who were also dual processors, were to be conducted jointly by CBER and ORA, with CBER leading. The CBER retained responsibility for assigning the classification, preparing the endorsement, and initiating regulatory action.

In December 1995, CBER and ORA issued a SOP concerning the joint inspection program. The CBER and ORA shared the lead for inspections of dual processors. The CBER led all other inspections, and continued with classification, endorsement, and regulatory actions. If CBER disagreed with ORA on its recommendations for regulatory action, ORA could appeal through an FDA ad hoc committee chaired by the Director of ORA's Office of Enforcement, and consisting of representatives of ORA, CBER, FDA's Office of Chief Counsel and, when appropriate, ORA's Office of Criminal Investigations.

For Fiscal Year (FY) 1997, FDA approved a change giving ORA the lead in all GMP inspections of plasma fractionators, except for pre-licensing inspections.[4] The ORA

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4. The purpose of a pre-licensing inspection is to ensure that the plasma fractionator can produce its products in a manner that conforms to government laws and regulations.

assumed responsibility for classification and endorsement of the inspectors' observations. The first ORA lead GMP inspection was conducted in November 1996.

Joint Inspections Were More Effective Than CBER Inspections

Joint CBER/ORA inspections of fractionators lasted three times as long, reported four times as many observations of objectionable conditions and practices, and resulted in five times as many enforcement actions as inspections involving CBER only. The following table summarizes the comparison between CBER and joint inspections.

OIG SUMMARY ANALYSIS OF INSPECTIONS REVIEWED			
	CBER	JOINT	TOTAL
Inspections	33	30	63
Observation-Average Form-483 Items Per Inspection	6	26	
Observation-Average Discussion Items Per Inspection	4	4	
Classification-No Action Indicated	6	2	8
Classification-Voluntary Action Indicated	17	15	32
Classification-Official Action Indicated	1	12	13
Enforcement Action-Warning/Untitled Letters	2	9	11
Enforcement Action-Intent-to-Revoke License/ Court Injunction	0	2	2

The 33 inspections conducted by CBER reported 201 observations of objectionable conditions and practices (Form FDA 483 observations), an average of about 6 per inspection. The 30 joint inspections reported 787 observations, an average of about 26 per inspection. The initiation of enforcement actions increased from 2 for CBER inspections to 11 for joint inspections (at the time of our review, CBER was considering taking enforcement action on 1 additional joint inspection).

Causes for the Differences in Observations

We were unable to determine the definitive cause for the increase in the number of reported observations resulting from the joint inspections. For the most part, the same fractionators were inspected by both groups of inspectors. Fifty of the 63 inspections that we reviewed involved fractionators that were inspected first by CBER and then jointly. Furthermore, both groups were required to use the same regulatory criteria in conducting

inspections, and based on our analysis of the types of observations reported, it appears as if the same criteria was used.

We did note, however, that the joint inspections generally resulted in a significantly higher number of observations in two categories--quality control/quality assurance (QC/QA) observations and air/environmental monitoring and water systems (AEMWS). The CBER inspections resulted in 18 QC/QA observations (9 percent) compared to 169 observations (21.5 percent) from joint inspections, and 22 AEMWS observations (10.9 percent) compared to 176 observations (22.4 percent) from joint inspections. Appendix B summarizes the findings of the 63 GMP inspections that we reviewed.

We did identify certain issues which we believe contributed to the differences in the numbers of observations reported. First of all, the number of inspectors increased in the joint inspections. On average, the 33 CBER inspections were conducted by 2 employees, while the joint inspections were conducted by 3 employees. Second, the time spent on-site at the fractionators increased under the joint inspections. The average CBER inspection lasted 3 days while the average joint inspection lasted 9 days on-site.

Perhaps the most significant issue, however, involved the inspectors themselves. The CBER inspectors were first and foremost scientists whose primary duties were not the inspection of plasma fractionators. According to information provided to us by CBER, the scientists who conducted the inspections spent only a very small percentage of their total time on inspections. Further, their limited experience was primarily in the area of pre-licensing inspections which were for the purpose of supporting pre-approval decisions relating to establishment and product licenses and supplements or amendments to these licenses. These inspections were not designed to support post-market obligations--primarily assuring compliance with GMPs. Conversely, ORA inspectors were full time inspectors with more experience in conducting GMP inspections.

Causes for Differences in Enforcement Actions

In our opinion, a primary cause for the increased number of enforcement actions resulting from joint inspections is the corresponding increased number of observations of objectionable conditions and practices being reported by inspectors. The number of observations reported by the joint inspections increased by 333 percent as compared to the number reported by CBER's inspections. Absent these observations, enforcement actions are extremely unlikely.

Since the classifications of the observations determine to a large degree whether enforcement action is appropriate, we reviewed the classifications that were completed on the 63 inspections that we reviewed to determine if CBER's classification threshold for its inspections was higher than the classification threshold for the joint inspections. As shown in the following table, that was not the case.

AVERAGE NUMBER OF REPORTED OBSERVATIONS BY CLASSIFICATION		
Classification	CBER	JOINT
No Action Indicated	0	0
Voluntary Action Indicated	7	15
Official Action Indicated	25	45

The Official Action Indicated classification is the most serious as it indicates that objectionable conditions of a serious nature were found and that corrective action must be taken. In the 1 CBER inspection that resulted in a warning letter, 25 observations were reported. In the 11 joint inspections that resulted in enforcement actions and 1 joint inspection under consideration for an enforcement action, the average number of reported observations was 45. Based on this analysis, it appears as if the number of reported observations is more likely to account for the difference in enforcement actions than a higher CBER threshold of enforcement.

In our review of the 63 inspection files, we noted 5 instances (3 involving CBER inspections and 2 involving joint inspections) where CBER did not agree with the inspectors' recommendation for enforcement action. The disagreements were generally based on lack of documentation or evidence supporting the recommendations. The CBER's nonconcurrence with the recommendations of inspectors does not appear to be inconsistent with the experiences of the other FDA Centers. For instance, in FYs 1995 and 1996, the FDA Centers with oversight responsibility approved, on average, 67 percent of ORA's recommendations for warning letters. During this same period, CBER approved 29 of 43 warning letter recommendations for all biologic products, also a 67 percent approval rate. The following table summarizes the warning letter activity.

FDA WARNING LETTERS – FYs 1995 and 1996						
Action	CBER	CDER	CDRH	CFSAN	CVM	Total
Recommended	43	165	164	192	41	605
Approved	29	123	103	132	20	407
Disapproved	12	12	61	52	21	158
Open	0	30	0	0	0	30
Abeyance	1	0	0	5	0	6
Unresolved	0	0	0	3	0	3
Withdrawn	1	0	0	0	0	1
Approval Rate	67%	75%	63%	69%	49%	67%

Timeliness and Documentation Problems Continue

Problems with timeliness and completeness of inspection documentation, some of which were previously reported in FDA internal reviews, continue. We noted delays in the preparation of the EIRs and the issuance of warning letters. We also noted that inspection files were missing classifications, and that some inspections were never classified; thus essentially precluding any enforcement action that might be appropriate.

Delays in the Inspection and Enforcement Process

As previously reported in internal reviews conducted by CBER and OSI, EIRs were not prepared timely. The CBER report stated that in the majority of instances the time between the inspection visit and the preparation of the EIR exceeded the recommended time frame for report preparation. According to the report, it is critical that the time frame be met for violative inspections to provide CBER officials the opportunity to critique the adequacy of the inspection, and to make the necessary recommendations regarding licensure, reinspection, or to issue warning letters. The report states further that timely EIR preparation is needed for all other inspections as well to enable CBER officials the opportunity not only to evaluate the inspection but to follow-up in a timely manner any areas that they feel may be problematic.

Our review of 48 non-violative EIRs showed that 25 exceeded the 45 work day time frame. On average, 136 work days were required to prepare these EIRs. The CBER inspections accounted for 18 of the EIRs that were late while the joint inspections accounted for 7 of the late EIRs. Our review of seven violative EIRs showed that four exceeded the 30 work day time frame. Three of the EIRs resulting from joint inspections exceeded the 30 work day time frame by 1 to 4 work days. The one EIR resulting from a CBER inspection required 125 work days to prepare.

Delays in preparing the EIRs contributed to delays in issuing warning letters. The one warning letter resulting from a CBER inspection was issued 180 work days after completion of the inspection. Much of this delay was traced to the fact that the EIR was not prepared until 125 work days after the inspection. Five warning letters issued as a result of joint inspection required an average of 60 work days to issue, an improvement over the CBER inspection but still far exceeding the maximum 30 work day time frame. In our opinion, the effectiveness of a warning letter is diminished if it is not issued timely upon the completion of the inspection.

Missing Documentation on Classifications

Our review of the 63 inspection files disclosed that documentation supporting the classification of 15 inspections (24 percent) was missing. Classification of an inspection occurs when CBER reviews and endorses the EIR. The classification is based on the

seriousness of the observed objectionable conditions and practices, and determines whether some form of corrective action or sanction is appropriate.

Of the 15 classifications missing from the inspection files, 11 were associated with CBER inspections and 4 were associated with joint inspections. While 8 of these inspections had fewer than 4 observations reported, 7 of the inspections had from 8 to 45 observations reported. We requested CBER to provide us with the missing documentation for the 15 classifications. We were informed that:

- 6 of the 15 classifications were never made. Three of the EIRs had 3 or less observations but the other 3 EIRs had 21, 23, and 25 observations, respectively. The CBER indicated that it would have sent out a warning letter to the fractionator with the 21 observations had it received the EIR timely (report was prepared about 64 days after the close of the on-site inspection). It did not comment on any appropriate enforcement actions for the EIRs with 23 and 25 observations.

- 8 classifications were made, according to CBER, but documentation to support the classifications were not present in the case files.

- 1 classification was made after we first brought the matter to CBER's attention. It was classified Voluntary Action Indicated and had eight observations.

CBER's Policy On Requesting Production Schedules Was Not Being Complied With

The Subcommittee requested that we determine if CBER's policy is to give plasma fractionators advance notification of inspections. It is not CBER's policy to provide advance notification to fractionators located in the United States. Advance notification could inadvertently result, however, from requesting production schedules only from those fractionators scheduled for inspections. Realizing this, CBER recently revised its policy regarding production schedules. Our review showed that the policy is not being complied with in that letters were not sent to licensed manufacturers requesting production schedules. As a result there is little documentation to show if and/or when the requests were made.

The CBER policy limits prenotification. A CBER SOP dating back to at least 1988 concerning pre-notifications states:

> "It is not the policy of CBER to announce annual inspections; however, prenotification is permitted under 21 CFR 600.21 and some inspections are routinely announced, e.g., all foreign inspections, all prelicense inspections, and

some scheduled inspections where active processing/manufacturing has not been observed for the last several inspections."

The SOP instructs inspectors to clear any prenotification with CBER's Office of Compliance and the Division that has product line responsibility. The CBER Inspection Manual, issued November 20, 1992, restates this longstanding policy.

The CBER reported to the Subcommittee that from 1994 through 1996, it had requested production schedules from biologic establishments in advance of 40 of 193 inspections scheduled, or almost 21 percent of the inspections scheduled. The requests varied in relation to the scheduled inspections. For instance, 4 requests were made at least 1 year before the scheduled inspection, 15 requests were made between 3 and 6 months before the scheduled inspection, 6 requests were made less than 3 months before the scheduled inspection, and CBER could not determine when the other 11 requests were made. In fact, all of the data provided to the Subcommittee was based on CBER's institutional memory, since records documenting when the requests for production schedules were made were not available.

On November 21, 1996, CBER issued a SOP, number OD-R-15-96, clarifying its policy on production schedules. The revised SOP states that a letter requesting production information will be mailed from CBER's ITF to each licensed manufacturer of a biological product on a bi-annual basis, or as deemed appropriate.

We requested documentation in the form of these letters to determine if the policy was being complied with. We were informed that CBER had telephoned all of the manufacturers sometime between the date of the SOP--November 21, 1996--and the end of January 1997. Contrary to the requirement of the SOP, letters were not sent. The CBER was able to provide documents showing that 22 manufacturers responded to the telephone contact by submitting production information (CBER provides oversight to approximately 150 biological establishments). The responses generally contained production schedules for the entire 6-month period requested, and were not targeted in on any particular point of time within that 6-month period.

In our opinion, CBER needs to comply with its policy to ensure that all manufacturers are contacted, and, more importantly, that they are contacted at the same time. Contacting only those manufacturers that are scheduled for an upcoming inspection is akin to giving those manufacturers advance warning of the inspections.

ORA's Biologics Advisory Committee Suggests Further Improvements

In April 1997, the ORA's Biologics Advisory Committee with input from CBER's Office of Compliance developed a proposed framework for a comprehensive ORA/CBER partnership for the regulation of the biologics industry. According to the Committee, the

proposal will allow FDA to focus highly skilled resources on violative situations and bring them to an expedited conclusion. The proposal is now being reviewed within FDA. We believe the proposal represents another major improvement in the inspection and enforcement process, not only as it applies to plasma fractionators but to the other biological establishments currently being inspected by CBER.

The proposal was designed to address several critical issues including inconsistencies in the inspection and enforcement process between CBER and ORA and among the ORA district offices, and the process for resolving ORA/CBER differences. Three specific groups, consisting of ORA and CBER representatives, are contemplated:

- An Implementation Group responsible for overall biologics policy as it relates to inspectional activities.
- A Blood Operations Group responsible for planning the direction the inspectional program will take, planning and scheduling work, and providing guidance documents as needed by on-site inspection teams.
- A Core Team of certified ORA investigators and compliance officers responsible for conducting the inspections.

For plasma fractionators, the Core Team would consist of a cadre of specially trained ORA investigators, CBER investigators, and specialized compliance officers from each organization. An ORA team member would serve in the lead role for all biennial or directed inspections. The compliance officers would become involved during the inspection when potential violative situations are identified.

The Committee recommended that the proposal be initially used in the inspection of plasma fractionators, and then expanded to other CBER product areas, such as biotechnology, allergenics and vaccines by October 1, 1999.

The results of our review of 63 inspections of plasma fractionators show that both the number of observations and enforcement actions increased after ORA became involved in the process. We believe that the ORA proposal, specifying the partnership roles of ORA and CBER, lends itself to further strengthening of the inspection and enforcement process.

Conclusions and Recommendations

Based on our review of 63 inspections performed either solely by CBER (33 inspections) or with ORA involvement (30 joint inspections), it is evident that ORA involvement resulted in a greater number of reported observations and enforcement actions.

The CBER proposes to expand ORA's lead inspection role to other biological products over a 3-year period. January 1998 is the anticipated completion date for transfer of biotechnology products; March 1998 for in-vitro diagnostic products; October 1998 for allergenics; and October 1999 for vaccines and remaining products. The ORA, with some CBER input, proposes to refine the entire inspection process. We believe FDA should expedite action on these proposals and ensure that there is a plan to implement them as fast as possible. We also believe that actions need to be taken on the other deficiencies that we have reported on.

We, therefore, recommend that FDA:

1. Review the proposal on the inspection process originally drafted by ORA's Biological Advisory Committee in April 1997 and implement it to the extent feasible.

2. Ensure that CBER has a viable plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biologics currently being inspected by CBER.

3. Adhere to time frames established for the preparation of EIRs and the issuance of warning letters.

4. Instruct employees of the importance of completing the classification of inspections; and require CBER to classify the inspections identified in this report as lacking documentation and take whatever enforcement actions that are appropriate based on the classifications.

5. Require CBER to comply strictly with the policy on requesting production schedules from biological establishments.

USE OF A TALK PAPER IN LIEU OF A PRESS RELEASE IN THE RECALL OF A PLASMA PRODUCT

The FDA issued a press release for the Odwalla juice recall and a talk paper for the Centeon albumin recall. We do not believe that the use of a talk paper in lieu of a press release had a significant impact on the albumin recall, however, deficiencies involving the albumin recall were included in an internal report requested by the HHS Blood Safety Committee.

Among the report's findings were those dealing with the MedWatch adverse event report and the FDA inspection and enforcement process, including FDA's lack of previous inspection coverage of albumin. According to the FDA's response to the report, certain corrective actions have been taken including the increased role of ORA in the inspection and enforcement process. Another cited improvement is the establishment of a FDA task

force to inventory all current procedures for handling reports of adverse events and product problems or defects, and to make changes that will result in a more effective and efficient system.

We believe the actions taken or planned will further strengthen FDA's inspection and enforcement process. While we did not review the effectiveness of the MedWatch system, we did note that albumin was regularly in the top 5 of 22 plasma products which were the subject of adverse event reports. We are recommending that the FDA task force determine if the intelligence gathered by the adverse event reports could be put to better use in the planning of inspections particularly with regard to the targeting of plasma fractionators and/or plasma products.

FDA Requirements For Public Warnings

Public warnings, as one element of a recall strategy, is addressed in 21 CFR Part 7 Section 7.42. The recalling firm, in consultation with FDA, develops a recall strategy. The strategy should consider the need for a public warning. If needed, the recall strategy should determine if the public warning should be through the general news media (national or local) or specialized news media, e.g., professional or trade press, or specific segments of the population (physicians, hospitals, etc.).

The FDA issues publicity when there is a scientific assessment of a likely association of a serious adverse reaction with exposure to the products, and where mass media publicity is felt to be the most effective means of communication, so that people will be aware of the situation and can take necessary precautions. According to FDA officials, publicity frequently needs to be initiated quickly to warn the public in a timely manner. Public warnings are often initiated before all the information, including laboratory tests, has been analyzed by FDA and before a recall has been classified. The FDA's Office of Public Affairs does not have firm criteria specifying which form of publicity to use for recalls. Rather, it has the flexibility to issue a press release, make a public statement, hold a press conference, and/or prepare a talk paper. The Office of Public Affairs determines which communication tool to use on a case-by-case basis, after consideration of such factors as the urgency of the information, the hazard involved, the distribution of the product, market availability, and the number of consumers affected.

A talk paper is prepared by the Office of Public Affairs to guide FDA personnel in responding with consistency and accuracy to questions from the public. The information contained in a talk paper is available to the public upon request. Talk papers are routinely distributed to media and consumers.

Use Of Press Release in Odwalla Recall

Odwalla, Inc. is headquartered in Half Moon Bay, California. Its juice processing plant is located in Dinuba, California. Odwalla products are distributed in California, Colorado, Nevada, New Mexico, Oregon, Texas, Washington, and Canada. Odwalla recalled 16 juice products including 12 apple juice-based juices, apple juice, carrot juice, organic carrot juice, and vegetable cocktail juice between October 31 and November 2, 1996. As of February 21, 1997, Escherichia coli contamination of juice products resulted in the death of a child in Colorado on November 8, 1996 and sickened 66 people.

A chronology of events surrounding the Odwalla recall is included as Appendix C to this report. While we did not evaluate the effectiveness of the recall, it is evident that both Odwalla and FDA reacted swiftly upon being notified of the problem by State and county officials. Odwalla and FDA were notified of the problem on October 30, 1996. Odwalla issued a "news advisory" the same day announcing its product recall. One day later, October 31, 1996, FDA and Odwalla issued a press release announcing the voluntary recall. Odwalla issued subsequent press releases and made the information available on the Internet.

Use of Talk Paper in Centeon Recall

Centeon is headquartered in King of Prussia, Pennsylvania and manufactures albumin in a plant located in Kankakee, Illinois. Between September 23 and October 9, 1996, Centeon conducted four recalls of plasma products, primarily albumin. Between August 23 and September 30, CDC initially identified 33 cases, including 11 deaths, with possible links to the recalled albumin. As of April 21, 1997, CDC was able to classify 2 cases with definite links to albumin, 6 cases with probable links, and 25 cases with no links. According to CDC, none of the deaths could be attributed to albumin.

A chronology of events surrounding the Centeon recall is included as Appendix D to this report. While we did not review the effectiveness of this recall (we were not requested to do so by the Subcommittee and the recall process was not complete at the time of our review), we believe that FDA's decision to issue three talk papers did not have an adverse impact on the recall. In addition to the three talk papers, FDA initiated an interview between the Associated Press[5] and a CBER official. The interview took place on September 27, 1996, 8 days after being informed that the sample tested by its laboratory was contaminated by Enterobacter cloacae, and 4 days after Centeon had upgraded its

5. The Associated Press represents about 6,000 newspapers nationally. We noted that 1 day after the meeting was held between FDA and the Associated Press, an article on the recall appeared in the *Philadelphia Inquirer*.

previous market withdrawal to a recall. The FDA also made the information available on the Internet. Centeon was also active in notifying its accounts, sub-accounts, hospitals and special interest groups of the albumin recall. Among the special interest groups notified were the National Hemophilia Foundation, the World Federation of Hemophilia and the American Blood Resources Association.

The FDA inspection of Centeon which began on September 27, 1996 ended on December 6, 1996. The inspection resulted in 87 observations and subsequently led to a consent decree that was entered on January 28, 1997. The consent decree required Centeon to cease distribution of all but two of its products while it brought its manufacturing standards into compliance with FDA statutes and regulations.

Internal Report on the Centeon Recall

At the request of the HHS Blood Safety Committee, a member of the Office of the Assistant Secretary for Legislation reviewed the circumstances surrounding the Centeon recall of albumin. Among the more serious findings included in the report were those dealing with: (1) FDA's response to the initial MedWatch adverse event report dated on August 24, 1996; and (2) the prior inspections of Centeon.

The report was highly critical of FDA's failure to respond to the adverse event report. Had it not been for the follow-up action taken by the initiating hospital on August 28, the delay in FDA's response would have likely increased. The report recommended that a thorough analysis of the MedWatch system should be considered to ensure that comprehensive medical reviews of adverse event reports are available at all times.

The report also questioned whether the current compliance system at FDA was sufficient to ensure the safety of biologic products. The report pointed out that FDA considered albumin to be a safe product with a long history of low-risk use. According to the report "albumin was not on the compliance radar screen prior to the recent contamination incident." Nevertheless, the report concluded that earlier inspections of Centeon's plant at Kankakee were a sign that environmental controls were insufficient and that there is a need to consider whether more forceful compliance policies are needed.

On January 24, 1997, the Commissioner of Food and Drugs responded to the internal report. He expressed agreement with the general thrust of the report that the Centeon problem could have been handled better. The Commissioner responded that FDA has assessed its performance, identified problems, and has taken steps to prevent future occurrences.

With regard to the MedWatch reports, the Centeon situation brought to light "unique and unjustifiable differences" in the way drugs and biologics adverse event reports were handled. These differences resulted in delays in acting on the Centeon report in a timely way. Improvements were made in policies and practices, and, according to the

Commissioner, since September 27, 1996, all adverse event reports on plasma products have been forwarded to CBER's Division of Biostatistics and Epidemiology within one business day for immediate evaluation which is in accordance with the new policy.

With regard to the inspection process, the Commissioner reported that it was evident in the Centeon situation that a lead FDA office for determining possible enforcement action was not clearly identified. As a result, FDA field offices will now take the lead in determining the necessity of inspection follow-ups. Further, FDA transferred the lead for periodic inspections of plasma fractionators and evaluation of the inspection findings from CBER to the field.

The Commissioner also reported that FDA has formed a task force to inventory all current procedures for handling reports of adverse events and product problems or defects. The task force will examine the ways in which reports are received and how the information is shared within FDA. The goal is to identify areas where improvement is needed and to make changes that will result in a more effective and efficient system.

Conclusions and Recommendations

We do not believe FDA's use of talk papers in lieu of a press release adversely affected the Centeon recall process especially in light of the press interview with the Associated Press and Internet distribution. The deficiencies identified in the report to the Blood Safety Committee are more serious, in our opinion. It appears as if FDA has or plans to make improvements in its inspection and enforcement process. As previously mentioned in this report, we believe ORA's increased role in the process will be extremely helpful. The establishment of a task force to continue monitoring performance is another noteworthy accomplishment.

In our opinion, one of the early focuses of the task force should be on the use of adverse event reports in targeting fractionators and/or products for inspection. The internal report prepared for the Blood Safety Committee stated that albumin was not on FDA's "compliance radar screen" prior to the Centeon incident. Our discussions with CBER personnel confirmed that inspections did not focus on albumin until after that incident because it was considered a safe product. Our review of adverse event reports submitted between January 1991 and April 23, 1997 showed that albumin was regularly in the top 5 of the 22 plasma products on which reports were received (Appendix E). Of the 3,386 adverse event reports received on the 22 plasma products, 209 (6 percent) reports involved albumin. Only four other plasma products were the subjects of more reports during this period. We believe this calls for further review by the task force.

We, therefore, recommend that the FDA:

6. Require the task force established in response to the internal report for the Blood Safety Committee to determine if the intelligence gathered by the

adverse event reports could be put to better use in planning inspections particularly with regard to the targeting of plasma fractionators and/or plasma products.

CBER's PARTICIPATION WITH AN INDUSTRY WORK GROUP TO REVIEW SALINE CONTAMINATION

The CBER chose not to implement the ORA's Chicago District Office recommendation to suspend the license of a plasma fractionator. Instead CBER participated with a work group organized by the plasma industry to address the potentially industry-wide problem of saline contamination. Both the HHS Office of General Counsel and OIG Office of Counsel believe CBER's participation with the industry group was neither illegal or unethical. The CBER prepared a report on saline contamination resulting from the work group activities.

We believe that FDA should consider further actions including: (1) determining if there is still a need to inspect the viral testing/inactivation procedures at the Hyland Division of Baxter Laboratories (Hyland); (2) following up on corrective actions taken by Baxter Healthcare Corporation (Baxter) and Haemonetics which were not previously included in the single safety alert; (3) requiring plasma collection and testing facilities to report all instances of saline contamination regardless of whether the plasma was released; and (4) finalizing the draft guides on the inspections of source plasma establishments and plasma fractionators.

Chicago District Office Inspection Identified Saline Contamination

The issue of saline contamination of samples used for viral testing of source plasma collected by certain plasmapheresis devices involves the backwash of saline into the sample collection tube when saline is reinfused to the source plasma donor at the completion of product collection to aid in volume replacement. Viral marker testing of saline contaminated samples may yield false negative results for hepatitis and HIV, and could result in the inadvertent use of potentially infectious units of source plasma in the manufacture of fractionated products.

Saline contaminated samples were identified during a March 1995 inspection at Baxter Screening Laboratory (BSL) conducted by an ORA inspector from the Chicago District Office. The BSL tests over one million units of plasma a year from 39 plasma centers nationwide. The plasma centers are contracted to supply plasma used in the manufacture of several fractionated products at Hyland. Baxter's Fenwal Division (Fenwal) manufactured the plasmapheresis devices used at the plasma centers. The BSL, Hyland, and Fenwal are related entities of Baxter.

The ORA inspection at BSL documented several samples that the laboratory had determined were saline contaminated, however, the plasma associated with those samples were not used in the manufacture of fractionated products but were discarded. According to a BSL official, saline contaminated samples have been identified by BSL since 1989. The ORA inspection concluded that BSL's investigation into the cause of the saline contamination was inadequate and that procedures may be inadequate to identify other saline contaminated plasma samples. In its March 27, 1995 response to Form FDA 483 findings, Baxter stated that Hyland's plasma pools used for the manufacture of finished products are tested for viruses. The viral load is further reduced by the large plasma pool size and the viral reduction procedures such as heat or solvent detergent treatment used in the manufacturing processes at Hyland. In effect, Baxter's position was that even if saline contaminated plasma was shipped to its Hyland plant, there would be no health hazard due to the testing and manufacturing procedures in place at the plant.

On March 30, 1995, the ORA Chicago District Office recommended that CBER suspend the fractionated product licenses issued to Baxter. The District Office also requested that: (1) other ORA district offices perform follow-up inspections at the plasma centers that had provided BSL with the saline contaminated samples; and (2) the Los Angeles District Office inspect the viral inactivation procedures in place at the Hyland facility where fractionated products are produced.

District Offices Conduct Follow-Up Inspections

Three follow-up inspections of source plasma collection facilities were conducted. The results indicated that BSL was inconsistent in its procedures for notifying collection facilities of saline contaminated samples. The BSL's daily computer test results sent to the facilities listed the contaminated sample as "not tested," rather than identifying the saline contamination problem. Two facilities stated that they had to call BSL to obtain an explanation for the samples not being tested. Only then did they learn of the saline contamination. The other facility reported that BSL notified it by telephone that a sample was saline contaminated. This facility performed an investigation and determined the cause to be operator error.

Two of the three ORA inspections resulted in no enforcement actions. The inspection of the third facility revealed significant deviations from standards and regulations and resulted in a recommendation to CBER for license suspension. Among the findings included an admission by a facility official that other plasma units had been found to be saline contaminated before the samples were sent to BSL for testing, however, no documentation was made of these instances, and no error and accident reports were made

to CBER because the units were not released from the facility.[6] The inspection found significant noncompliance in the areas of training and supervision, donor suitability determinations, record keeping, and standard operating procedures. A CBER Health Hazard Committee agreed that a danger to health existed and CBER suspended the licenses of this facility on April 21, 1995.

CBER's Response to ORA's Inspection

On April 4, 1995, CBER convened a Health Hazard Committee comprised of medical and scientific staff of OBRR to review the ORA recommendation to suspend the product licenses issued to Baxter. The committee concluded that the inspection findings did not provide sufficient information to determine existence of an imminent danger to health that warrants suspension of the licenses. In its April 5 disapproval letter to the Chicago District Office, CBER noted that the investigator's observations concerning sample integrity had identified important issues that warranted further review and follow-up. The CBER stated that it intended to raise these issues during an upcoming meeting with Baxter on April 13, 1995.

On April 6, 2 days after the Health Hazard Committee had met, CBER called the Los Angeles District Office and informed it that it was not necessary to inspect the viral inactivation procedures in place at the Hyland facility as was recommended by the Chicago District Office. The CBER said that the recommendation to suspend Baxter's product license had been disapproved, and that the District Office did not need to go in to verify validation of plasma fractionated products as this was a CBER obligation.

On April 13, representatives of CBER's Office of Compliance and OBRR, the Chicago District Office, and Baxter met to discuss the saline contamination issue. Baxter stated that the saline contamination resulted from failure to adhere to the instructions for use of its Autopheresis C plasmapheresis devices used to collect the source plasma. Baxter provided an action plan including a customer notification letter dated April 13, 1995, stressing adherence to the operator's manual and strongly recommending additional steps to further diminish the possibility of saline contamination. Additional steps included placing a hemostat on the plasma collection tubing at the end of the plasma collection procedure and removing the plasma collection container from the weight scale prior to saline reinfusion. In addition to verifying that all users received the notification, Baxter would modify the operator's manual and training video to reflect the revised procedures, and would audit compliance with the new procedure.

The CBER continued to assess the available information on saline contamination. It determined that two device manufacturers--Baxter's Fenwal Division and Haemonetics--

6. When an error or accident occurs that may affect the safety, purity or potency of blood, licensed blood establishments are required to self-report the incident to FDA. The FDA has provided guidance to the blood establishments as to what constitutes a reportable error or accident.

produced the majority of the collection devices used in the source plasma industry. The CBER estimated that Haemonetics has about 60 percent market share and Baxter the remaining 40 percent. The CBER also determined that saline contamination had the potential to affect the entire source plasma industry and, therefore, decided to discuss the issue at the July 13, 1995 meeting with the American Blood Resources Association. This association represents firms that collect and produce blood and blood-related products. During the July meeting, CBER presented draft recommendations it developed for source plasma collection and testing facilities. The CBER recommended that these facilities examine and, if necessary, modify their procedures and training programs related to the prevention, detection, and investigation of saline contamination.

Saline Ad-Hoc Work Group Activities

In response to CBER's concerns, the American Blood Resources Association recommended that an ad-hoc work group, made up of plasma collection facilities, testing laboratories, and the two device manufacturers--Baxter and Haemonetics--be formed to discuss the saline contamination issue and to provide recommendations to prevent its occurrence. The group was known as the Ad-hoc Test Sample Dilution Work Group. The CBER was asked to participate in the work group led by the American Blood Resources Association. The CBER participants were from its Office of Compliance and OBRR. The CBER placed its draft recommendations to industry in abeyance until the ad-hoc work group's efforts could be evaluated.

The work group met over the next several months and its activities were documented in an August 19, 1996 summary report prepared by CBER. The CBER's report agreed with proposed ad-hoc work group solutions which included:

- design changes to the collection devices by the two device manufacturers to better detect and prevent saline contamination due to operator error during collection;
- increased training for operators of the collection devices; and
- increased communication between all parties when saline contamination is identified.

In addition to the ad-hoc work group proposed solutions, CBER also issued changes to its guide to inspections of viral testing labs designed to alert inspectors to the possibility of saline contaminated plasma. The CBER made similar revisions to its guide to inspections of source plasma establishments, however, the revisions are in draft form and have not been cleared for final issuance.

CBER's Participation Not Illegal But Further Actions Are Needed

Both the HHS Office of General Counsel and the OIG Office of Counsel believe that CBER's participation with the industry formed ad-hoc work group was neither illegal or unethical. The HHS Office of General Counsel added that the situation was not unusual. The FDA routinely cooperates with industry through such means as conferences and meetings to develop regulatory strategies.

We also solicited the views of a CBER official that participated with the work group. The official did not believe that partnering with industry in this instance represented a conflict of interest. The CBER's participation allowed it to monitor the industry's proposed solutions. Overall, CBER reported that it viewed participation in the ad-hoc work group as a success.

Although the focus of our review was to determine if CBER's participation in the work group was legal and ethical, we did note other issues associated with the saline contamination situation that, in our opinion, need further review by FDA.

Inspection at Hyland

On April 6, 1995, CBER notified the Los Angeles District Office that it was not necessary to inspect the viral inactivation procedures in place at the Hyland facility. We confirmed that the Los Angeles District Office did not make this follow-up inspection. The CBER officials told us that the inspection was not necessary because the members of the Health Hazard Committee which had determined that a health hazard did not exist, were knowledgeable about the effectiveness of the viral inactivation procedures used in the production of Baxter's products and had considered these procedures during their assessment of the health hazard.

We noted that a GMP joint inspection of Hyland was conducted in August 1996. The inspection resulted in 25 observations of objectionable conditions and a warning letter was issued on October 18, 1996. We reviewed the Form FDA 483, the EIR and the warning letter and found no mention made of any review of Hyland's viral/testing inactivation procedures. The ORA inspector who participated in the inspection was not aware that the inactivation procedures were included in the 1996 inspection. He informed us that an inspection of Hyland, including the viral testing/inactivation procedures, is underway as of May 12, 1997. If this is the case, no further action is needed.

Medical Device Safety Alerts

Some of the corrective action proposed by Baxter and all of the corrective action proposed by Haemonetics was not monitored adequately by CBER to ensure that the actions were taken as planned and that they were effective. The reason for this lack of monitoring is

that safety alerts were not issued for these actions. We believe FDA needs to consider if safety alerts are now appropriate.

Based on Baxter's April 13, 1995 action plan, the Chicago District Office recommended to CBER that the firm's actions be classified as a voluntary medical device safety alert.[7] The CBER concurred on November 17, 1995. This was the only safety alert issued relative to the saline contamination situation. No alert was issued for additional actions taken by Baxter that were not included in its initial plan, nor was an alert issued to monitor the corrective action proposed by Haemonetics.

The FDA defines a medical device safety alert as a communication voluntarily issued by a manufacturer, distributor, or other responsible person to inform health professionals and other appropriate persons of a situation that may present an unreasonable risk of substantial harm to the public health by a device in commercial distribution and intended for human use, in order to reduce or eliminate the risk. Safety alerts are handled by ORA district offices in the same manner as recalls. They go through the stages of alert, recommendation, classification, field notification, firm notification letter, effectiveness checks and status reports, FDA audit checks, and termination recommendations.

The Chicago District Office issued audit checks which consist of a personal visit, telephone call, letter or a combination thereof made for the purpose of verifying that all of the firms specified by the recall strategy have received notification and taken appropriate action. Five plasma centers/blood banks were visited and one plasma center was contacted by telephone. All six locations had received the safety alert, and the Chicago District Office concluded that the overall safety alert effort was effective.

In a report to FDA, Baxter estimated that 4,633 Autopheresis C devices were distributed to 95 blood banks and 166 plasmapheresis centers nationwide. Baxter sent notification letters, revised user manuals and training videos to 258 direct accounts and 7 corporate offices of commercial plasmapheresis centers. Baxter confirmed receipt through Federal Express proof of delivery or faxed communications.

Subsequent to the safety alert, Baxter made a software modification that, in Baxter's view, should prevent the potential for saline dilution. At the end of the collection cycle and prior to the saline reinfusion, the operator is prompted to seal the disposable set and remove the product bag and plasma line used for testing. The machine will not allow the operator to continue until the product is removed. This is determined through the product weight scale sensor. Baxter field tested the modification during March 1996 and estimated that implementation would begin in early summer and be completed within 6 months. As of October 1996, Baxter reported that 90 percent of the instrument

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7. An intercenter agreement dated October 31, 1991 between CBER and CDRH specifies that CBER is the lead center for regulating certain medical devices utilized in the collection, processing or administration of biological products.

conversions have been completed. The modification was not subject to a safety alert or to audit checks to determine the effectiveness of the modifications.

The Haemonetics PCS plasma collection device was also never subject to a safety alert, and thus audit checks were not issued although the Haemonetics reportedly made changes to its device to prevent the potential for saline contamination. These changes included a modification to the collection bottle set tubing by Alpha Therapeutic Corporation, the manufacturer of the bottle and to the PCS pinch valve assembly; and revision of the PCS software that would report a plasma bag weight change greater than 4 grams since the last collection cycle (indicating a possible saline clamp failure). The firm estimated that conversion of all machines would begin in May 1996 and take about 6 months.

Communications

An important recommendation resulting from the ad-hoc work group was to increase communication, documentation and investigation among testing laboratories, collection centers, and device manufacturers when saline contamination is encountered and to document and investigate reports of possible saline contamination. The Chicago District Office's inspection of BSL and subsequent inspections of the collection facilities that had submitted saline contaminated samples revealed that those firms had not adequately reported or investigated the known instances of saline contamination even though most were aware of the problem.

We asked CBER if any of the firms involved in those inspections had submitted reports to CBER, either error and accident reports (EARs) or medical device reports (MDRs), that contained references to saline contamination. The CBER stated that they had not since neither were required under FDA regulations. The CBER stated that under current regulations for EARs, testing laboratories and collection facilities are not required to report identified instances of saline contamination. Units of collected plasma are under quarantine until screening tests are performed. If a unit is found to be saline contaminated or tests positive for HIV or hepatitis the unit is removed from quarantine and destroyed. An EAR would be required only if the contaminated unit was mistakenly released for further processing. An MDR is required for any event associated with a death or a serious injury. Malfunctions of devices that are likely to cause or contribute to a death or serious injury would also be reported under the MDR.

Although communications may have improved among testing laboratories, collection centers, and device manufacturers, there is no assurance that CBER will be connected to the improved communication lines. The BSL knew about the saline contamination problem since 1989 but it apparently did not inform CBER. Other information indicates that Haemonetics was aware of this problem since 1992, but again CBER was not notified. It was not until March 1995 that CBER was made aware of this problem as a result of an inspection conducted by the Chicago District Office.

Since saline contamination is a unique problem--CBER determined it had the potential to affect the entire source plasma industry, and the industry responded with a task force--we believe a unique solution is required. According to CBER, current regulations did not require reporting of the saline contamination through either the EAR or MDR reporting systems. As a result, a problem known to the plasma industry was not reported to FDA. We believe that plasma collection and testing facilities should be required to notify CBER of instances of all known saline contamination regardless of whether the contaminated products were released, until CBER is convinced that the saline contamination problem is corrected.

CBER Guides for Source Plasma Establishments and Fractionators

The CBER is in the process of revising its inspection guide for source plasma establishments and drafting a compliance program guide for plasma fractionators. The revisions to the source plasma guide contain a section dealing with saline contamination. The CBER informed us of the industry's initiatives and alerted the ORA district offices to the saline contamination problem in a September 20, 1995 teleconference.

One of the purposes of the draft compliance program is to provide information and guidance to inspectors and to prepare them to conduct biennial inspections of plasma fractionators. The draft program mentions the importance of viral inactivation/removal and the need for validation. We believe FDA should accelerate the approval process for the guide and the compliance program.

Conclusions and Recommendations

According to the OIG Office of Counsel and the HHS Office of General Counsel, CBER's participation with the industry work group was neither illegal or unethical. Overall, CBER reported that it views its participation in the ad-hoc work group as a success. Our review, however, identified issues that were not fully addressed during CBER's examination of the saline contamination problem or during its involvement with the American Blood Resources Association's ad-hoc work group. We, therefore, recommend that FDA:

7. Verify that the inspection of Hyland, ongoing as of May 12, 1997, includes a review of viral inactivation procedures. If the procedures were not included, require such an inspection.

8. Review the changes made to the plasma collection devices to determine whether they meet the criteria for classification as medical device safety alerts.

9. Consider requiring plasma collection and testing facilities to report all incidents involving saline contamination.

10. Finalize and implement the draft changes to the inspection guide for source plasma establishments and the compliance program for plasma fractionators.

FDA'S RESPONSE AND OIG COMMENTS

On June 3, 1997, we received FDA's written response to the recommendations contained in a draft of this report. The comments consisted of editorial and factual comments and the status of implementation of our recommendations. We made those editorial and factual changes to this report that were appropriate and supported by documentation. The FDA's written response is included in this report as Appendix F.

The FDA generally agreed with our recommendations and has begun implementing them. Most importantly, FDA has developed a plan for regulating all biologic products. The plan entitled, "Team Biologics--A Plan for Reinventing FDA's Ability to Optimize Compliance of Regulated Biologics Industries," is dated May 28, 1997. It redefines the working relationship between CBER and ORA. It also sets dates to transition lead inspection responsibilities for all biologic products currently being inspected by CBER to ORA. The FDA also noted that the ongoing inspection of Baxter's Hyland facility (OIG recommendation number 7) resulted in a Class III recall. Specifically, Baxter has recalled 9 lots of Antihemophilic Factor (Human).

Although FDA's response to our report was generally positive, we believe two of our recommendations were not fully addressed by FDA. In responding to our recommendation dealing with the possibility of safety alerts for the changes made to the plasma collection devices (OIG recommendation number 8), FDA stated that a safety alert has been issued for the Baxter device, and that CBER was consulting with ORA to determine if any regulatory action is justified for the Haemonetics device. We were aware of the safety alert referred to by FDA in its response. However, as noted in this report, subsequent to this safety alert, Baxter made a software change that, in its opinion, should prevent the potential of saline contamination. We believe that FDA should determine whether this Baxter software modification meets the criteria for classification as a medical device safety alert.

In responding to our recommendation dealing with mandatory reporting of saline contamination incidents (OIG recommendation number 9), FDA stated that it was considering issuing a memorandum to industry clarifying when saline contamination constitutes a reportable event. We believe that the memorandum should be issued and that all incidents of saline contamination should be reported to FDA, regardless of the disposition of the plasma. Without this intelligence, CBER will not have the information needed to assess whether proposed industry solutions have been fully effective in correcting the saline contamination problem.

APPENDICES

PLASMA FRACTIONATORS

Fractionator	Manufacturing Location
Abbott Laboratories	North Chicago, Illinois
Alpha Therapeutic	Los Angeles, California
Baxter Healthcare Corporation	Brussels, Belgium
Baxter Healthcare Corporation	Los Angeles, California
Bayer Corporation	Berkeley, California
Bayer Corporation	Clayton, North Carolina
Cangene Corporation	Winnipeg, Canada
Central Laboratory Blood Transfusion Service Swiss Red Cross	Berne, Switzerland
Central Laboratories of the Netherlands Red Cross Blood Transfusion Service	Amsterdam, Netherlands
Centeon, L.L.C.	Kankakee, Illinois
Centeon Pharma GMBH	Marburg, Germany
Gentrac, Inc.	Middleton, Wisconsin
Immuno-US	Rochester, Michigan
Instituto Grifols, S.A.	Barcelona, Spain
Kabi Pharmacia	Stockholm, Sweden
Massachusetts Public Health Biologic Laboratories	Boston, Massachusetts
Michigan Biologic Products Institute	Lansing, Michigan
Oesterreichisches Institut fur Haemoderivate	Vienna, Austria
Ortho Diagnostic Systems, Inc.	Raritan, New Jersey
Parke-Davis	Dublin, Ireland
Parke-Davis	Rochester, Michigan
Pasteur Merieux Serums et Vaccins	Lyon, France
Speywood Biopharm, Limited	Wrexham, United Kingdom
The Upjohn Company	Kalamazoo, Michigan
V.I. Technologies	Melville, New York
Wellcome Foundation, Limited	Dartford, United Kingdom

FORM FDA 483 OBSERVATIONS

Type of Observation	CBER FDA 483 Observations		Joint FDA 483 Observations	
	Inspections Cited		Inspections Cited	
Air/Water	22	10.9%	176	22.4%
	10	30.3%	24	80.0%
Building/Facilities	10	5.0%	15	1.9%
	7	21.2%	8	26.7%
Equipment	20	10.0%	41	5.2%
	12	36.4%	16	53.3%
Labeling	19	9.5%	19	2.4%
	10	30.3%	13	43.3%
Laboratory	4	2.0%	28	3.6%
	4	12.1%	10	33.3%
Production	26	12.9%	94	11.9%
	11	33.3%	19	63.3%
Quality Control/ Quality Assurance	18	9.0%	169	21.5%
	11	33.3%	23	76.7%
Raw Materials	5	2.5%	23	2.9%
	5	15.2%	7	23.3%
Records	17	8.5%	40	5.1%
	12	36.4%	17	56.7%
Software	0	0.0%	23	2.9%
	0	0.0%	2	6.7%
Standard Operating Procedures	39	19.4%	108	13.7%
	18	54.5%	22	73.3%
Storage	15	7.5%	36	4.6%
	11	33.3%	13	43.3%
Training	0	0.0%	7	0.9%
	0	0.0%	4	13.3%
Unreported Changes	6	3.0%	8	1.0%
	5	15.2%	6	20.0%
Total Observations	201	100%	787	100%
Total Inspections Cited	27	81.8%	28	93.3%

CHRONOLOGY OF EVENTS SURROUNDING THE ODWALLA RECALL

October 21, 1996 Reports of Escherichia coli contamination first surfaced. Initial reports of food contamination were investigated by State and county officials from the Washington State Department of Public Health and the Seattle-King County Department of Public Health.

October 30 State and county officials held a joint news conference regarding the possible contamination of Odwalla apple juice product. The Seattle-King County Department of Public Health asked Odwalla to pull all its products containing apple juice from the retail market until further notice.

Odwalla agreed and issued a "news advisory" announcing its product recall of fresh apple juice, 12 other apple based juice products, carrot juice, organic carrot juice, and vegetable cocktail juice due to several confirmed cases of Escherichia coli bacteria in the State of Washington. In most cases, Odwalla's fresh apple juice was linked to those diagnosed with the bacteria.

The FDA Commissioner was notified of the Odwalla apple juice recall at about 6:00PM EST. A teleconference was set up with CFSAN representatives, the Associate Commissioner for Regulatory Affairs, officials from FDA district offices in Seattle, San Francisco, and Denver, the Seattle-King County Department of Public Health, State Health Departments for Washington, Oregon, Colorado, and California, the Center for Disease Control, and Odwalla. All parties agreed that the epidemiological data from the studies performed by the Seattle-King County Department of Public Health and the Washington State Department of Public Health, very strongly implicated Odwalla apple juice. The FDA initiated an investigation of the Odwalla production plant in California.

October 31 The FDA issued Press Release P-96-17 announcing the voluntary recall of all Odwalla brand apple juice products. The press release noted 13 confirmed cases of Escherichia coli illnesses between October 15 and October 24. Ten of the 13 cases were linked to Odwalla apple juice. Odwalla issued another press release in conjunction with a press conference it conducted regarding its recall. Odwalla also dispatched 175 trucks to remove apple juice products from store shelves throughout the West and parts of Canada.

The FDA and CDC met with various industry groups, including the U.S. Apple Association, to discuss the Escherichia coli outbreak associated with Odwalla apple juice products.

November 1 Odwalla began providing the apple juice recall information on the Internet.

November 2 Odwalla announced that its recall has been completed (product has been removed from shelves in 4,600 retail outlets).

November 4 Odwalla issued a press release confirming FDA's finding of Escherichia coli bacteria.

November 15 Odwalla issued a press release stating that FDA officials have not found any Escherichia coli bacteria in its Dinuba, California plant.

December 16-17 The FDA held a public meeting to discuss the Escherichia coli outbreak.

CHRONOLOGY OF EVENTS SURROUNDING THE CENTEON RECALLS

August 23, 1996 A 50 year old male patient in a hospital in Wichita, Kansas experienced an adverse event after being treated with albumin, a plasma product. One vial of albumin, which was later determined to be contaminated with Enterobacter cloacae bacteria.

August 24 The hospital in Wichita, Kansas reported the adverse event to Centeon and the MedWatch System. According to the MedWatch report filed by the hospital, the patient complained of "shakes and chills" after receiving the first dose of albumin, and again after a second dose. Both the patient's blood and the patient's bottle of albumin were cultured "gram negative rods" which means there is bacteria present.

August 28 An employee of the same hospital contacted ORA's Wichita Resident Post to follow-up on the hospital's report. The employee informed the Resident Post investigator that the patient had suffered from uncontrollable shivering, increase in temperature to 104.9F, and fluctuation of his blood pressure within 5-10 minutes after receiving albumin. The investigator was also informed that both the patient's blood and the patient's bottle of albumin cultured Enterobacter cloacae bacteria. The Resident Post contacted ORA's Kansas City District Office (KAN-DO) who then contacted ORA's Division of Emergency and Investigational Operations (DEIO) for directions on how to proceed.

August 29 The DEIO contacted CBER's OBRR Division of Hematology for guidance. The Division advised DEIO on the sampling and testing procedures and notified CBER's Office of Establishment Licensing and Product Surveillance (OELPS) Division of Product Quality Control (DPQC). The KAN-DO initiated an investigation of the Wichita hospital's pharmacy.

September 3 Centeon mailed a letter describing the incident to CBER's OELPS Division of Biostatistics and Epidemiology (DBE) as a 15-day Adverse Event Report. According to the report filed by Centeon, the albumin bottle used by the patient and the patient's blood both came back with the same isolate, Enterobacter cloacae.

September 4 The Wichita Resident Post collected 10 samples at the hospital.

September 10 The Wichita Resident Post sent samples obtained from the hospital to DPQC for testing.

September 11 The CBER-DBE received Centeon's 15-day Adverse Event Report, which was mailed on September 3rd.

September 13 The FDA test results confirmed the existence of bacterial growth. The DPQC scientists decided additional tests were required to confirm the positive results and asked for more samples of the product. The DPQC also sent isolates from the original sample to one of its contractors to identify the bacteria.

September 16 The DPQC notified the Wichita Resident Post that the first sample was positive for Enterobacter cloacae and additional samples were needed for testing.

September 18 The DPQC reported that the second sample tested negative and requested that the Wichita Resident Post obtain a third sample.

September 19 The laboratory contractor identified the bacterial growth in the original sample as Enterobacter cloacae. The DPQC notified CBER's Office of Compliance of the results and the Office of Compliance called Centeon to determine their intent in light of the results.

September 20 Centeon telephoned 28 direct accounts and 232 sub-accounts that received the defective lot (17,000 vials) and initiated a voluntary market withdrawal. Centeon instructed its accounts to cease use of the lot and return the product to its distribution center in Illinois.

September 23 After Centeon discovered the presence of cracks in the returned vials, it upgraded the market withdrawal to a recall, and re-contacted by telephone the 260 direct and subaccounts. The telephone contacts were confirmed in writing by an "Urgent Biological Recall" notice sent via Federal Express.

September 24 Centeon sent a "Statement on Voluntary Biologic Recall" (dated September 23) via First Class Mail to 7,143 hospitals advising them of the recall. Centeon also sent this document to special interest groups, including the National Hemophilia Foundation, the World Federation of Hemophilia and the American Blood Resources Association. The document was made available to the press upon request.

The CBER-DPQC received the third albumin sample from the Wichita hospital.

September 27 Centeon reported an adverse event in Green Bay Wisconsin to DBE. Between September 6 and September 16 the patient had received 37 vials of the same lot of albumin associated with the Wichita case. On September 16, the patient had a positive blood culture for Enterobacter cloacae.

The CBER completed its health hazard evaluation and within one hour conducted an interview with the Associated Press (AP) detailing the albumin recall. The AP services approximately 6,000 newspapers and news services. The following day, an article addressing the recall appeared in the *Philadelphia Inquirer*. The Centeon corporate headquarters is located in the Philadelphia, Pennsylvania area.

The CBER-DBE reviewed the 15-day alert report mailed by Centeon on September 3rd.

The FDA Chicago District Office initiated, with CBER's permission, an inspection of the Centeon facility in Kankakee, Illinois. The inspection and confirmed that dropped pallets containing vials of albumin and other products caused the problem.

October 2 Centeon expanded the recall of albumin to nine additional lots bringing the total number of vials recalled to over 100,000. During this period the National Notification Center (NNC), contracted by Centeon, telephoned and faxed 7,812 hospitals, clinics, and intravenous infusions centers to the attention of the Director of the Pharmacy and the Director of the Blood Bank, informing them of the recall. The NNC followed up with a first class mailing to the hospitals. These notifications were also made to 2,156 dialysis centers, 167 endocrine/obstetrics specialists, 1,964 fertility clinics and many special interest groups. Recall letters were sent to the estimated 600 direct accounts.

October 3 The FDA issued Talk Paper T-96-65 on the expanded recall, and the AP released an article on the recall.

October 4 Centeon initiated a third recall, for one lot (1,600 vials) of another plasma product, Monoclate P antihemophilic factor (human). Centeon faxed an "Urgent Biologic Recall Notice" to the 24 direct accounts who received the recalled lot. Hard copies were mailed to these accounts on October 7. The FDA issued Talk Paper T-96-67 and the AP released an article on the Monoclate P recall.

October 9--October 11 As a precautionary measure, Centeon expanded the albumin recall to all in-date lots of albumin and Plasma Plex PPF, another albumin product. The expanded recall included an additional 975 lots of albuminar and 290 lots of Plasma Plex PPF. Centeon began telephoning 5,194 sub-accounts informing them of the expanded recall. Between October 9 and 10, NNC telephoned and faxed 7,812 hospitals, clinics, and intravenous infusion centers informing them of the recall. On October 11, the NNC followed up with a first class mailing to 7,812 hospitals, 2,156 dialysis centers, 1,964 fertility clinics, 167 endocrine/obstetrics specialists, and 1,964 fertility clinics.

The FDA issued Talk Paper T-96-69 on the expanded recall. The recall was also covered by the AP.

ADVERSE EVENTS FOR PLASMA PRODUCTS: 1991 - 1997

Plasma Product	91	92	93	94	95	96	97*	TOTAL
Immune Globulin Intravenous (Human)	118	143	87	401	334	255	57	1395
Antihemophilic Factor (Human)	9	20	33	30	68	399	4	563
Alpha-1 Proteinase Inhibitor (Human)	57	34	91	80	160	22	1	445
Immune Globulin (Human)	12	18	28	54	45	87	4	248
Albumin (Human)	23	26	26	25	24	72	13	209
Factor IX Complex	1	4	0	1	2	87	0	95
Rho(D) Immune Globulin (Human)	1	1	1	3	35	47	0	88
Coagulation Factor IX (Human)	2	2	14	11	11	17	0	57
Respiratory Syncytial Virus Immune Globulin Intravenous (Human)	0	0	0	0	0	3	46	49
Thrombin	7	10	3	8	3	10	8	49
Plasma Protein Fraction (Human)	0	3	5	4	9	15	1	37
Rho(D) Immune Globulin Intravenous (Human)	0	0	0	0	4	24	1	29
Cytomegalovirus Immune Globulin Intravenous (Human)	0	0	7	0	8	6	4	25
Digoxin Immune Fab (Ovine)	6	8	3	4	2	0	0	23
Antihemophilic Factor (Porcine)	0	8	5	1	2	2	0	18
Antithrombin III (Human)	0	0	0	1	3	13	0	17
Hepatitis B Immune Globulin (Human)	1	0	3	4	7	1	0	16
Rabies Immune Globulin (Human)	0	2	0	2	4	1	1	10
Anti-Inhibitor Coagulant Complex	1	1	0	0	1	3	0	6
Varicella-Zoster Immune Globulin (Human)	0	0	1	0	3	1	0	5
Tetanus Immune Globulin (Human)	0	0	0	0	1	0	0	1
Hemin for Injection	0	0	0	0	1	0	0	1
TOTAL	238	280	307	629	727	1065	140	3386

* Through April 23, 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

FDA'S RESPONSE

Date: JUN - 3 1997

From: Lead Deputy Commissioner, FDA

Subject: Review of the Discussion Draft of the Food and Drug Administration's Inspection Process for Plasma Fractionators (CIN: A-03-97-00350)

To: Joseph J. Green
Assistant Inspector General
For Public Health Service Audits

I appreciate the opportunity to review and comment on the Office of Inspector General Discussion Draft of the Review of Food and Drug Administration's Inspection Process of Plasma Fractionators.

I am providing the Food and Drug Administration's (FDA) comments to the report and its recommendations. FDA's comments fall within three major categories, editorial, factual and the status of implementation.

MAFriedman

Michael A. Friedman, M.D.

Attachment

AGENCY COMMENTS ON OFFICE OF INSPECTOR GENERAL DISCUSSION DRAFT REPORT ENTITLED, "FOOD AND DRUG ADMINISTRATION'S INSPECTION PROCESS FOR PLASMA FRACTIONATORS" (CIN: A-03-97-00350)

I. Editorial

Executive Summary, page i, second paragraph, third line - insert after the word " responsibility": "This situation stems from the fact that biologic inspections were not conducted by FDA before the responsibility for conducting biologic inspections was transferred to the FDA during the 1972 reorganization ."

Executive Summary, Page ii - Sixth bullet, first, line, change the word "Drugs" to "Drug".

Background, Page 1, first paragraph, first line - Change to read: "The Food and Drug Administration (FDA) receives its primary regulatory authority through the Federal Food, Drug and Cosmetic Act. The FDA is responsible for helping to ensure the safety..."

Page 1, first bullet - Rewrite to read: "CBER is the Center within FDA that regulates biological and related products including blood, vaccines, and biological therapeutics manufactured for interstate commerce or sale."

Page 1, third bullet- Rewrite to read: "CDER regulates human drugs manufactured for interstate commerce or sale".

Page 2, first paragraph, third line - Change to read "CBER is the Center within FDA that regulates blood, blood products and other biologics."

Page 2, paragraph 3 at the end of the first sentence - Add "Plasma may also be obtained by separation from collected whole blood".

Page 2 at the end of paragraph 6 - The definition of a biological product is found in the PHS Act section 351(a). Like biologics, drugs are defined in section 201(g)(1) of the FD&C Act. Therefore, biologics are also drugs.

Page 2, last paragraph, line 3 - The number 200 appears to include plasma fractionators but it excludes blood and plasma collection facilities. CBER/OBRR regulates approximately 300 licensed blood establishments and approximately 2300 registered intrastate blood establishments.

Page 2, first paragraph, replace first line with - "CBER's regulatory authority is found in the Federal Food, Drug, and Cosmetic Act, and the Public Health Service Act."

Page 3, first paragraph, replace the second and third sentences with - "The Inspection Task Force (ITF) schedules and participates in the planning of establishment inspections. Within CBER, blood and blood product inspections are conducted by OBRR."

Page 3, first paragraph - Change the first sentence to read "ORA's regulatory authority is found in the Federal Food, Drug and Cosmetic Act and the Public Health Service Act.

Page 3, first paragraph, following the sentence ending in "post-market controls" - Add a new sentence: "In addition, ORA conducts pre-approval inspections for drugs and devices."

Page 3, second paragraph, fifth line - Delete the number "6" and change to "5" regional offices.

In the sentence beginning with,"Inspections are conducted..." following the "trained to inspect", add: "more than one product area, i.e., Foods, Drugs, and Devices. "A specialist is trained to inspect/investigate certain entities and becomes highly skilled in that area. A generalist is trained in multiple areas and disciplines. GMP compliance may be among them."

Page 6 (footnote) -Although the footnote contains three accurate statements about MedWatch, it does not reflect its role in outreach efforts to educate health professionals about reporting and to inform them quickly of important new safety information.

Page 8, first bullet - Change to read "The Federal Food, Drug, and Cosmetic Act 21 U.S.C. 301 et. seq. and /or the Public Health Service Act (42 U.S.C. 262-264), "

Page 8, second bullet - Change to read "Good Manufacturing Practices as defined under 21 CFR Parts 210-211, 600-680, and if a device, Part 820, and"

Page 9, third paragraph, first line - beginning with "An endorsement of an EIR is required to....",Change to read: "An endorsement of an EIR serves to..."

Page 10, second paragraph, Administrative actions, third line - Change to read " A license revocation resulting from violations of the licensing standards or regulations withdraws the firm's authority to ship a biological product in interstate commerce. A suspension also withdraws the firm's..."

Page 10, third paragraph- Judicial actions, seventh line - Change last sentence beginning with Referrals to read: "In most instances, referrals for criminal prosecution proceed only after the firm has had an opportunity to address the charges."

Page 10, fourth paragraph, Product recalls - After the last sentence add, "Section 351(d)(2)(A) of the Public Health Service Act authorizes the FDA to order a biologic recall upon a determination that a batch lot or other quantity of a product presents an imminent or substantial hazard to the public health."

Page 10, fifth paragraph - Sentence beginning with: "Inspections of fractionators":..insert after the word "fractionators" "who were also dual processors, were to be".

Following the last sentence ending in the word action, add a new sentence to read: The 1992 agreement placed a greater emphasis on domestic drug manufacturers. The field staff participation in the inspections of fractionators was enhanced in 1994. The participation of the field staff in the inspections of foreign manufacturers is dependent on available resources, including travel funds and investigators available to travel. (Twelve of the 26 fractionators are foreign manufacturers).

Page 11 - Correct the last sentence by deleting "FDA's Office of General Counsel" and replacing with "FDA's Office of the Chief Counsel and,....".

III. Insert into shaded box on page 11 - **"Joint inspections of Plasma Fractionators involving ORA resulted in more reported observations of objectional conditions and more enforcement actions than inspections conducted solely be CBER."**

Insert in lieu of third paragraph on page 11 - *"Inspections involving ORA staff (these inspections also involved CBER staff and are referred to in this report as joint inspections) resulted in four times as many observations and three times as many enforcement actions as inspections involving only CBER staff."*

Page 18, paragraph 1, last line - Change the word, "bi-annual" to " semiannual."

II. Factual

Pages I and ii - The report refers to "internal talk papers." Talk papers are public documents routinely distributed to media and consumers, as well as being published on the FDA's Home Page on the world-wide web. To characterize them as "internal is incorrect.

Page ii - The report states: "Although FDA did not issue a press release on the plasma product albumin, it did initiate a meeting with the Associated Press which represents about 6,000 newspapers." A more accurate statement would be: "Although FDA did not issue a press release on the plasma product albumin, it did call the Associated Press and arranged an interview with the appropriate FDA personnel. The AP did publish a story about the albumin recall on its wire which services more than 6,000 newspapers and hundreds of

broadcast outlets (television and radio) across the country."

Page ii, third bullet - concerning CBER's policy to not pre-notify and the SOP on obtaining production schedules. Fourth line down beginning with CBER recently established ....Change to" "CBER recently established a written Standard Operating Procedure (SOP) for obtaining production schedules, dated November 20, 1996. CBER did not comply with the SOP because letters to all licensed manufacturers were not mailed per the SOP. We were informed that the Office of Compliance made a decision to contact the manufacturers by telephone to expedite obtaining production schedules while a draft letter was pending.

Executive Summary, page iii, third bullet - Change to: "CBER concurred with the Los Angeles District's recommendation to defer an inspection of a plasma fractionator that had been recommended by the Chicago District." Continue with, "A regularly scheduled..." following the last sentence of this bullet ending with the word "procedures".

Page 2 - Substitute for Paragraph 5 - There are 26 US licensed plasma fractionators who manufacture plasma derivatives. These 26 manufacturers are located world wide. In fact, 12 of the 26 are located in foreign countries. Twenty of the 26 manufacturers process human blood. The remaining six, process animal blood. Nine of the 26 manufacturers also manufacture products regulated by other FDA Centers. These fractionators are called dual processors. A listing of licensed fractionators can be found in Appendix A. The majority of the 26 manufacturers may be characterized as "primary" fractionators, and may also operate as an "intermediate" in that they may also further manufacture a bulk paste or powder received from another fractionator into a finished product. While some manufacturers may be licensed to manufacture one or more plasma derivatives, they may not have done so for a number of years.

Page 3, first paragraph - Describes the inspection program at CBER prior to implementation of the ORA lead for plasma fractionation inspections. As written, the report suggests that CBER's Office of Establishment Licensing and Product Surveillance (OELPS) has been involved in routine, inspections of plasma fractionators. It should be noted that this has not been the case. From 1992-1995, a total of 40 inspections of plasma fractionators were performed (CBER alone and joint). OELPS' Division of Establishment Licensing (DEL) was involved in only nine of these inspections; four of which were prelicense, and one (Michigan) which resulted in a warning letter. DEL's involvement really began in Fiscal Year 1996, which is the same time that the field's participation grew. It should be noted that there had not been an emphasis on GMPs focus during most of the inspections performed pre-1996.

The increase noted for observations related to GMPs may be due, in part, to DEL's involvement in inspections of plasma fractionators.

Page 3, first paragraph, second sentence - beginning with "The ITF schedules...." following the word "inspections", begin a new sentence to state: "The ITF team members prepare Establishment Profiles which consists of the manufacturer's compliance history, previous EIRs and 483s, a list of pending supplements, errors & accident reports, adverse event reports, and additional information that is necessary to perform an inspection. Profiles are provided to all team members. The team member responsible for the specific product line holds a pre-inspection meeting with both CBER staff and Field ORA staff and during these meetings specific guidance is provided to the inspection team. In addition, during the inspection, the team is encouraged to call the ITF for guidance and direction when it is necessary. The ITF coordinates with ORA's biologics team to resolve problems. In addition, the ITF reviews, endorses, and classifies CBER inspection reports. The team is also involved in developing inspection policy and assists in training FDA inspectors. The Office of Compliance believes that the ITF serves an important function."

Page 9, first bullet - Delete this bullet.

Page 9, Section on "Inspections of Plasma Fractionators" - second paragraph beginning, "At the conclusion ..." ,change the last sentence in the paragraph beginning with: "The EIR ..." to read: "FDA policy states that non-violative EIRs should be completed within 30 days of the inspection. Violative EIRs which are classified OAI and prompt a regulatory action recommendation, i.e., a Warning Letter, which must have Center concurrence, should be completed by the District within 15 days so that the Center has 15 days to review the report and the evidence, that support the issuance of the letter."

Page 16, first paragraph - This should include a statement that the 45 day time frame for non-violative reports was established prior to 1992. In efforts to harmonize with written agency policy, CBER changed the 45 day policy in 1995.

Page 17, following bullets on inspection report classifications - Add a statement: "We have been advised on May 27, by the current team leader of the ITF that those EIRS lacking an endorsement/classification are being classified and evaluated to determine appropriate follow-up action. "

Page 22, paragraph 3 - The quotation from FDA's Office of Public Affairs should be revised to conform with a statement that was provided to Susan Strinkowski as follows:

"FDA issues publicity when there is a scientific assessment of a likely association of a serious adverse reaction with exposure to the products and where mass media publicity is felt to be the most effective means of communication, so that persons will be aware of the situation and can take necessary precautions."

Page 22 - Modify the first sentence of the third paragraph: "According to officials of the FDA's OPA, sometimes public health warnings must be issued before the recall strategy is

formulated and before a direct link has been established between the recalled product and the adverse events."

Page 23, first paragraph, fifth line - The report states: "One day later, October 31, 1996, FDA and Odwalla jointly issued a press release announcing the voluntary recall: A more accurate statement would be: "One day later, October 31, 1996, FDA and Odwalla issued press releases announcing the voluntary recall."

Page 23, third paragraph, fifth line - The report states: "In addition to three talk papers, FDA initiated a communicator to discuss the recall with the Associated Press on September 27, 1996, eight days after being informed that the sample tested by its laboratory was contaminated by Eneterobacter cloacae, and four days after Centeon had upgraded its previous market withdrawal to a recall." With regard to the timing, OPA arranged the interview within an hour of being notified by CBER that it had completed its health hazard evaluation and that it believed general press notification was appropriate even though albumin is administered solely by health professionals and would not likely be in the hands of consumers.

Page 23, third paragraph - Change the last sentence to read "Among the Special Interest groups notified were the National Hemophilia Association, the World Hemophilia Foundation, The American Blood Resources Association, and the Committee of Ten Thousand."

Pages 23,

fourth paragraph, second line and 24 - Change the sentence to read "The inspection resulted in 87 observations and subsequently led to a consent decree that was entered on January 18, 1997. The consent decree required Centeon to cease distribution of all but two of its products while it brought its manufacturing standards into compliance with FDA's statutes and regulations."

and Appendix D - Seem to imply that the September 27, 1996, AP meeting was the only outreach conducted by the Agency. MedWatch played a significant role in disseminating information about the Centeon recall. On October 1, 1996, October 3, 1996, and October 15, 1996, copies of the September 23, 1996 Urgent Recall Notice, the October 3, 1996 Talk Paper, and the October 9, 1996 Recall Announcement were faxed to over 120 health professional organizations who have joined as MedWatch partners. Additionally the October 9, 1996 Centeon Recall announcement was posted on the MedWatch Internet page and was also summarized in the MedWatch column in the March 1997 Medical Bulletin.

Page 24, last paragraph - Change to read "...Centeon situation that a lead FDA office for determining whether an enforcement action was necessary was not clearly identified. As a

result, FDA field offices will now take the lead in determining the necessity of inspection follow-up...."

Page 25 - The draft report refers to a "press conference." To clarify, OPA arranged an interview, not a press conference.

In the Appendix Chronology, the draft report incorrectly states"The FDA (P-96-17) and Odwalla jointly..." the press release was not a joint press release.

Page 25 - Consider "It is important to note that the number of adverse event reports associated with a given product is largely influenced by the frequency with which the product is used in clinical practice as well as the patient population in which it is used."

Page 28, paragraph 3 - Following the Los Angeles District Office, " insert: "to discuss an inspection of Hyland's viral inactivation procedures" following the word "disapproved", please insert a period. New sentence: "The LA-DO recommended that the inspection be deferred due to the disapproval of the suspension. CBER concurred with the District because CBER could verify the validation of the viral inactivation process during the next inspection. The verification of the viral inactivation process was a CBER obligation and responsibility."

Page 30, fourth paragraph, following the opening phrase - "On April 6, 1995, CBER...", change the statement"CBER concurred with the Los Angeles District."

Appendix D - gives the chronology of events for the Centeon recalls. It includes the date of receipt by Division of Biostatistics and Epidemiology (DBE) of the 15-day report from Centeon, but does not include anything about MedWatch's receipt of the report. It may be useful to include the MedWatch information since that may indicate the earliest signal of the problem.

Appendix D, page 2 of 3 under "September 25" - The report cited was not sent to MedWatch but to DBE from Centeon by fax on September 27.

Appendix D, page 3, first line - It is stated that CBER asked the field to limit its investigation to the known defective lot. In fact, CBER asked the field to focus its major attention on the known defective lot, but did seek investigation of other potentially involved lots or products.

Appendix D - The method of computing this table could result in an over count in some cells. It was compiled by adding up numbers (that were provided by DBE) subsetted according to suspect product, manufacturer, and year of report. However, reports with multiple suspect products (e.g. 2 or 3 different brands of Antihemophilic Factor) would be counted multiple times. It is beyond our scope to re-compute the entire table, but to give

one example: FDA received 267 "unique" AHF (Human) AERs in 1996 (not 399 as indicated in the table).

III. Status of Implementation

The OIG recommended that FDA:

1. Review the proposal originally drafted by the Office of Regulatory Affair's ("ORA") Biological Advisory Committee in April 1997 and implement it to the extent feasible.

Status

Relevant FDA staff have reviewed and modified the proposal. FDA conceptually accepts the proposal and is actively implementing the proposal.

2. Ensure that the Center for Biologics Evaluation and Research ("CBER") has a viable plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biological products currently being inspected by CBER.

Status

CBER has already begun implementing a plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biological products currently being inspected by CBER.

3. Adhere to time frames established for the preparation of Establishment Inspection Reports ("EIRs") and the issuance of warning letters.

Status

ORA has taken steps to ensure that its managers will remind their employees of their obligation to adhere to the time frames established for the preparation of EIRs and the issuance warning letters. Specifically, element #2 or ORA's Consumer Safety Officer performance standard and ORA's Field Management Directive manual provide guidance to ORA managers and employees regarding FDA's "reporting writing" requirements (including letters) and the preparation of EIRs.

4. Instruct employees of the importance of completing the classification of inspections; and require CBER to classify the inspections identified in this report as lacking documentation and take whatever enforcement actions that are appropriate based on the classifications.

Status

This task is underway and CBER will complete its classification of the eleven relevant inspections before the June 5, 1997 hearing. Future classifications will be made in the appropriate time frames.

5. Require CBER to comply strictly with the policy on requesting production schedules from biological establishments.

Status

CBER has already taken steps to ensure that requests for production schedules are made on a consistent basis and do not amount to a de facto prenotification of an inspection. As the new inspection plan described above is implemented, CBER and ORA will determine if there continues to be a need for obtaining production schedules.

6. Require the FDA task force, established in response to the internal report for the Blood Safety Committee, to determine if the intelligence gathered by the adverse event reports could be put to better use in planning inspections, particularly with regard to the targeting of plasma fractionators and/or plasma products.

Status

A team of FDA employees has been selected and charged with determining if intelligence gathered by the adverse event reports could be put to better use in planning inspections, particularly with regard to the targeting of plasma products. This team consists of employees from CBER, ORA, and FDA's MedWatch Program. The team will be chaired by the Acting Deputy Director for CBER, Mark Ellengold.

The team members include: CBER employees Dr. John Finlayson, Dr. Norman Baylor, Dr. Gene Murano, Dr. Marcel Salive, and Ms. Peg Tart; MedWatch employee Dr. Steven Goldman; and ORA employee Hector ZuaZua.

7. Verify that the inspection of Hyland, ongoing as of May 12, 1997, includes a review of viral inactivation procedures. If the procedures were not included, require such an inspection.

Status

The inspection of Hyland is ongoing and does include a review of Hyland's viral inactivation procedures. As a direct of this inspection, Hyland has initiated a class III recall of several lots of Factor VIII. Specifically, Hyland has recalled 8 lots of its Hemofil-M and one lot of American Red Cross' AHF-M.

8. Review the changes made to the plasma collection devices to determine whether they meet the criteria for classification as medical device safety alerts.

Status

A safety alert has been issued for the Baxter/Fenwall plasma collection system. CBER is consulting with ORA headquarters and FDA district offices to determine if any regulatory action is justified for the Haemonetics plasma collection system.

9. Consider requiring plasma collection and testing facilities to report all incidents involving saline contamination.

Status

FDA regulations already require the reporting of errors and accidents by licensed firms. Saline contamination of the tubing segment used to test for infectious diseases for Source Plasma (a licensed product) or other plasma products must be reported as an error or accident, if the products are released for distribution. This requirement does not presently exist for registered firms. In accordance with prior OIG recommendations, however, a revised rule has been drafted to extend the above mentioned reporting requirement to all registered firms. CBER is also considering whether to issue a memorandum to the industry clarifying when saline contamination of the tubing segment constitutes a reportable event, and revising the Compliance Program to include a review of the appropriate files to ensure compliance.

10. Finalize and implement the draft changes to the inspection guide for source plasma establishments, and the compliance program for plasma fractionators.

Status

CBER is in the process of finalizing and implementing the draft changes to the inspection guide for source plasma establishments, and the compliance program for plasma fractionators.

Mr. SHAYS. Thank you very much. I'd like to just get a sense, to start, the impact of, Ms. Steinhardt, this last chart. I don't really grasp the implications of it. So I want you to just walk me through it a little more in depth.

Ms. STEINHARDT. OK. The chart graphs the amount of time that it takes FDA to review a report that is submitted by a facility. The facility is required to submit a report of any errors and accidents, including anything that may warrant a recall.

Mr. SHAYS. Right.

Ms. STEINHARDT. And once it gets this, this chart outlines the amount of time that it takes FDA to review that report, from the time it's submitted to FDA until it determines whether to recall.

Mr. SHAYS. A course of action.

Ms. STEINHARDT. Right. And it says that in about 70 percent of the time it takes the agency more than 7 months to confirm a recall. That is from the time it gets the report.

Mr. SHAYS. But the company, itself, can recall an item?

Ms. STEINHARDT. Yes. That's right.

Mr. SHAYS. And, in most cases, if the company has determined that they have contaminated blood, an infected supply, wouldn't they just intuitively and for their own, for the protection of the patients and the users and for the company's protection, recall it?

Ms. STEINHARDT. In three out of four cases they do.

Mr. SHAYS. How many?

Ms. STEINHARDT. Three out of four cases. It's the company, themselves, that initiate the recall, 75 percent of the time.

Mr. SHAYS. Right.

Ms. STEINHARDT. And, in fact, it's the companies, themselves, the facilities, themselves, that are responsible for carrying out a recall.

Mr. SHAYS. Now, have you provided us statistics that tell us when FDA review with a particular delay how often it decides then to take action and have a recall?

Ms. STEINHARDT. This chart is only for those cases where there was a recommendation for a recall.

Mr. SHAYS. OK.

Ms. STEINHARDT. This is in the subset of cases that proceeded to have a recall recommendation from FDA. In 70 percent of those cases, it took 7 months or longer.

Mr. SHAYS. So what I'm seeing is, in 1 to 6 months it took 27 percent of the cases—1 to 6 months—7 to 12, 25 percent——

Ms. STEINHARDT. Correct.

Mr. SHAYS. And——

Ms. STEINHARDT. Close to half the time—47 percent—it took more than a year.

Mr. SHAYS. And after a year they then decided to have a recall?

Ms. STEINHARDT. Correct.

Mr. SHAYS. That's—yes, ma'am?

Ms. CROSSE. This is to confirm the recall. This is not for the first step of recommendation of recall. This is to confirm the recall, to confirm that this recall has occurred.

Mr. SHAYS. OK. This is the bottom line to what I want to know. I want to know how many cases would it have taken more than 6 months before the FDA ordered a recall?

Ms. STEINHARDT. 150 cases out of 300.

Mr. SHAYS. 150 cases out of 300, the FDA would have made a determination——

Ms. STEINHARDT. Confirm.

Mr. SHAYS. Now, confirm—I need to understand what you mean by confirm.

Ms. STEINHARDT. When it's published. When the decision is made final and it's published.

Mr. SHAYS. But is it possible that it had been recalled already?

Ms. STEINHARDT. It's possible that it could have been recalled, that the product actually could have been recalled before then.

Mr. SHAYS. Well—but I think you know where I'm going. I want to know when did the FDA require a recall that wasn't taking place before then, and how often would we have seen a case that would have been more than 6 months or more than a year.

Ms. STEINHARDT. Do we know that?

Mr. SHAYS. Do you understand what I meant?

Ms. STEINHARDT. Yes, I do. In 25 percent of the cases where there was a recall, it was FDA who initiated it.

Mr. SHAYS. OK.

Ms. STEINHARDT. So, three out of four cases the manufacturer or the facility had already taken an action.

Mr. SHAYS. And that's the ones I'm—now, of the 25 percent of the recalls that FDA initiated, how many of those took more than a year before they were——

Ms. STEINHARDT. Presumably 70 percent. Oh, more than a year. I'm sorry; 47 percent.

Mr. SHAYS. So, more than 50 percent of the cases that the FDA decided to have a recall were not ordered until a year after the fact.

Ms. STEINHARDT. Close to 50 percent. Right.

Mr. SHAYS. Now, I make an assumption that the FDA made a recall because the blood supply was not safe, the product was not safe.

Ms. STEINHARDT. Right. They made a determination. Now, let me be clear, it's not FDA that makes the recall.

Mr. SHAYS. OK. Let me just say—and someone else who wants to respond to this part, if someone else is more closely related to it, I'd just as soon—yes. Please identify yourself. And would you also leave a card afterwards to our—OK.

Ms. D'ALESSIO. I'm Jacqueline D'Alessio.

Mr. SHAYS. You can just pick it up, so you don't have to bend over if you'd like.

Ms. D'ALESSIO. That would help.

Mr. SHAYS. Yes.

Ms. D'ALESSIO. If in 25 percent of the cases FDA is prompting a facility, and there are 300 of the cases altogether, that means that there's about 75 percent of the cases that FDA needs to prompt the facility. If you assume that in 50 percent of those cases it takes more than a year, that's about 40 or so cases.

Mr. SHAYS. Now, in those 40 or so cases then—and that may be a year after they've been notified, correct?

Ms. D'ALESSIO. Notified? Yes, that there was an error and accident.

Mr. SHAYS. And how much time would it have been on the market before they were notified? What would the range be?

Ms. D'ALESSIO. About 6 months, I think. We have a pie chart.

Ms. CROSSE. On average it took 4 months from the time that the facility detected the error and accident until they filed the report with FDA.

Mr. SHAYS. OK.

Ms. D'ALESSIO. But we don't know how long it was between the detection and the actual occurrence.

Mr. SHAYS. OK. What I want to know from FDA when it comes before us is, one, why that would happen, and what is the solution. If I were using any of these products, I would be pretty outraged—if I had been using them—and it took a year before FDA came to a conclusion.

Ms. STEINHARDT. There is one other point that I think is important to add here.

Mr. SHAYS. Sure.

Ms. STEINHARDT. Which is that some blood products can be stored for a time before they're actually transfused, but a lot of whole blood products have to be used within a matter of days. And in my mind it raises some questions about—at least for some portion—the value of a system that takes this long to carry out.

Ms. D'ALESSIO. May I add one more thing?

Mr. SHAYS. Sure.

Ms. D'ALESSIO. In the vast majority of the cases, the blood facilities are amply capable of recognizing a very serious error and accident and they will recall the blood even before they've notified FDA. It's the cases where the blood facility does not recognize the seriousness of the even that we're talking about here. And, as far as we know, FDA has no requirement. When they recognize the potential seriousness and are evaluating it, there is no requirement that they contact the facility and ask them to quarantine the blood until they're done with their review.

Mr. SHAYS. OK. Do you have any comment about this here?

Mr. ROSLEWICZ. We did look at this issue about 2 years ago, for the committee, with regards to the licensed and the unlicensed facilities. We found similar results as GAO is talking about in terms of the length of time it takes to issue the recall. And maybe Tom has some of the specifics with him.

Mr. SHAYS. Tom.

Mr. ROBERTSON. Yes. I think when we looked at it we took a sample of the error and accident reports that were coming in, and found that, for the most part, the action was taken by the blood establishment before they even sent the error and accident report in. When you're talking about a delay of over 1 year for a recall, you're not talking about a delay in the actual recall, you're talking about a delay in the recall classification. That's where FDA classifies the recall as a class 1, class 2, or class 3.

Long before that happens, we found that corrective action was taken. And we found certain problems with the process, but that wasn't one of them. We didn't find, I believe, one case where there was a risk to the health because of that delay. Corrective action was taken. And you'll find that in most cases—in almost every case—and they put it right on the error and accident report—when

the blood establishment prepares that they put their corrective action right on the report.

Mr. SHAYS. But was the corrective action recall?

Mr. ROBERTSON. Yes, sir. They don't call it a recall. They destroy the blood. They get the blood if they can—and certain times they identify the problem after the blood has already been shipped and infused in a patient. Now, when we looked at it, we found problems with the timeliness of submitting the error and accident reports. They were delayed quite a bit.

And, as a matter of fact, FDA didn't have any specific criteria as to when they should be turned in. I think the term they used was promptly. But promptly was never defined. But we didn't find any problem with the health hazard.

Mr. SHAYS. Let me just get to other issue——

Ms. STEINHARDT. Can I just add on this point, though, that the information about this came—what we got came from FDA, that 25 percent of those cases were ones where they had to take the actions as opposed to those facilities.

Mr. SHAYS. Right. And I think we just need to understand the significance of it. But I'm just trying to put myself in the position of someone who uses these products. And the letters—I was tempted to take these letters and read some of them. It's people who literally stay by the phones, have fax equipment, have children who are highly dependent on blood supply products and, obviously, would die or their health would seriously deteriorate if they didn't have it. So, we're all on the same wavelength. They need this product. But they need it safe.

And you read through some of this and you realize, what a way to exist. And the focus that I have—and my interest is, we do have a tiered system. We do donor screening. We do donor deferral. We do blood testing. We do blood quarantining. And the compliance monitoring, which includes the inspections and recalls. And that's kind of a big focus of what I'm at least interested in today.

And on the surface this looks quite alarming. And before this hearing is over today we're going to really need to get into it. Why don't I let Mr. Towns have the floor. And just beforehand, if I could—given that we have our Members on both sides of the aisle here, I'd like to do a little housekeeping here.

I ask unanimous consent that all members of the subcommittee be permitted to place any opening statement in the record and the record remain open for 3 days for that purpose. And without objection, so ordered.

And I ask further unanimous consent that all witnesses be permitted to include their written statements in the record. And without objection, so ordered. Mr. Towns, you have the floor.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me also thank you again for holding this hearing. I know we've had three hearings on this issue. And this is the fourth. And I think it's a very important issue. And we cannot have enough hearings on it. Because as long as people are concerned, we need to see what we can do to address those concerns.

Just recently I was on an airplane flight and a gentleman recognized me and he came over and took a seat. And, according to him—he said it's possible to reduce the risk to the blood supply.

However, such measures would cost additional money, he says, and we'd probably have to change procedures to a degree if we did that. Are there any estimates or have any studies been done to assess how much that cost will increase and whether the patient or customer will be willing to pay the high price if this is true?

Ms. STEINHARDT. Well, I can say we didn't do—at least of the actions we recommended we think should be taken, we didn't do any specific cost estimates. So we don't know how much some costs would increase. But I think it's important to point out that some of the things that we're talking about—donor notification, recipient notification—are practices that many blood facilities in the country are already undertaking. And what we're talking about would just extend that to all blood facilities and it would extend the notification to some kinds of viral infections that are not covered under current practices.

Ms. CROSSE. Could I just add?

Mr. TOWNS. Sure.

Ms. CROSSE. Also, we think that some of these actions would be offset by savings at later stages in the process. For example, if you notified donors that they were permanently deferred and the medical reasons for that deferral, you could eliminate them returning at a later date to donate blood. So you would save the costs of screening and possibly, if they went to a different center, the possibility of having to test that blood at a later time. So, while some of the actions would have costs, they might have some offsetting savings in terms of not having to go through as many steps of the process, particularly the testing of blood products, which is quite expensive.

Mr. ROSLEWICZ. While we have not done any specific cost-benefit studies in the Inspector General's office, there certainly on some of the recommendations could involve additional costs. Sometimes it can be just a matter of changing a regulation which doesn't necessarily increase the cost too much. But on the other hand, for example, in the plasma fractionator industry, as ORA shifts over to taking the lead on doing some of those reviews, the Food and Drug Administration certainly has to give consideration as to whether there are sufficient resources to do that or do they need to reallocate the resources differently.

But we in the Inspector General's office have not at this point done any such cost-benefit analyses of these kinds of things.

Ms. STEINHARDT. If I could just add one important point to note, which is, not just the costs, but the benefits. If you look at the benefits to the American people since a lot of these measures have been put into place—this quality assurance system—in 1984 there were over 700 cases of transfusion related AIDS. In the 12 years since then, in that whole period, there have only been 38. And I think that's a considerable benefit to offset looking at the costs that we're already incurring.

Mr. TOWNS. Let me add one other point that was raised that this gentleman felt that to be able to do a lot to correct the problem when it exists, that many of the blood banks were unlicensed—but actually the facilities that were involved in collection and processing and distribution of blood were unlicensed. And he said,

therefore, it makes it difficult to do a lot to them. Could you respond to that?

Mr. ROSLEWICZ. The blood banks that are unlicensed—it is generally because they are intrastate only. They don't transmit their products between States. And that's why they're unlicensed and they're not required to submit error and accident reports. But they have been asked to volunteer to submit their error and accident reports.

In a report that we did several years ago, one of our recommendations was that the policy be changed there to make it mandatory that they submit the error and accident reports just as the licensed facilities do. I believe that GAO supports that recommendation and FDA has a proposed regulation I think in April of this year, where they're proposing to make that a regulatory change.

Mr. TOWNS. I think that when you look at that, that within itself makes people feel uncomfortable. I think when you can think about being over 2,000 unlicensed facilities, about a lot of reasons, people would feel uncomfortable for the fact that they're not licensed, even though we know that there's regulations and all that, in terms of Federal regulations. And, also, I think that the key here is the confidence.

And if people don't have confidence this could be a real problem. Do you want to react? Yes?

Ms. STEINHARDT. Well, I think the fact that they're not licensed by FDA doesn't mean that they're operating without any oversight. Because they don't engage in interstate commerce they aren't subject to licensure by a Federal agency. But they may be, and in fact usually are, licensed by the State in which they are operating. So there is oversight there. And they are, as we indicated, subject to FDA requirements—to many FDA requirements, particularly for blood safety. Ultimately they are responsible for blood safety.

The point that we're making here is that one of the key features of this quality assurance system is error and accident reporting. This is a way of keeping track of what's happening, to take any corrective actions as quickly as possible to prevent errors and accidents in the future. And this part of the system—this key piece of the system—is that these facilities, because FDA doesn't require it of them, it's only voluntary. And it can be fixed. It can be readily fixed. And FDA has indicated that it intends to do that. We think it's important to the integrity of the system.

Mr. TOWNS. Right. And it should be fixed. It is my understanding that there is some controversy regarding whether FDA inspectors should use a check list approach or a more narrative approach in the inspection of facilities. Can each of you tell me which approach you would prefer and why?

Ms. STEINHARDT. Well, if I can start. The issue we have with FDA's inspection reports is that they simply—and we really don't care whether they use a checklist approach or a narrative approach. What we care about is that they indicate on their inspection reports what they've actually done. The policy that they have now with regards to inspection reports is that the reports will presume that the inspectors will have covered everything that they're supposed to cover unless they indicate otherwise. And we think it's

just not a very reliable system. We found some of the inspection reports are quite complete. Others only say, this facility was in compliance. They never indicated what they looked at, what areas they covered. And we found some examples where clearly the inspections couldn't have covered some areas. But there's no documentation.

Ms. CROSSE. Right. We don't think it's necessarily a problem that they do not cover all areas at every inspection. They may need to focus their attention to certain areas. We don't expect that they would stay there for weeks to try to do an in depth examination of absolutely every aspect, particularly for a facility that engages in a full range of activities and has a large number of donors.

However, we think that they need to indicate for the next inspector, and for the people back in the district offices and at CBER who have to review the reports, exactly what was done on that inspection so that they can have a clearer understanding of what type of examination was conducted during that inspection.

Mr. TOWNS. Yes.

Mr. ROSLEWICZ. I believe the checklist approach is certainly useful in terms of making sure that you cover all the different areas that you're required to inspect. But I believe that there's also a need for some narrative for some of the reasons that GAO pointed out in terms of future inspectors coming along the previous year to try to understand what was looked at in the past year. Simply a check mark sometimes won't tell you what problem you found or what recommendations you might make to fix it. So I think a combination of both would certainly be beneficial.

Mr. ROBERTSON. Yes, I agree with that. As auditors, for every audit that we start, we have an audit program. We don't necessarily put everything in the audit report itself. But in our working papers, you can tell exactly what we did do. I think this would be a good idea for FDA. Now, they're coming up with a guide. And I think when they're coming up with the guide, as they're drafting it, this might be something they will want to take a look at.

Mr. TOWNS. Right. Thank you. I guess this is probably for GAO. In fact, it is. You noted in your report that better donor screening has refined the volunteer blood donor pool. However, as you know, there is a commercial pool as well. What kinds of actions or guidelines do you believe would be effective in reducing the risk from people who are paid for their blood.

Ms. STEINHARDT. Yes. That's a very good question. Not a lot is known about this pool of donors. But what is known I think raises some questions and suggests the need for some more information. As you pointed out, the commercial industry—the plasma products industry—relies mostly on paid donors. And from some data that are available we know—and I'll point—the red bars are voluntary blood banks, and the blue bars are plasma centers. And this is data tracking HIV prevalence rates among donations in California from 1989 to 1994.

And you can see that among plasma centers—those blue bars—the prevalence of HIV in the donor pool was considerably higher. Now, the good news here is that in both the blood banks and the plasma centers the prevalence rates began to decline. But they're still a lot higher among plasma donors. And this obviously has im-

plications for HIV prevalence, but it also links to other kinds of high risk behaviors and the possibility of other kinds of infectious diseases within this population.

In the plasma industry—plasma products, themselves—there's very good techniques, very effective techniques for viral inactivation of HIV. And I think there is not a lot of concern there. But there is some concern about other types of viruses that may be prevalent in this donor pool. And we just don't know much about it. And they may not be caught in these same inactivation techniques. So, it's some newly emerging kinds of infectious agents that we're concerned about.

There have also been other studies that have been done that indicate that there is higher risk among paid donors than volunteer donors. And, in fact, FDA a number of years ago required facilities to indicate whether a blood was coming from those paid donors. But these are—the data are sort of spotty about this. And we think that there are enough indications to suggest that it's worth looking at in greater depth.

Mr. TOWNS. All right. Thank you very much, Mr. Chairman. Thank you. I yield back.

[The prepared statement of Hon. Edolphus Towns follows:]

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OPENING STATEMENT OF

REP. EDOLPHUS TOWNS

RANKING DEMOCRATIC MEMBER
OF THE SUBCOMMITTEE ON HUMAN RESOURCES

JUNE 5, 1997

The American blood supply is one of the safest in the world. Continuous and vigilant federal oversight plays a major role in ensuring that safety. I believe that efforts to continue this trend of safety should include consideration of the necessity for additional federal regulation of currently unlicensed blood facilities and the expansion of current regulations governing licensed facilities.

This is the third hearing convened by Chairman Shays concerning the Food and Drug Administration's role in protecting the nation's blood supply. Two hearings on this subject were held by Mr. Shays during the 104th Congress. Those hearings culminated in the issuance of a report entitled, "Protecting the Nation's Blood Supply from Infectious Agents: The Need for New Standards to Meet New Threats,". The report sets forth several findings and recommendations to ensure the safety and security of the blood supply. I want to commend the Chairman for his work in this area. It is my understanding that the Administration has taken action to fulfill most of the Committee's recommendations and I look forward to hearing testimony on that issue.

However, I am afraid that there is an area of concern that the committee has not addressed and may not address, and that is the issue of unlicensed blood facilities. There are approximately 2,800 facilities that routinely perform blood collection, processing, storage and distribution. Of those facilities, about 1000 are licensed and are required to follow federal regulations. However, the remaining 1800 facilities are unlicensed and not required to follow federal regulations.

Although these facilities are required to register with the FDA, any compliance with federal regulations is purely voluntary. FDA requires licensed blood facilities to report errors and accidents. However, unlicensed blood facilities voluntarily submit error and accident reports and are on their honor to promptly correct any problems or deficiencies. Licensed firms must report any manufacturing problems that may affect the safety, purity or potency of their products. Unlicensed firms are not required to report problems. A GAO report has concluded that unlicensed blood facilities are under reporting their errors and accidents and are significantly less

likely to submit error and accident reports, even where product recalls occur.

Therefore, Mr. Chairman, it seems to me that our focus on federal oversight efforts is less than thorough if we cannot figure out some way to mandate licensing and regulatory compliance for more than half of the facilities responsible for collecting, processing and distributing of blood in this country. It seems to me that the danger to the blood supply lies in these facilities. I am told by my counsel that there is no federal oversight because these establishments are not involved in interstate commerce. However, it seems to me that we must find a way to regulate these facilities. A person getting a transfusion does not care whether the blood crossed a state line, he only cares whether the blood or blood product is safe. It seems to me that the lack of federal authority in this area is a loophole big enough to drive an epidemic through.

Again, Mr. Chairman thank you for holding today's hearing and I look forward to hearing the testimony of the witnesses.

Mr. SHAYS. Thank you very much. What aspects of GAO's report did the FDA oppose? Where do you have your most lines of contention?

Ms. STEINHARDT. I would say in the area of inspections and reporting. I think by and large the agency agreed with most of our recommendations. But the one area that we seem still to have some difference is with inspection reports, and, in particular, on the way in which the reports are documented. I talked about this a little earlier in the response to Mr. Towns' question. FDA continues to believe that the system they now have for requiring inspectors to indicate only those areas that they don't cover in an inspection is sufficient, and we simply disagree.

We think that whatever an inspector observes ought to be documented for the record. And I would just note here the fact that FDA, itself, in its inspection of facilities, requires facilities to keep documentation of their quality assurance, quality control procedures. And they would cite a facility for the absence of documentation of what they've done. And they ought to follow the same kinds of standards and principles in their inspection and procedures.

Mr. SHAYS. I know that Mr. Towns got into this a bit. But I'd like you again to tell us what you think the solution is between licensed and unlicensed. And it all involves the issue of interstate.

Ms. STEINHARDT. Right.

Mr. SHAYS. We license those that are interstate and don't those that are intrastate. But what is the solution to that?

Ms. STEINHARDT. FDA can simply require the unlicensed facilities to report error and accident reports. They have the authority, we believe. And, in fact, I know that they're proposing—they've announced that they're going to propose such a regulation.

Mr. SHAYS. Yes. There's no logical reason not to have them report.

Ms. STEINHARDT. And the data suggest that there's a good reason to have such a requirement.

Mr. SHAYS. Right. OK. I'm treading back into your chart again on the delay of time. Because it sounds like we have a disagreement between you, Mr. Robertson—the GAO and the Inspector General—in terms of the significance of the chart. The chart seems to be valid, and yet, Mr. Robertson, your point to me is, don't worry, because it doesn't say anything.

Mr. ROBERTSON. No, sir, I'm not saying that. I guess what I'm saying is, the ones that we looked at—we looked at the error and accident reports. I think we looked at about 150 of them. They came in from the establishments and all had instances of what they did in response to the error or accident.

The problem that I see is that when you have that delay in the classification, you really have to rely on what the establishment said. Now, when we're adding what they said it looks like everything is perfect. But if you classify it as a recall, then the FDA is required to do some monitoring. So that would be the effect. And I think we mentioned that in our report that we issued back in 1995 or so.

But without the classification the action was taken. But there is not assurance that what the establishment said they did, they actually did—No. 1—and, No. 2, that it was effective. So, one of the

purposes of making the recall classification is to do—I think FDA calls them audits. They go out there and they verify that the problem that was reported is now corrected.

Mr. SHAYS. OK.

Mr. ROBERTSON. So, it doesn't necessarily mean that the product remains out on the market.

Mr. SHAYS. Have you made a recommendation to FDA that there not be such a time lapse between notification and a decision?

Mr. ROBERTSON. I think our report dealt mainly with the error and accident reports. And one thing we did look at—of the 100 or more that we looked at, there were 17 that FDA took a good look at and decided that there was a potential for a recall. We looked at those 17 in detail. We found that 5 of their 17 were not processed properly, and we made recommendations.

Mr. SHAYS. I don't really think you were responsive to my question. You had a point that you wanted to make. I'm happy to have you make that. But the question is, did the Inspector General's office weigh in on whether or not there should be corrective action in shortening the time in which the FDA is notified and then makes an order?

Mr. ROBERTSON. We made a recommendation to them within the timeframe of when they're notified.

Mr. SHAYS. Yes.

Mr. ROBERTSON. That was the extent of our recommendation with regard to the timeframe.

Mr. SHAYS. What happened? What about the timeframe?

Mr. ROBERTSON. We recommended that they have a 45-day timeframe.

Mr. SHAYS. OK.

Mr. ROBERTSON. That when the error and accident is identified they have to be notified within 45 days. I don't believe that it has been implemented yet.

Mr. ROSLEWICZ. The way the regulations were written indicates that the error and accident report should be submitted promptly. But there was no definition of what is prompt. So, our recommendation was to set something to the effect like 45 days.

Mr. SHAYS. Yes. OK. If we have some more recalls, larger recalls, what implication do I make from that? That the screening process before was bad or that we have a better process now to do recalls and we should have had more recalls in the past? I'd like both of you to respond to that. Do you understand what I'm asking? Do I make an inference that if we have a lot more recalls now, that things are more serious or better, better in the sense that we now can identify that we should have recall and we're taking action whereas, in the past, we should have had a recall and didn't? I'm just trying to understand how I interpret significant numbers of recall and know if that's a good thing or a bad thing.

Ms. STEINHARDT. I think it's really hard to tell. You know, you can increase the number of cases, of problems that you detect because the system is working better. And you can take that as a sign that the system is working better, or you can take it as a sign that overall the problems are actually increasing. I don't know that there's any way to definitively tell. I think——

Mr. SHAYS. OK. Yes. I'm trying to find that out.

Ms. STEINHARDT. How you can tell. I think this is an area——

Mr. SHAYS. Let me just preface my comment again and say, there can be almost a temptation to say, this is terrible, we have another recall, the whole system is falling apart. Or we can say, at least this last line, we're more on top of it. And then I'd want the time span to be real quick. But I'd say maybe that's good.

So I'd like to know—and you have no opinion—I don't want you to have an opinion if you don't. You don't know how to read that yet?

Ms. STEINHARDT. No. And the other thing I don't know is whether the right approach here is to try and figure out how to make this system more efficient just by cutting down the number of days or if maybe there's a whole other way to go about this.

Mr. SHAYS. Well, one thing I know we're going to do, we're going to make the system more efficient. Even if the Inspector General makes the conclusion that action had already been taken, it shouldn't take more than a year if people's lives are threatened. And then we just need to find out what the FDA needs to do to make sure that doesn't happen. I'd like you to take a pass at this. If we hear more recalls, larger blocks of recalls, should I view that as proof that the system is breaking down or that, at least in that final stage, we're doing a better job of catching things we should have caught in the past?

Mr. ROSLEWICZ. OK. Our audits certainly didn't move in that direction. That was not one of our objectives.

Mr. SHAYS. OK.

Mr. ROSLEWICZ. But it seems to me that if you're having more recalls, for example, the plasma fractionator—the chart I'm showing here. As ORA became involved we started to see more regulatory actions being taken as a result of more in depth inspections being conducted.

Mr. SHAYS. Right.

Mr. ROSLEWICZ. They've increased tremendously. When CBER was doing the inspections, there was an average of six observations per inspection. As they began to include ORA in these inspections, the number rose to 22 on the average. Now that ORA is doing them themselves, the number of observations being filed on an inspection is up to 49 on an average. So what you see is there's more potential there for identifying problems as you do more in depth inspections. I don't know if that's exactly getting to your point.

Mr. SHAYS. OK. Do you want to make another pass?

Ms. STEINHARDT. Yes. I think we're getting to something very important here. There needs to be—and it's an issue that we did raise in the report. There needs to be some way of analyzing the information. Obviously, if it's reached a stage where a recall is indicated, it means that something wasn't working earlier in the screening process. There's several layers of this quality assurance system that the blood had to go through to get to this point. And it didn't get screened out before this point. So, something wasn't working before then.

There should be a kind of feedback mechanism here. FDA should be looking—and the facility, itself—should be looking at what's going on beforehand in the earlier layers to make sure that it doesn't reach that point. And that's one of the concerns we have—

that there isn't necessarily that kind of rigorous analysis of data coming out of the system that would allow us to tell.

Mr. SHAYS. Can you outline, again, when you analyze the recalls, what was the primary reasons we're having recalls? Was there any one area?

Ms. STEINHARDT. Excuse me while I check.

Mr. SHAYS. No. Why don't you just step right up and get in that seat. And if you just identify yourself.

Ms. D'ALESSIO. Thank you. Jacqueline D'Alessio. I must say a lot of them were post-donation information, so the blood center did not know the information from the donor at the time of the donation. It may be that the donor came back subsequently and made an admission regarding some risk behavior. Or perhaps called on the telephone to say that they had come down with some other disease, something like that.

We can tell you about the proportions for error and accidents, but I don't believe we have the information regarding the types of problems for the recalls necessarily. But they really ran the gamut, from bacterial contamination to releasing units that were repeat reactive for various diseases to more minor problems.

Mr. SHAYS. Say the last thing again. It was muffled a bit.

Ms. D'ALESSIO. To more minor problems. Oh, to releasing units that were repeatedly reactive on their screening test and should have been discarded instead of distributed.

Mr. SHAYS. Is that bad management?

Ms. D'ALESSIO. That particular case is. But if I could make a comment about your original question regarding whether this means the process is working better or worse. One point that's very important to remember is that we now have a large number of new tests that we never had before. And we were unknowingly releasing a large amount of blood that was positive for hepatitis and other diseases. So, in that sense, the recall process is really working very well if we can get the blood back before it's been transfused.

Mr. SHAYS. OK. With the Inspector General, is the bottom line of the chart——

Mr. TOWNS. Would the gentleman yield?

Mr. SHAYS. Yes, sir.

Mr. TOWNS. Could we get her title.

Mr. SHAYS. Your title? Everybody has a title. You can even make it up.

Ms. D'ALESSIO. Senior analyst, Ph.D.

Mr. SHAYS. Thank you. Does the IG believe that the FDA's enforcement policies for the blood industry are better implemented by the Office of Regulatory Affairs, which is really a field force, rather than the Center for Biologics? Is that the bottom line—determination—I should make from you in that chart?

Mr. ROSLEWICZ. The bottom line in that chart—what we're showing is that as ORA became more involved with CBER doing joint inspections, it was a transition between 1992 and——

Mr. SHAYS. You're giving me the long answer. I want the short answer. Do you agree with the statement I made that this chart would lead us to believe that enforcement policies for the blood in-

dustry are better implemented by the Office of Regulatory Affairs than by the Center of Biologics?

Mr. ROSLEWICZ. Yes.

Mr. SHAYS. OK.

Mr. ROSLEWICZ. Also, on the other issue we were talking about, the MedWatch system that FDA asked——

Mr. SHAYS. On the what?

Mr. ROSLEWICZ. The MedWatch system, which reports adverse events, like a hospital if they have a problem with their produce they can just call that system and put in the data. One of the recommendations that we made to FDA was to try to better use that system, to take advantage of the information that is put into that system in terms of coming up with quicker recalls.

Mr. SHAYS. I have one last question that Anne Marie is insistent that I ask. What percentage of the current inspections of plasma fractionators are resulting in regulatory actions?

Mr. ROSLEWICZ. What percentage?

Mr. SHAYS. Yes. What percentage of the current inspections of plasma fractionators are resulting in regulatory actions? Fifty percent of the plasma inspections scheduled by the FDA in an accelerated timeframe following the Centeon incident in the fall of 1996 have resulted in regulatory actions. Is that right?

Mr. ROSLEWICZ. That is correct. The inspections that are being conducted with ORA as the lead—I believe there are 19 of them in 1997 that we have data on so far—50 percent of those have resulted in regulatory action. That's what we were told by——

Mr. SHAYS. Why don't you followup on this question?

Ms. FINLEY. Thank you, Mr. Chairman. In the IG's testimony, you state that there are 19 ORA lead inspections of plasma fractionators and that 10 of them have resulted in enforcement actions, including one injunction. Is it also true that there has been one notice of intent to revoke, one consent decree and seven warning letters as a result of those inspections?

Mr. ROSLEWICZ. Those figures are correct, I believe. But Tom, you wanted to say something?

Mr. ROBERTSON. Yes. Our audit was basically the 63 inspections. And of the 30 where ORA was involved, there were 11 enforcement actions—11 out of 30—and there was one more that they were working on. So let's say 12 out of 30. We ended our review as of the end of March 1997. Since then we were told by FDA that additional inspections took place, and that's where they're getting the 50 percent.

Mr. SHAYS. Now what's the significance of the question and the answer?

Mr. ROBERTSON. We didn't audit the 50 percent. We were recently told that 50 percent of the inspections that were performed with ORA now taking the lead are resulting in enforcement actions.

Ms. FINLEY. If 50 percent of the inspections are resulting in enforcement actions, is it fair to assume that 50 percent of plasma fractionators are not in compliance with FDA's GMPs—good manufacturing practices?

Mr. ROBERTSON. Yes.

Ms. FINLEY. Thank you.

Mr. SHAYS. That's the significance. OK. Ed.

Mr. TOWNS. Thank you very much, Mr. Chairman. There seems to be some confusion or a controversy about the FDA's presentation of inspection findings to directors or owners of facilities. What does FDA do with the inspection results and what does it require or expect of the facility directors in response to adverse findings? Would you help clear that up?

Mr. ROSLEWICZ. When the inspection is done there is a form 483 where they document all the findings that they're coming up with. These are certainly shared with the facility. And it is turned over to CBER for classification as to what one of the three classifications should be applied based on the results of that inspection. CBER then makes a determination as to whether there is no action indicated, whether there should be a regulatory action taken, injunction or license suspension or warning letters or whatever the situation would be in that particular inspection. So, the process is there. It's shared with the facility. And it's also CBER's responsibility to make that determination.

Ms. STEINHARDT. We surveyed 45 blood facilities. And this was a real problem that they perceive. It's really not clear what actually is required of them. Many of them feel that they're not kept well-informed about what's expected of them by the inspections. This is not true across the board. But it was true for a significant number. And I don't know if you want to elaborate.

Ms. CROSSE. Well, we found that many of the facilities felt that they were not getting good explanations in all cases of what the problems were that the inspections were identifying. However, it is FDA's policy that the facility be presented only at the close of the inspection with the form 483 observations of any conditions that might warrant correction if the inspector has identified such conditions. At the time period that we reviewed in our study, they were not being presented with a full copy of the inspection report that was written up after the inspectors returned to their office.

And, in fact, they were having to file a Freedom of Information request to receive a copy of the inspection report that was performed on their facility. And we understand from FDA that that policy has been changed, that they are now being sent copies of the full inspection reports. But at the time in which we surveyed the facilities, they didn't feel that they were getting the full information about what the inspectors were discovering when they came and did the inspection in their facility.

Mr. TOWNS. Shouldn't they routinely get a report?

Ms. CROSSE. Well, that was not the case at the time, but we understand that that policy has been changed by FDA subsequent to the time in which we did our work. To us it made sense that they be able to get that information without having to go through a Freedom of Information request.

Ms. STEINHARDT. And it certainly explained why—at the time we did our survey—it explained why a number of companies felt sort of baffled or uninformed about how they were being inspected.

Mr. TOWNS. That's the reason why, Mr. Chairman, I think the checklist really plays a very important role. Because at least there's some indication as to what the person actually saw or looked for. I think that becomes even more important to have it.

So, thank you very, very much, Mr. Chairman. And I also hope that we can continue to push in this direction, because there still seems to be some real problems out there.

And I think we need to sort of keep working to make certain that our blood supply is really safe. And inasmuch as you hear of maybe one incident—and I know we say that it is the safest. But the point is that there is some problems. And I think that we all have to acknowledge that fact and continue to work toward it. And in some instances it might require some resources. In other instances it might just require some changing of policy. So thank you very much, Mr. Chairman.

Mr. SHAYS. Thank you very much. I just want to, unfortunately, open one door again. And that is the whole issue of the unlicensed. Because I'm really wrestling with this. We basically have 3,000 facilities give or take?

Ms. STEINHARDT. Right.

Mr. SHAYS. You say that 700 are licensed, but they represent 90 percent of the blood supply activity.

Ms. STEINHARDT. Right.

Mr. SHAYS. You have 2,300 that have about 10 percent of the blood supply. Am I to infer that because they are not licensed, they may—and we know that the unlicensed facilities don't have as many recalls. It would be logical to me that they should have it proportionately the same. That would seem logical to me. And so I have the sense that they should have some recalls from the unlicensed intrastate facilities that aren't taking place. And I'm going to be asking FDA to deal with that. But I want to know, are there other way that these unlicensed facilities may simply not be up to the standard that we would want or does FDA, in other ways, ensure that these facilities are up to standard?

Ms. STEINHARDT. Well, the key here is the error and accident report. That's the information on what's going on other than the inspection itself. It's the information mechanism that FDA relies on to let them know what's going on within the facilities. And that's why—the statistic here is that they account for 10 percent of the blood supply but only 1 percent of the error and accident reports. That's a significant difference.

And that's why we think it's a really good starting point that at least if you can require them to submit the error and accident reports, then at least you can keep better track of whether there are other kinds of problems going on within those facilities that FDA ought to know about.

Mr. SHAYS. So, bottom line: it's an area for a good look. Now, is the GAO or IG looking at the unlicensed facilities? Are you taking a special look at these facilities? Do you have anything planned to do?

Ms. STEINHARDT. Well, we looked at them as we did all the other facilities in this. And that's, I think, of all the area that we observed, that's the one that we think is the most important—just getting them.

Mr. SHAYS. No. I've asked another question. I've asked the question of whether—you said the reporting—they only report 1 percent. They're 10 percent of the blood supply, but they're only 1 percent of the accident reports or recall. And I'm asking, does that

lead us to believe there may be other problems as well with the unlicensed facilities in terms of other practices?

Ms. CROSSE. Could I respond to that?

Mr. SHAYS. Yes.

Ms. CROSSE. There's a distinction here between the filing of the error and accident reports, where there is a great disparity in terms of the percentage of the reports that are coming from the facilities that are underreporting.

Mr. SHAYS. Right.

Ms. CROSSE. However, of those reports that are filed, almost equivalent proportions go on to have an investigation of potential recall by FDA. About 5 percent of reports filed by licensed whole blood facilities are investigated as potential recalls. About 7 percent of those error and accident reports that are filed by the unlicensed facilities are investigated as potential recall situations. So that's very close.

The plasma facilities. Of the reports that they've filed, about 39 percent are investigated as potential recalls. So we're not seeing a great disparity in terms of the reports that are filed.

Mr. SHAYS. Let me ask you this. What is the significance of being licensed or unlicensed?

Ms. CROSSE. In terms of the primary safeguards in the system, they are required to comply with the same—donor screening requirements, testing requirements, deferral register requirements.

Mr. SHAYS. OK.

Ms. CROSSE. So——

Mr. SHAYS. What aren't they required to do?

Ms. CROSSE. They aren't required to report to FDA.

Mr. SHAYS. That's the only thing?

Ms. CROSSE. If they have errors and accidents.

Mr. SHAYS. Is that the only difference?

Ms. STEINHARDT. But that's significant because that's the system.

Mr. SHAYS. No. First off. It is significant. So I don't want to belittle it. But I just want it to be clear. Is that the only difference?

Ms. CROSSE. No. There are some other differences in terms of the requirements they have to comply with if they're making modifications in their own facility, if they're moving equipment around. Licensed facilities have greater requirements placed upon them in dealing with FDA for that. An unlicensed facility does not have the same requirements in those regards. But the primary safeguards that are in place for the collection and processing of blood products are the same.

Mr. SHAYS. OK. Would you like to respond. And let me just conclude this panel by saying—first off, would you like to respond to anything that——

Mr. ROBERTSON. No, sir.

Mr. SHAYS. OK.

Mr. ROSLEWICZ. The only other thing I would add to that—I think your question, if I understand it originally was, have we actually perhaps gone to an unlicensed facility to determine if there are any error and accident reports that they haven't——

Mr. SHAYS. Right.

Mr. ROSLEWICZ [continuing]. Or even if how many or what the extent is at these facilities.

Mr. SHAYS. Or just looked at these facilities and said, are there differences between licensed and unlicensed that Congress needs to be aware of?

Mr. ROSLEWICZ. We have not done that as part of our audits that we've done so far.

Mr. SHAYS. OK. Is there any question that you wish that we had asked you that you feel needs to be part of the public record? This is really my out so later you don't say, if you'd asked this we would have told you and it was significant. I am asking you to tell me—to ask yourself any question I should have asked that you would later on say I should have asked.

Ms. STEINHARDT. I think almost everything—well, I would say everything we want to say we included in our testimony and our reports.

Mr. SHAYS. OK.

Ms. STEINHARDT. And ask that they be part of the record.

Mr. SHAYS. They will be part of the record.

Mr. ROSLEWICZ. Yes. I think our audit report is very detailed. It's quite lengthy, as a matter of fact, with facts and figures. And the written testimony, itself, also carries our key points that we wanted to make.

Mr. SHAYS. Any question that you wish we had asked? Any area that you wish we would have gotten into?

Mr. ROBERTSON. No, sir.

Mr. SHAYS. OK. We're done. Thank you very much. We appreciate both the GAO and Inspector General being here.

Mr. ROSLEWICZ. Thank you.

Mr. SHAYS. Our final panel is Dr. Michael Friedman, Deputy Commissioner of Food and Drug Administration. I call him the Acting Commissioner. Accompanying him are Kathryn Zoon, Director, Center for Biologics Evaluation and Research; Jay Epstein, Director, Office of Blood Research and Review; and, Ronald Chesemore, Associate Commissioner for Regulatory Affairs. I'm going to ask you to stay standing. We're going to swear you in, and we're really happy you're here. Do we have anyone else who might be responding?

[Witnesses sworn.]

Mr. SHAYS. And everyone has responded in the affirmative. Dr. Friedman, great to have you here and good to have your staff. And I'm looking forward to your testimony and asking questions. Thank you.

STATEMENTS OF MICHAEL FRIEDMAN, LEAD DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY KATHRYN C. ZOON, DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH; DR. JAY S. EPSTEIN, DIRECTOR, OFFICE OF BLOOD RESEARCH AND REVIEW; AND RONALD G. CHESEMORE, ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS

Dr. FRIEDMAN. Thank you very much.

Mr. SHAYS. And I just note that we are joined by a former mayor of Cleveland, Mr. Kucinich. Thank you.

Dr. FRIEDMAN. Thank you, sir. Mr. Chairman and members of the subcommittee, I'm Michael Friedman and I serve as the lead

Deputy Commissioner of the Food and Drug Administration. With me today, as you've mentioned, Mr. Chairman, are Mr. Chesemore, the Associate Commissioner of Regulatory Affairs, Dr. Zoon, Director of the Center for Biologics Evaluation and Research—the center primarily responsible within the agency for the scientific and regulatory activities for blood and blood products—and Dr. Jay Epstein, Director of the Office of Blood Research and Review.

This committee has demonstrated a keen interest in blood issues in the past. And so I appreciate this opportunity to discuss FDA's role in regulating and protecting the Nation's blood supply. Each year in this country about 14 million units of whole blood are drawn from about 8 million donors. The products made from this blood are transfused into 3.5 million Americans. Some of this blood—an additional 12 million units of source plasma—are further processed into products such as clotting factors and immunoglobulin.

Blood and blood products are vitally important to our health care system and are often used to keep the most ill and the most severely injured of our citizens alive. Let me begin, sir, by reiterating clearly that blood products have never been safer and that the American blood supply is among the safest in the world. But having said this, because of the biologic nature of blood itself, there exists risks to anyone who receives a blood product.

Nonetheless, we are absolutely committed to taking appropriate steps to making these products as safe as we possibly can. We must acknowledge that there have been weaknesses and inconsistencies in our regulatory oversight of blood and blood products in the past. Based on constructive criticism and advice received from this committee, from GAO, from OIG and IOM, and, of course, based on our own on-going commitment to improve what we do, we have implemented a number of substantial improvements in our blood program.

And if I may, I'd like to highlight some of the recent changes we have made. As you know, sir, since 1993 the Office of Regulatory Affairs has been primarily responsible for blood bank inspections. And as you've just heard, as of the fall of 1996, the Office of Regulatory Affairs has taken the lead responsibility for the inspection of plasma fractionators. CBER's staff cooperate in this endeavor. Their scientific input is valuable and useful. But ORA has the lead.

Second, since this time—since the fall of 1996—we've conducted a thorough reinspection of all plasma manufacturers producing products for citizens in the United States. As you have seen, we found significantly more violations than had been noted in the past. And these observations are being acted upon in a much more timely manner.

These efforts are aimed at preventing problems. Nonetheless, we know that there is more that needs to be done. The Center for Biologics Evaluation and Research is in the process of restructuring exactly how it handles reports of blood and blood products emergencies, and is now reacting much more appropriately and much more promptly. We also have changed how we communicate with the public, patient groups and others affected by recalls and withdrawals of blood products. And, moreover, we are reaching out to include more consumers and patient representatives whose valu-

able input helps increase the quality of our decisionmaking. This is especially true for the hemophilia community who participate in this way.

We also are restructuring how blood issues are managed within the Center for Biologics Evaluation and Research. We've recently named a new medical deputy director for this center. And this individual will be in charge of all the CBER components dealing with blood and blood products. And he will continue to increase the pace of our efforts to markedly improve how we manage this very important portfolio.

These are just some brief comments, an overview, if you will, of the steps that we are taking. We are not satisfied. We clearly recognize that a good deal more needs to be done. We are committed to reviewing and revising as necessary all regulations and guidance that we provide to industry to assure that they are complete, that they are current, that they are appropriate and that they are clear, so that industry understands its responsibilities.

We also are committed to identifying areas where new advice may be needed. And we're addressing new scientific problems as they are identified. Among the areas that still require additional consideration, we know that one of great interest to this committee has been the issuance of look back notification involving individuals who may have been infected with hepatitis C through blood products.

The Public Health Service Advisory Committee established by Secretary Shalala, as was promised to you, Mr. Chairman, has taken several notification options under consideration. We expect much more precise guidance on these options at their next meeting coming up later this summer.

FDA has worked with its sister agencies, especially CDC, to address the public health concerns of the approximately 4 million individuals thought to be infected with hepatitis C virus, some of whom may well have been infected through blood transfusion.

I am personally committed to blood safety. Shortly after coming to the Food and Drug Administration in the fall of 1995, I began holding meetings on a regular basis with senior FDA managers, especially those from the Center for Biologics Evaluation and Research, to begin to discuss aspects of our blood safety program. These meetings continue. And we will get the job done. I am holding specific FDA staff responsible for the success of this effort, just as I expect you, Mr. Chairman, to hold me publicly and personally accountable for this.

America's blood safety program must provide the finest public health protection that is possible. FDA must be vigilant in ensuring that the blood supply is as safe as it can be. We appreciate the chance to be here to answer questions raised by the previous panel and other issues that you'd like us to address. Thank you, sir.

[The prepared statement of Dr. Friedman follows:]

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I. INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Michael Friedman, Lead Deputy Commissioner of the Food and Drug Administration (FDA). I appreciate this opportunity to discuss the status of FDA's regulation of blood, blood products, and plasma, as well as our notification, recall, and enforcement practices. I also would like to review the substantial progress FDA has made since the Committee on Government Reform and Oversight (Committee) issued its 1996 report[1] on blood safety and to indicate opportunities for further improvements. Accompanying me are Mr. Ron Chesemore, Associate Commissioner for Regulatory Affairs; Dr. Kathryn Zoon, Director of the Center for Biologics Evaluation and Research (CBER), the Center responsible within FDA for regulating blood and blood products; and, Dr. Jay Epstein, Director of the Office of Blood Research and Review (OBRR) in CBER.

II. BACKGROUND

The blood supply plays a critical role in the American health care system. While the United States is recognized as having one

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[1] *Protecting The Nation's Blood Supply From Infectious Agents: The Need For New Standards To Meet New Threats*, Committee on Government Reform and Oversight, H. Rept. 104-746, August 2, 1996.

of the safest blood supplies in the world, assuring this safety poses formidable challenges. Each year, approximately 14 million units of whole blood are drawn from about 8 million volunteer donors to make products that are transfused into more than 3.5 million Americans. Some of this blood, and an additional 12 million units of source plasma, is further processed into products referred to as derivatives.

Plasma is the fluid (non-cellular) portion of circulating blood. Plasma contains albumin, clotting factors, and other important proteins of medical value. Plasma units intended for making derivatives are transferred to manufacturing facilities where they are pooled with other units. The fractionation process chemically and physically separates the plasma components. Derivative products are manufactured from intermediate materials obtained in the process. These products include albumin, used to restore plasma volume in treatment of shock, Factor VIII and Factor IX which are used as clotting factors for hemophiliacs, and immune globulins used to prevent and treat infectious diseases.

There is always some degree of risk in receiving blood or plasma products. For example, blood can transmit infectious disease, because blood donors may harbor undetected or undetectable communicable diseases. As this Committee noted in its 1996 report, "The public is not well served if patients are permitted

to believe that there is no risk in blood transfusions or in the use of blood derived therapies." Given the finite risk[2], and the fact that millions of Americans depend on blood and blood products, the effort to ensure the safety of the blood supply is a high priority for FDA.

Despite the risks associated with blood products, let me stress again that the United States blood supply is one of the safest in the world. Our role is to manage more effectively future risks and utilize modern science in maintaining the quality of the United States blood supply.

We do acknowledge, however, that there have been aspects of FDA's regulatory oversight of the blood and plasma industry which have been the subject of criticism and that have required correction. To address these problems we have instituted, and are continuing to institute, substantive changes, both procedural and managerial, in order to correct these problems and to further improve protection of the public health.

A five layer system of overlapping safeguards forms the core of the blood safety system established by FDA. This system starts at the blood collection center and extends to manufacturers and distributors of blood products. The five layers are as follows:

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[2] The current CDC estimate for risk for HIV is 1:450,000; for HCV 1:10,000; and, for HBV 1:500,000.

- First, donor screening is performed. Potential donors are provided educational materials and asked specific questions by trained personnel about their health and medical history. Potential donors whose blood may pose a health hazard are asked to exclude themselves.

- Second, after donation, the blood is tested for blood-borne agents such as HIV-1, HIV-2, HBV, HCV, HTLV-1, syphilis, and CMV (some collections). Donors also are excluded based on risk of malaria, CJD, and acute illness.

- Third, blood establishments must keep current a list of individuals who have been deferred as blood or plasma donors and check all potential donors against that list to prevent use of units from deferred donors.

- Fourth, blood products are quarantined until the products have been thoroughly tested and the donation records have been verified.

- Fifth, blood establishments must investigate any breaches of these safeguards and correct system deficiencies that are found by the firms or through FDA inspection. Licensed firms must report to FDA any manufacturing problems, e.g., errors or accidents that may affect the safety, purity, or potency of their products.

In addition to these layers of protections, many plasma derivative products also are processed to inactivate viruses that may be present. At the present time, the technology to inactivate heat stable, non-lipid enveloped viruses, such as the Hepatitis A virus, while preserving the functions of the plasma proteins, is not available.

FDA regularly and frequently reviews all of its efforts to assure blood safety. Additionally, FDA works closely with the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) so that the latest science is brought to bear in the oversight of the blood supply. FDA also regularly interacts with patient groups, academicians, and industry scientists to remain current with outstanding issues of concern and technological advances.

Program safeguards are augmented by the oversight and audits of FDA's blood program provided by Congress, the General Accounting Office (GAO), and the Office of Inspector General (OIG). FDA has benefitted from outside recommendations and carefully considers any recommendations that may enhance the quality of the nation's blood supply.

III. FDA REGULATORY OVERSIGHT -- IMPROVEMENTS

Over the past two years FDA has made a number of substantial improvements to its regulation of the nation's blood supply. The areas which I will discuss in this testimony include: product safety, emergency response, inspection activity, dissemination of information to the public, blood banks, and future plans for the blood program within FDA.

A. PRODUCT SAFETY

In the past two years, FDA has issued new regulations and guidances to improve blood safety and deleted some obsolete regulations. Several committees have been established, or reformulated, to provide scientific and other advice to FDA to help ensure the safety of blood and blood products.

The Secretary of Health and Human Services raised blood safety to the highest levels of the Department of Health and Human Services (DHHS). The Assistant Secretary for Health was designated to be the 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 is the Blood Safety Committee (BSC) which includes the Directors of NIH and CDC, and

the Commissioner of FDA. BSC has been meeting periodically since January 1996. BSC receives input from the Advisory Committee on Blood Safety and Availability (Advisory Committee).

The Advisory Committee was created in response to a commitment made by the Secretary of DHHS in her testimony before this Committee in October 1995. The Advisory Committee includes consumer representatives, scientific experts, ethicists, and representatives of regulated industry. Its purpose is to provide a forum to examine broad public health and societal implications of blood safety issues. The Advisory Committee held its first meeting in April 1997.

Since its inception in 1996, BSC has been informed of adverse events or emergency situations whenever they are likely to have broad public health impact or require increased coordination between the public health agencies. For example, an issue involving a specific incident of a product made from a donor who was subsequently diagnosed with Creutzfeldt-Jakob Disease (CJD) was brought to BSC's attention. BSC will be informed, and provide input, whenever FDA intends to take action that might be precedent setting or controversial.

FDA has made significant changes in its Blood Products Advisory Committee (BPAC). FDA has acted to eliminate any potential conflicts and possible undue industry influence by appointing new

members in 1996 and revising its charter. FDA had restructured BPAC initially in 1994 expanding consumer representation through voting consultants. In 1995, the charter was revised to expand the possibility for voting representatives with consumer interests. FDA removed committee members with any appearance of a conflict of interest, except for a single non-voting industry representative. FDA also added a representative of CDC as a permanent member of BPAC. A representative of NIH is present as a consultant. This NIH representative has been allowed temporary voting privileges at BPAC meetings. BPAC plays an important role providing technical advice to FDA on scientific issues relating to safe and effective blood products and related medical devices. BPAC agendas are discussed with the Committee chairs prior to the meeting to help them prepare for the meeting. BPAC members also are sent background information on each agenda item. Since FDA's testimony before this Committee in October 1995, BPAC has met seven times covering a wide range of issues from HIV test kits to emerging new diseases to public notification issues.

FDA has provided a number of guidances in the past two years to the blood and plasma industry in an effort to ensure that the most up to date processes are utilized. In March 1996, FDA issued additional clarification of its August 1995 recommendation that blood establishments implement the HIV-1 p24 antigen test when the test was approved. FDA approved the test to screen blood donors for HIV-1 p24 antigen in March 1996 and

establishments then were advised to use the test within three months of commercial availability. FDA recommended that the HIV-1 p24 antigen test be used to screen blood donors, in addition to antibody tests, thus providing additional screening. It is estimated that the use of the screening test could prevent up to 25 percent of the cases of AIDS from transfusions. These tests improve blood safety by further closing the "window period" before antibodies to HIV develop. The "window period" is the time early after infection when a person may be infectious but markers identified by testing are not yet present.

In May 1996, FDA issued further recommendations to blood establishments for the testing of whole blood, blood components, source plasma, and source leukocytes for the antibody to Hepatitis C Virus encoded antigen -- anti-HCV.

In July 1996, FDA issued recommendations for the quarantine of prior collections from donors who subsequently test reactive for HCV, HBV, and HTLV currently being screened for in blood donors.

In September 1996, FDA issued a final regulation on "Current Good Manufacturing Practices for Blood and Blood Components: Notification of Consignees Receiving Blood and Blood Components at Increased Risk for Transmitting HIV Infection." This final rule requires that blood establishments and consignees quarantine previously collected whole blood, blood components, source

plasma, and source leukocytes from donors with reactive screening tests for HIV. Blood establishments also must perform confirmatory testing for donations that test reactive for HIV and notify consignees who received whole blood, blood components, source plasma, or source leukocytes from prior collections of such products so that they may take further action. FDA's rule, along with a companion Health Care Financing Administration (HFCA) rule, should result in the notification of transfusion recipients who received blood from donors who later tested positive in confirmatory tests for HIV.

In December 1996, FDA issued guidance to blood establishments on the deferral of donors who immigrated from countries with HIV-1 Group O. FDA also advised manufacturers of test kits to modify their kits to enhance sensitivity to detect HIV-1 Group O specimens.

FDA has required that plasma derivative manufacturers file monthly reports on adverse reactions associated with their products. Letters were sent to manufacturers in October 1996 and December 1996 notifying manufacturers that, pursuant to 21 C.F.R. § 600.80, reports on any infectious disease transmission associated, or possibly associated, with any licensed biological product, be filed monthly. This is to ensure that incidents involving potential transmission of infectious agents are dealt with in an expeditious manner.

n December 1994, FDA instituted lot release testing for HCV RNA n all immunoglobulin products that have not undergone one or ore validated viral inactivation or removal steps. Since then, DA developed, and made available to manufacturers, a more ensitive assay for RNA extraction, and subsequent detection of CV RNA by RT-PCR, in intravenous and intramuscular mmunoglobulin products. FDA trained manufacturers in the use of he RT-PCR technique for use as a lot release procedure.

Factor IX reference standard was developed by FDA and has been ccepted as the world standard. A Factor VIII standard is being eveloped. Additionally, new lot release panels (standards) were eveloped for HIV, HBsAg, and HTLV-II.

n addition, FDA, in conjunction with CDC and NIH, published uidelines, such as the "U.S. Public Health Service Guidelines or Testing and Counseling Blood and Plasma Donors for Human mmunodeficiency Virus Type 1 Antigen," in the March 1, 1996 CDC orbidity and Mortality Recommendations and Reports.

DA has taken an aggressive stance with respect to potential new hreats. FDA actions were discussed extensively in our testimony efore this Committee on January 29, 1997.

DA, in an effort to further develop its policy on CJD, formed a pecial Advisory Committee on Creutzfeldt-Jakob Disease which

first met in June 1995. This CJD Advisory Committee, composed of outside experts, including academic and Government representatives; consumer groups, including the National Hemophiliac Foundation (NHF); and industry groups, was rechartered in June 1996 for two additional years and is now known as the Transmissible Spongiform Encephalopathies Advisory Committee (TSE Advisory Committee), charged with advising FDA on issues related to all transmissible spongiform encephalopathies.

The risk for transmission of CJD through blood and blood products is considered to be only theoretical. Nevertheless, FDA has acted proactively to defer high risk donors and has recommended the voluntary withdrawal of affected products. In December 1996, FDA issued a memorandum to all registered blood and plasma establishments and establishments engaged in manufacturing plasma derivatives concerning revised precautionary measures to reduce the possible risk of transmission of CJD by blood and blood products.

There is presently no test available to screen blood donors for the presence of CJD. In fact, there is still scientific controversy over the nature of the causative agent. Recently there have been a number of withdrawals of plasma products because of the identification of donors who contributed to the plasma pool who subsequently died of CJD or were identified as having been at risk for CJD.

Recently, manufacturers have approached FDA concerning the use of nucleic acid (PCR) tests to test plasma pools for infectious agents such as HIV. Such testing could result in donor notification, retrieval of prior collected "lookback" units and possible recipient notification. The accuracy of test results is critical since donor notification may be involved. FDA would carefully evaluate the safety and efficacy of such tests in reviewing any applications seeking approvals. The issue of PCR testing of plasma pools has been considered by BPAC and BPAC voted to adopt PCR testing of plasma pools. FDA is now preparing a Federal Register notice seeking public comment on this issue.

FDA has brought the recommendation of limiting the size of plasma pool size to BPAC for discussion on several occasions. The issue of safety in the face of unknown or theoretical threats is a difficult issue. FDA believes that restricting pool size could have some limited health benefits, including limiting the spread of rare infectious agents for which there are no screening tests and no adequate inactivation procedures. FDA, therefore, remains interested in considering setting practical upper limits for pool size and will request that all manufacturers of plasma derivatives update their product license files to include specific information regarding pool size.

FDA works closely with its sister public health agencies to ensure the safety of the blood supply. FDA receives input from

CDC and NIH on issues of blood safety through several mechanisms in addition to the BSC. Employees of NIH, CDC, Health Resources Services Administration (HRSA), and the Department of Defense participate in the Interagency Working Group on Blood Safety and Availability which holds teleconferences approximately monthly to discuss issues affecting blood safety. CDC also has created a position of Assistant Director for Blood Safety in the Division of Viral and Rickettsial Diseases to facilitate interactions on these issues.

FDA collaborates with CDC and NIH on emerging public health issues through epidemiologic, laboratory, and other scientific studies. A few recent examples include: assessment of the risk of disease transmission from idiopathic CD+4 T-lymphocytopenia; ongoing surveillance study of HIV and hepatitis in clotting factor recipients; surveillance for novel strains of HIV such as HIV-1 group O; assessing the risk of transmission of CJD through blood and blood products by epidemiologic criteria and laboratory studies; studies of donor behavior related to use of voluntary deferral criteria; assessment of new donor testing technologies such as HIV-1 p24, HIV Western blot, HTLV screening, and many others.

CDC participates in product investigations on both a formal and an informal basis. CDC may assist FDA by conducting epidemiologic studies or assisting with scientific analysis.

Three recent examples are: Centeon Albuminar-epidemiologic assistance to identify products at risk for bacterial contamination; Alpha HIV antibody positive pool-scientific studies to determine whether there was an inherent problem with a licensed test kit; and Alpha Factor VIII and Factor IX epidemiologic and laboratory studies to investigate transmission of Hepatitis A virus from clotting factors. All of these efforts ensure that CDC and NIH have input at the highest levels of FDA and DHHS on blood safety matters.

B. EMERGENCY RESPONSE PROCEDURES

FDA has implemented fundamental changes in its internal operations to more effectively respond to emergency situations and potential emergencies. The change in emergency response procedures was necessitated by the recognition of a not sufficiently prompt response to a report of an adverse reaction to a plasma product.

On August 23, 1996, a patient in Wichita, Kansas, had an adverse reaction after receiving a plasma product. A hospitalized patient had been given Albuminar-25, manufactured and distributed by Centeon. Within 15 minutes the patient developed symptoms of septic shock. Ultimately, the patient recovered. The bottle of Albuminar tested positive for Enterobacter cloacae and the patient's blood culture also was positive for Enterobacter

cloacae. The hospital reported the adverse reaction to FDA on August 24, 1996, through FDA's MedWatch[3] system and to the company. CDC was contacted about the case by the Kansas State Epidemiologist on September 4, 1996.

Despite the timely notification to FDA and the serious nature of the report, the MedWatch report was not identified as an emergency in its initial stages of processing. There also was a report to a field office that was not treated in an emergency fashion when reported to CBER. It was not until 27 days after the initial filing of the report that the emergency nature of the report was fully appreciated. On September 23, acting on FDA's advice, Centeon issued a voluntary recall of Albuminar and notified its consignees. Subsequent to the voluntary recall notification, CBER designated the Centeon incident as a Class I recall[4] and notified the media to publicize the matter so that affected individuals could take action.

The Centeon situation brought to light differences in the way adverse reaction reports for drugs and biologics were handled by FDA. Because of these differences, the MedWatch report on

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[3] The MedWatch system is a voluntary reporting system to report adverse reactions to regulated products.

[4] A Class I recall is a situation in which there is reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequence or death. 21 C.F.R. § 7.3(m)(1).

Centeon's Albuminar was not acted on promptly. As a result of this incident, the following procedures are now in place for the MedWatch system.

As voluntary reports involving biologics products come into the MedWatch central triage unit (CTU) a copy is made and sent to CBER within one business day. The original report is sent to the Center for Drug Evaluation and Research (CDER)(the Center responsible for the MedWatch program) for data processing. In addition, the contractor taking adverse event reports over the phone notifies CBER immediately when any CBER reports come in. The copy is evaluated immediately by CBER staff and forwarded as needed to appropriate CBER scientific and regulatory staff. After hours, the Medwatch answering machine greeting refers callers to FDA's Emergency Operations if no one is immediately available to take their call and they want FDA to know about an urgent problem. The overall 1-800-FDA-1088 Medwatch phone tree also was changed to refer persons making MedWatch reports to Emergency Operations if their call is urgent and they are calling after hours, on weekends, or holidays.

The mandatory reports that are sent in by biologic manufacturers, as opposed to the voluntary reports that are usually sent in by clinicians, are sent directly to CBER where a copy is kept by the safety evaluator and the original is sent to CDER for processing.

All reports associated with plasma derivative products are given the highest priority for review at all levels. To ensure rapid positive identification of plasma derivative products, up-to-date copies of CBER product lists are available at the CTU, the Telephone Unit (an outside contractor that handles adverse event telephone calls), and the CDER Division responsible for data processing (Surveillance and Data Processing Branch). All plasma derivative products involving documented, or possible, infectious disease transmission, are shared immediately with the Deputy Director, OBRR, and the Deputy Director, Division of Hematology, for evaluation to determine public health risk.

The manner in which field reports, that are potential emergencies, are handled also has been changed. Such reports, including complaints, calls, or reports, are handled by the Division of Emergency Investigations and Operations. This is now consistent with practices throughout FDA. As part of this effort, FDA has established an emergency response team consisting of members of FDA field offices, headquarters, compliance officers, and product experts to rapidly assess a situation and initiate corrective action.

While FDA did have systems in place to deal with emergency situations once an emergency was recognized, FDA has made significant improvements in its procedures for initially identifying an emergency situation. We also have established

standard procedures to define the actions that need to be taken by different offices within CBER when confronted with an emergency or potential emergency situation.

CBER has finalized Standard Operating Procedures (SOP)[5] for dealing with situations that might constitute a threat to public health. The SOP details the responsible parties to whom information must be given, their accessibility at all hours, and procedures for notification when emergencies, recalls and significant adverse events are identified.

Another problem brought to light with the Centeon recall was the attempt by certain plasma derivative manufacturers to characterize recalls as market withdrawals.[6] There have been several manufacturers who have initiated multiple product retrievals that were characterized as market withdrawals which FDA subsequently determined to be recalls. Two of these recalls were assigned Class I Recall classifications by FDA. The characterization of any recall, and particularly Class I recalls, as "market withdrawals," can be serious. Given the seriousness of the situation, the manufacturers re-issued letters to

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[5] *Emergency Operations*, SOP # OD-R-17-97 (April 14, 1997).

[6] Market withdrawals are defined as a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by FDA or which involves no violation, e.g., normal stock rotation practices, routine equipment adjustments and repairs, etc.(21 C.F.R. § 7.3(j)).

consignees properly designating the actions as recalls and provided instructions to secondary distributions for extension of the recalls to their customers. FDA has dealt with each plasma derivative manufacture involved in such recalls on an individual basis to assure that product removals were properly conducted. In addition, FDA recently addressed a letter to all plasma derivative manufacture specifically calling attention to their responsibilities concerning the classification of product recalls and market withdrawals. FDA also has engaged in discussion with trade associations and other organizations to encourage industry-wide attention.

FDA also has formed a task force to continue reviewing all current procedures for handling reports of adverse events. This task force is examining ways that FDA receives reports and how to improve internal communication and handling of these issues so that the public health is better protected.

C. INSPECTION ACTIVITIES

Based on internal assessment of inspection activities, and consistent with outside recommendations, FDA has transferred lead responsibility for periodic inspections of plasma fractionators (manufacturers who further process plasma and other blood derivative products) to the Office of Regulatory Affairs (ORA). Along with a transfer of the lead responsibilities in inspections

and field emergency response, FDA has adopted a new model and approach to the inspection of plasma fractionators. This new approach emphasizes a complete assessment of compliance with good manufacturing practices (GMPs). In addition, the approach includes an assessment of the manufacturer's procedures in handling and investigating reports of adverse experiences and subsequent notification of these adverse experiences to FDA. Transfer of the lead to ORA will advance FDA's goals of internal consistency and efficiency as the inspection process for fractionators is now comparable to inspections for other regulated products.

ORA conducts inspection activities through FDA's five regional offices and multiple district and field offices. The field inspectors are trained to inspect primarily for GMPs. Prior to April 1992, CBER alone had responsibility for inspections of plasma fractionators. In April 1992, CBER and ORA agreed to conduct joint inspections of plasma fractionators with CBER serving as the lead. In December 1995, CBER and ORA issued an SOP for joint inspections that had CBER and ORA sharing the lead on inspections. In Fiscal Year 1997, ORA assumed the lead for periodic inspections of plasma fractionators including evaluation of inspection findings and recommendations for appropriate regulatory action. To ensure the capabilities of the field to take the lead for these inspections, FDA intends to provide field staff more intensive training in biologic product manufacturing

and, at the same time, provide CBER product specialists with more intensive training on inspection techniques with an emphasis on documentation of GMP deficiencies. OIG's analysis of prior CBER inspections concluded that CBER inspectors "were first and foremost scientists whose primary duties were not the inspection of plasma fractionators."[7] The inspections by CBER "were not designed to support post market obligations -- primarily assuring compliance with GMPs. Conversely, ORA inspectors were full time inspectors with more experience in conducting GMP inspections."[8]

In the wake of the Centeon incident, FDA decided that an intensive review and inspection effort was needed to assure ourselves, and the public, of the safety of plasma manufacturing. FDA adopted a plan to conduct a compressed schedule of inspections of all plasma fractionators. There are a total of 26 licensed plasma fractionators. Twenty-two of these plasma fractionators currently are supplying product for the United States market. As of the date of this testimony, we have reinspected 100% of the plasma fractionators currently supplying product to the United States market in Fiscal Year 1997. Four manufacturers, all foreign firms, were not inspected as they are

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[7] Department of Health and Human Services, Office of Inspector General, *Review of the Food and Drug Administration's Inspection Process of Plasma Fractionators* (Discussion Draft, May 1997) at p. 12. The OIG provided FDA with a Discussion Draft and has permitted FDA to cite from that draft for purposes of this testimony.

[8] Id., at p. 12-13.

not currently producing product for the United States market. Three of these firms are renovating their facilities and one firm is temporarily shut down but expects to resume operations in the near future. Upon resuming production and prior to distribution of product to the United States, all four foreign firms will be inspected.

A review of the results of establishment inspections from Fiscal Year 1993-1996, and those in Fiscal Year 1997, emphasizes significant inspection differences. In general, inspections under the lead of ORA have resulted in more in-depth inspections. The Form 483s (the form used to report findings of the inspection) contain more substantive items including items previously which may only have been "discussed" with a firm and not necessarily noted on the 483. The final Establishment Inspection Report (EIR) is received in the CBER Office of Compliance (OC) on a more timely basis. To date, there have been five Warning Letters issued in Fiscal Year 1997, one Notice of Intent to Revoke, and one injunction based on a consent decree related to plasma fractionation inspections. The following table provides some comparative figures:

Plasma Fractionator Inspections*	Insp. Length (days)	Days from Insp. to EIR Rec'd in OC	Avg. and Total No. Of 483 Items
FY 1993 10 Inspections	Avg. 3.2 **MEDIAN 4** Min. 1 Max. 4	228.7 **109** 34 669	Avg.5.1 **MEDIAN 2.5** Total 51
FY 1994 15 Inspections	Avg. 3.2 **MEDIAN 3** Min. 2 Max. 6	121 **125** 26 245	Avg. 5.5 **MEDIAN 4** Total 83
FY 1995 11 Inspections	Avg. 7.3 **MEDIAN 4** Min. 2 Max. 39	133.6 **98** 17 391	Avg. 14.3 **MEDIAN 8** Total 157
FY 1996 14 Inspections	Avg. 7.1 **MEDIAN 5** Min. 3 Max. 40	70.6 **48** 20 280	Avg. 12.4 **MEDIAN 12** Total 174
FY 1997 ** 21 Inspections	Avg. 10.9 **MEDIAN 6** Min. 4 Max. 71	36.8 **38** 9 52	Avg. 30.2 **MEDIAN 26** Total 543

* Includes only annual and biennial inspections.
** The entire cycle of inspectional activity is not complete for all inspections.

ORA and CBER have formed a Biologics Program Committee (BPC) to address the roles of each office and to identify points of differences between CBER and ORA inspections which need additional clarification, coordination, and resolution. In as much as all blood product reinspections are led by ORA, it is anticipated that ORA will assume the lead role in periodic

inspections for other CBER biological products over the next three years.

This Committee in its 1996 report recommended that in conducting inspections, FDA cease pre-notification of plasma manufacturers of planned inspections. Prior to 1996, CBER would request production schedules of plasma fractionators immediately prior to scheduling an annual or biennial inspection but would not pre-notify the manufacturer. The request, however, resulted in some manufacturers accurately guessing when an inspection was about to occur. To avoid this result, CBER implemented a new SOP[9] in November 1996 which directs that letters be sent on a periodic basis to all manufacturing firms to obtain production schedules. (Pre-license approval inspections are conducted by pre-notification as is consistent with other FDA Centers.) The OIG report noted that in the recent reinspection process, FDA had not precisely followed the SOP but had instead called the firms to obtain the production schedules.[10] The phone calls were necessitated by the abbreviated time frames associated with the compressed inspection schedule for the 22 inspections this calendar year. In the future, this SOP will be implemented as written.

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[9] *Request for Industry Production Schedules for the Purpose of Planning and Scheduling Biennial Inspections,* # OD-R-12-96.

[10] Supra, at 18.

D. DISSEMINATION OF INFORMATION TO THE PUBLIC

This Committee made a recommendation in its 1996 report that FDA "develop an effective system of recall notification for blood and plasma products." In response to the Committee's concerns and other recommendations, FDA has provided enhanced public access concerning recalls and withdrawals of blood and blood products and has increased public input in the discussion regarding policy development on withdrawals and notification of plasma products.

FDA has made information concerning recalls and withdrawals widely available to interested and affected parties. A voice information system with toll free lines has been set up with information on fractionated product recall and market withdrawal information. A fax information system has been put into place allowing "fax-on-demand." FDA's Home Page on the Internet's World Wide Web contains information about recalls and market withdrawals of fractionated blood and plasma products. An automated e-mail system has been created to provide information to those requesting notice of such actions and other CBER information.

In November 1996, the Pubic Health Service (PHS) held a workshop, "Informational Meeting: Notification of Plasma Product Withdrawals and Recalls," to discuss and obtain public input on notification of the public on recalls and ongoing investigations.

Participants included employees of FDA, NIH, CDC, consumer groups, and industry. This meeting was organized to obtain input from consumers and industry on when and under what circumstances notification of end users should be made.

FDA has been working with industry and consumer groups to determine when consumers should be notified and the best method for notification. FDA's current position, discussed at the public meeting in November 1996, is that the manufacturers and blood establishments should carry the ultimate responsibility for public notification. The manufacturer is in the best position to notify end users because they are the most knowledgeable about their consignees. Nevertheless, FDA recognizes its role and the important public health need to make consumers immediately aware of product recalls and withdrawals.

FDA has initiated a dialogue with manufacturers, distributors, and consumers about designing a notification system that will serve all users, especially consumers who maintain personal custody of the derivative product. The manufacturer presently only notifies its consignees of the recall or withdrawal. FDA communicates by telephone about product recalls, withdrawals, quarantines, and other matters of safety interest to consumer groups such as the NHF and the Committee of Ten Thousand (COTT), as appropriate.

To improve communication and cooperation, FDA employees have participated in NHF annual meetings and at meetings of NHF's Medical and Scientific Advisory Council twice yearly. NHF and COTT were asked to participate in national and international meetings sponsored by FDA including: the November 1996 "Information Meeting: Notification of Plasma Product Withdrawals and Recalls" and the "International Conference on the Virological Safety of Plasma Derivatives."

Consumer groups, including NHF and COTT, participate as members of BPAC. In addition, consumer groups have been invited to present information to BPAC on issues such as consumer notification and warning labels. FDA also has discussed its interest in the development of warning labels on plasma derivative products.

Informational meetings between consumer groups and FDA have been held periodically to discuss issues of patient concern. Recently, NHF has been invited to meet with FDA on a quarterly basis over the next year to improve communication about FDA practices and procedures.

At the first meeting of the Advisory Committee in April 1997, the issue of Hepatitis C (HCV) lookback and notification of recipients was considered. The notification of transfusion recipients potentially infected with Hepatitis C was another

recommendation of this Committee in its 1996 report. A final decision has not been made on HCV lookback by the Advisory Committee, however, all aspects of this recommendation are being examined.

HCV lookback has been extensively discussed at meetings of BSC in 1996. At the request of BSC, an Inter-Agency Working Group on Blood Safety and Availability analyzed this issue. Issues dealing with the feasibility of personal notification; potential percent of recipients unable to be notified, alternative means of notification for the most at-risk recipients and other issues were considered. The Working Group developed several options and recommendations. DHHS adopted two of the Working Group's options including physician targeted outreach and a public information campaign to identify HCV infected persons. It is important to recognize that DHHS has taken an active role in recipient notification encouraging the dissemination of information through other means than personal notification. CDC is working with voluntary and professional organizations, such as the American Liver Foundation, to educate providers and the public through advertisements and other communications about viral Hepatitis-related liver disease, with an emphasis on Hepatitis C. Also, CDC, in partnership with the Hepatitis Foundation International, on November 22, 1997, will air an interactive satellite teleconference entitled, "Hepatitis C: Diagnosis, Medical Management and Prevention." The program will feature

presentations by nationally recognized experts and will provide supplemental printed materials to facilitate patient identification, diagnosis, medical management, and counseling. The Advisory Committee has the matter of "directed lookback" under active consideration.

FDA continues to utilize its Office of Public Affairs (OPA) to disseminate information to the press and media on issues of concern, including recalls and market withdrawals. FDA's *Regulatory Procedures Manual*, Chapter 7, *Emergency Procedures* (May 1997) provides that OPA is "responsible for issuing publicity and preparing answers to press inquiries about emergencies." Questions have been raised as to the nature of press notification and the best method of disseminating the necessary information -- i.e., whether there should be a press release, press advisory or an FDA Talk Paper.[11] OIG reviewed one particular incident related to blood and blood products -- the recall involving Centeon. During the Centeon crisis, FDA prepared several Talk Papers and provided information immediately on its FDA Home Page on the Internet. FDA communications, including Talk Papers, resulted in Associated Press coverage of the Centeon recalls. FDA also arranged press interviews with its blood experts. The OIG concluded that:

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[11] FDA Talk Papers provide background information for use in responding to inquiries.

> We do not believe that FDA's use of talk papers in lieu of a press release adversely affected the Centeon recall process especially in light of the press conference with the Associated Press and Internet distribution.[12]

FDA is firmly committed to providing accurate and timely information to the public about recalls and market withdrawals. The timing of such public notification is a delicate balancing act as definitive information is often lacking at the initial stages of a potential emergency situation. For example, until lab tests are conducted, the exact product that may have caused an adverse reaction can not always be determined. Until manufacturing records are examined and traced, the specific lot number of a distributed product may be difficult to ascertain. FDA continues to work on improving the dissemination of important information to the public.

This Committee's 1996 report recommended that DHHS disseminate more clinically useful information on blood safety issues. The Interagency Working Group on Blood Safety and Availability formed a subcommittee to look at how to carry out this recommendation. A survey of the blood industry for educational materials is presently underway.

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[12] Supra, at 25.

Several sources have recommended that FDA must articulate its requests or requirements in forms that are understandable and implementable by regulated entities since regulators must rely heavily on the performance of industry to accomplish blood safety goals. In particular, when issuing instructions to regulated entities, FDA agrees that it should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for consideration. To assist in this determination, in February 1997, FDA published a notice in the Federal Register, 62 Federal Register Vol.39, 8961 (February 2, 1997), announcing a new FDA document entitled, "Good Guidance Practices," which sets forth FDA's policies and procedures for the development, issuance, and use of guidance documents.

FDA is working to implement, as regulations, those recommendations that it believes are necessary for public safety. Historically, as new scientific information was gathered, FDA would develop recommendations based on this information to assure the safety of the blood supply. Recommendations were made, in lieu of regulations, because of the length of time needed to develop regulations and the importance of moving quickly to protect the public health. These recommendations, however, usually have been adopted by industry as part of their standard operating procedures. Once part of their standard operating procedures, they must be adhered to by the manufacturers. If not, such failure would be noted in an inspection.

In June 1994, FDA announced that it was conducting a review of all blood regulations as part of the Vice President's Reinventing Government Initiative. FDA sought public comment on changes that were needed to blood regulations. In January 1995, FDA held a public meeting to receive comments on "Review of Regulations for General Biologics Licensing and for Blood Establishments and Blood Products." Opportunity was provided for both industry and the public to comment to FDA on needed changes to blood regulations and over 140 comments were received. These comments included suggestions for changing the blood regulations, as well as suggestions for improving FDA's operations.

As a result of items suggested, FDA has taken several actions: 1) FDA brought issues for discussions at the BPAC including hemochromatosis and donor suitability issues; and, 2) FDA has been working on developing a regulation requiring infectious disease testing for blood borne pathogens that would provide for a quicker implementation of the testing requirement. Other areas requiring new regulations or updating of the regulations were identified. As a first step, FDA announced the elimination of obsolete regulations that were no longer needed. FDA is continuing to act on the reinvention of these regulations and on the comments received from the public and industry.

III. BLOOD BANKS

FDA has the responsibility to monitor over 800 licensed blood collection facilities and over 2,200 registered facilities. Licensed blood facilities may engage in the sale, transport, and exchange of blood and blood products across state lines. Unlicensed facilities do not ship across state lines but must follow the same safety procedures as licensed facilities. Licensed facilities are required to file error and accident reports (EARs) with FDA in the event of errors and accidents in their procedures and facilities which may result in an unsuitable unit of blood being available for distribution.

To provide more protection for donors and recipients of blood, FDA is developing a proposed rule to require unlicensed establishments to report errors and accidents to the Agency. In addition, a National Heart, Lung, Blood Institute (NHLBI) grantee is studying blood banking errors from a systems perspective, drawing on the experience of other fields where zero tolerance for errors is the norm. NHLBI and FDA will review the results periodically to see if implementable improvements over present practice are discovered.

In 1996, the CBER Errors and Accidents Reports System (CEARS) was established. This database made all EARs, including a brief description of the incident, electronically available to field

personnel. CEARS is a menu-driven computer program which provides for the display of information from the CBER database containing EARs relating to biologics. This system is an invaluable asset to field personnel because they are able to download the data in various formats (i.e., summaries, key problems, etc.) for review prior to inspections of blood collection facilities.

The blood industry has evolved from a loosely organized medical service into a major manufacturing industry - an industry which 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.

FDA is committed to holding blood banks to these standards. In the past few years, there have been a number of legal actions designed to hold blood collection facilities to strict standards.

FDA sought and obtained a Consent Decree for Permanent Injunction for the American Red Cross in May 1993 because of problems found during inspection of those facilities. American Red Cross collects approximately 45% of all whole blood donations in the United States.

In April 1996, FDA obtained a Consent Decree for Permanent Injunction for Blood Systems, Inc. (BSI), doing business as United Blood Services, because FDA's inspections revealed continuing problems with adherence to GMPs. BSI collects blood at 17 licensed facilities and multiple blood collection sites in 13 states.

In December 1996, FDA obtained a Consent Decree for the New York Blood Center (NYBC). NYBC agreed to strengthen its quality assurance/quality control programs; improve management and supervision of technicians performing blood screening tests and to make improvements in its records management. NYBC recently announced it would contract out certain testing operations.

FDA recently suspended the license of Intermountain Health Care (IHC) blood center in Utah because of numerous GMP violations. This action stopped the interstate movement of IHC's products. At the same time, FDA asked IHC to cease its intrastate operations, and the firm agreed. American Red Cross recently announced its plan to assume responsibility from IHC for serving the needs of the citizens of Utah for blood and blood products, but all such changes must be approved in advance by FDA.

A question was raised previously regarding FDA procedures for checking the origin of blood from other countries and whether FDA could identify whether blood diversion was occurring from a high

risk country to a low risk country. The February 3, 1997, revised Import Alert #57-01, "Automatic Detention of Blood and Blood Components including Human Plasma and Serum," provides guidance to FDA staff to eliminate improper entries of blood and blood components. The Import Alert specifically addresses items that must appear on the immediate container label for imported blood products that are not covered by an unsuspended and unrevoked United States license or valid short supply agreement. Among other items, the label must include the names and address of the establishments that are collecting, preparing, labeling, or pooling the source material.

In addition, CBER's OC is currently developing a revised compliance policy guide for imported blood products for use by the district offices. FDA conducts inspections to audit foreign blood establishments to verify licensure for those products exported to the United States when licensure is required and to ensure no product diversion.

IV. FUTURE PLANS FOR IMPROVING FDA BLOOD PROGRAM

FDA is committed to vigilant regulation and monitoring of blood and blood products in the United States. A number of critical changes have been implemented that already have yielded significant improvements as will future plans.

FDA intends to make significant organizational and management changes at CBER. The Director of CBER has announced recently the selection of a Medical Deputy Director. The Medical Deputy Director will be responsible for direction and coordination of all the offices and components within CBER that deal with blood and blood products. Presently, the responsibility for blood is diffused through OBRR, OC, and the Office of Establishment Licensing and Product Surveillance (OELPS). The Medical Director will now have the ultimate authority and responsibility to ensure that all of the essential regulatory functions are coordinated and carried out in a timely fashion. The Medical Director will have access to all individuals within CBER who work on blood-related issues and will be able to reassign these individuals to those tasks deemed most important to the regulatory oversight of the blood supply. One of his first priorities will be to develop a list of those regulatory actions that need the most immediate attention. We are confident that this management change will have a significant impact.

FDA, and the new CBER Medical Deputy Director, will continue the reinvention of blood and blood regulations with the goal of simplifying paperwork and the movement to a standards based approach to regulation. The Biologics License Application (BLA) implementation is proceeding and will provide a single application in place of the establishment license application (ELA) and the product license application (PLA) that are now

required. Efforts to develop standard manufacturing operating procedures for specific blood products will continue. The emphasis will remain on quality assurance.

FDA intends to continue its identification and prioritization of its rule-making needs. Those guidelines previously issued in the form of guidances and recommendations will be evaluated to determine which are essential to the safety of the blood supply and need to be issued in the form of regulations. Concurrently, regulations for donor suitability, product standards, and compatibility testing need to be updated. Outdated regulations, such as GMPs for blood and standards for recovered plasma, need to be revised. Lookback issues on several levels will be evaluated. Regulations to require manufacturer of plasma derivatives to incorporate manufacturing procedures for viral inactivation or removal will be considered.

The effort to improve ORA/CBER cooperation and communication will continue through its TEAM BIOLOGICS. Joint training and rotating details of personnel will be continued, as well as inspection coordination and report evaluation.

FDA needs to improve its evaluation and analysis of its 483s, EIRs, and EARs. Attention to trends in these reports will assist FDA in developing policies and procedures for implementation, as well as possibly identifying new threats to the blood supply.

Research activities also will aid in the identification of new threats to the blood supply. FDA will continue to develop a paradigm for identifying and addressing emerging infectious diseases with CDC and NIH.

To better leverage limited resources, FDA intends to work to better coordinate blood and plasma regulatory activities with State and other regulatory authorities on accredited inspections and harmonized requirements.

V. CONCLUSION

FDA faces significant challenges in helping to assure the safety of the blood supply. We must strive for zero tolerance for errors in the regulation and management of the blood and blood products industry. At the same time, there has to be sufficient information for the public to understand the risks associated with using blood and blood products. All of this must be done without compromising the supply of blood and blood products that is vital to the health of the American people. We already have done a great deal. Major changes have been made in product safety, our response to emergencies, inspection activities and inter-agency cooperation.

Now, efforts must continue to improve our internal operations. We are absolutely committed to these efforts and we will not rest

until we are assured that the blood supply is as safe as is possible.

Thank you for the opportunity to testify.

Mr. SHAYS. Thank you. Why don't you start by just responding to some of the dialog that took place earlier with the charts and so on.

Dr. FRIEDMAN. I'd be happy to.

Mr. SHAYS. Well, the charts disappeared on us.

Dr. FRIEDMAN. That's OK.

Mr. SHAYS. You've got them in front of you.

Dr. FRIEDMAN. And you have them as well.

Mr. SHAYS. Right.

Dr. FRIEDMAN. It would help, sir—focus me on——

Mr. SHAYS. Why don't we take on license first?

Dr. FRIEDMAN. All right, sir.

Mr. SHAYS. Tell me what that chart says to you. We've accepted the assumption that 10 percent of the blood supply is done by unlicensed organizations and that only 1 percent of the recalls.

Dr. FRIEDMAN. We can't give you better estimates of what actually may be occurring in those unlicensed facilities in terms of numbers of error and accident reports. Our commitment is to bring these unlicensed centers under the same reporting requirements as the licensed facilities, because we think that that inconsistency is neither sensible nor appropriate. And so, regulations are in the process of being finalized for issuance—a proposal for those regulations is being prepared for issuance, because it's my intention to have those centers treated the same way as the licensed centers.

Mr. SHAYS. And how long will that process take? You're smiling.

Dr. FRIEDMAN. Well, Mr. Chairman, that's the one question that I know you always ask, and it's the one if I can give the very best answer on that I can. These proposals are in a near final form now. We hope within the next few weeks to have them out of the agency to the department and OMB. I am really asking for this because I believe our recommendations that have been made now for, I believe, more than a year, perhaps closer to 2 years. I very much want to get these out and done. And it's my intention to focus on these very intently.

Mr. SHAYS. You didn't design the process of which regulations go through FDA, OMB and so on. But I just need to know—the bottom line would be at best, when would the earliest?

Dr. FRIEDMAN. If OMB were to take a full 90 days, which is their prerogative——

Mr. SHAYS. Right.

Dr. FRIEDMAN [continuing]. Then it's my intention to have them to OMB and to the department by the first of next month, which would be July.

Mr. SHAYS. Right.

Dr. FRIEDMAN. That would be—it could be as late as October——

Mr. SHAYS. OK. That what?

Dr. FRIEDMAN [continuing]. That those proposals would be issued. There then would be a comment period.

Mr. SHAYS. Right. Of how many days?

Dr. FRIEDMAN. I always ask for the shortest possible comment period consistent with getting good comments.

Mr. SHAYS. Does OMB decide that?

Dr. FRIEDMAN. No. There's some flexibility in that. Typically there's a 2-month comment period—60 days.

Mr. SHAYS. All right.

Dr. FRIEDMAN. But I commit to you, sir, that we're going to try and speed that process along at every point.

Mr. SHAYS. Right. Well, what we'd like to do is followup and encourage that process to move along.

Dr. FRIEDMAN. And we do have a history of interacting with your staff on these things as they go through. And we'd be happy to continue that.

Mr. SHAYS. But we'll also try to encourage OMB to try to move forward as well.

Dr. FRIEDMAN. Thank you, sir.

Mr. SHAYS. Can I infer that there are other differences between a licensed and an unlicensed facility that are significant?

Dr. FRIEDMAN. There are—that's what I was going to say. I'm not sure that many of these distinctions are important from this committee's point of view. I'll ask those with me to please elaborate on this. The agency has some additional leverage in terms of dealing with licensed facilities. We have certain powers over those facilities that others do not. The reporting requirements you already know. I would ask those with me to please offer other information.

Mr. SHAYS. Sure.

Dr. FRIEDMAN. Please, Dr. Zoon.

Ms. ZOON. I'd be happy to start and perhaps others might add. With unlicensed blood banks there are a number of controls and points of oversight that we do have.

Mr. SHAYS. Now, you get the ability to do that not through interstate commerce. How do you get the ability to regulate them?

Ms. ZOON. Well, they have to comply with the regulations that the FDA issues.

Mr. SHAYS. I guess the issue is——

Ms. ZOON. What authorities?

Mr. SHAYS. No. Why is the recall the one area that you don't seem to regulate? And maybe that's meaningless history. It's logical to me that an unlicensed facility is unlicensed given that it's intrastate. But yet you're allowed to have tremendous impact over these facilities in other ways. You have oversight over them except in this one area. And I was just curious how you get your oversight over an intrastate facility?

Ms. ZOON. We have oversight by the Food, Drug and Cosmetic Act.

Mr. SHAYS. OK.

Ms. ZOON. And we also have control under the Public Health Service Act as it applies to communicable diseases.

Mr. SHAYS. OK. But you do have the authority to require these unlicensed facilities to provide reports and recall and so on?

Ms. ZOON. Through regulations, yes.

Mr. SHAYS. But you don't have the ability to license them?

Ms. ZOON. That is correct.

Mr. SHAYS. OK. All right. Did you have anything else that you wanted to say? Any other comment?

Ms. ZOON. Well, you had asked me what types of controls we have, and I was just going to say that they needed to comply with regulations. They needed to be inspected. There are also State controls independent of Federal controls. And the last two were that

they're subject to the FD&C Act and the Public Health Service Act under the communicable diseases provision.

Mr. SHAYS. OK. Any other comment? Now, the Inspector General, through this chart, responded to my question by saying, yes. And I said, does the IG believe that the FDA's enforcement policies are better implemented by the Office of Regulatory Affairs where you have field offices, rather than the Center for Biologics? And we had both represented here. And I'm not looking for an internal battle, but I would like a candid response to what you think about that.

Dr. FRIEDMAN. Let me say that if one accepts the model that there needs to be participation by both centers—and that will be my thesis here—having the Office of Regulatory Affairs take the lead for that activity brings this component of the products that we regulate into coherence with all the other things that we do. There are real economies of scale. There are real organizational values in having more uniform procedures for how certain kinds of inspections are made.

I absolutely underscore the value of having CBER's scientists involved in these inspectional activities. But I think that we've demonstrated that there's a great deal to be gained by having ORA as the lead organization. Our testimony has some of the documentation of that. The number of findings that are expressed.

Mr. SHAYS. Right.

Dr. FRIEDMAN. The days involved in doing the inspections. And the timeliness—an issue that you were focusing on earlier—how quickly—what is the interval between the completion of the inspection and the generation of written documents and so forth. In all three of those areas there has been an improvement since the involvement of ORA as the lead in these inspections.

Mr. SHAYS. So, it's the policy that ORA should be taking the lead?

Dr. FRIEDMAN. They are taking the lead, sir. Since roughly November 1996 they have been the lead for the plasma fractionators. For whole blood they have been the lead—it's varied depending on the different facilities——

Mr. SHAYS. Right.

Dr. FRIEDMAN [continuing]. For a longer period of time. We are moving to having ORA be the primary lead for all biologics. That's vaccines, allergenics, so on and so forth. But for the purposes of our discussion here today, ORA is in the lead for plasma fractionators, for whole blood, components and so forth.

Mr. SHAYS. OK. Let me go to this chart here and have you respond to that.

Dr. FRIEDMAN. Yes.

Mr. SHAYS. The time for errors and accident reports submission to recall confirmation. I first need to know what this tells you and then I want to know the implications.

Dr. FRIEDMAN. Let me begin by saying I'm not sure what this tells me. And the reason is—and I don't mean this to be critical. I was a little confused by the presentation.

Mr. SHAYS. No. I understand.

Dr. FRIEDMAN. And after our discussions here today, we will be touching base with them to go through this in more detail. What I would first point out to you, sir——

Mr. SHAYS. Let me just ask you this.

Dr. FRIEDMAN. Yes.

Mr. SHAYS. One, confused in what it's saying or the implications? In other words, whether this is——

Dr. FRIEDMAN. Confused in what it's saying.

Mr. SHAYS. Whether it's factually correct or whether, even though it's factually correct, whether it's significant.

Dr. FRIEDMAN. In all of those areas.

Mr. SHAYS. So you question whether it's factually correct?

Dr. FRIEDMAN. Well, or relevant.

Mr. SHAYS. OK.

Dr. FRIEDMAN. If I interpret this correctly, these data come from October 1992 to April 1993. And if that's true then we're talking about 4 years ago. And this may be true for then.

Mr. SHAYS. OK.

Dr. FRIEDMAN. What's more relevant to me now, and the question that I don't have an answer for you today, sir—I'm sorry——

Mr. SHAYS. That's OK.

Dr. FRIEDMAN [continuing]. Is what are the numbers that we have in a more current year. I do not have those. And I would find that a great deal more valuable to me. Because, to be entirely candid, we have criticisms of the timeliness with which we processed things in 1992, 1993——

Mr. SHAYS. OK.

Dr. FRIEDMAN. And I'm not trying to say that everything is fixed. But that's a long time ago.

Mr. SHAYS. But one of the beautiful things is that we can followup. And we will followup. And can we make it part of the record, as well? And we'll make it part of the record. I would like to hold the record open to just see if you can provide us some more current data.

[The information referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 25 1997

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
and Intergovernmental Relations
Committee on Government Reform and Oversight
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

This letter is to provide: 1) information promised at the June 5, 1997 hearing, "FDA Regulation of Blood Safety," and also requested in the July 1, 1997 letter from your Subcommittee clerk, concerning the number of establishments inspected every two years and the current data on the time between receipt of error and accident (E&A) reports and the initiation or confirmation of blood product recalls; and, 2) a further response to your May 22, 1997 request for documents relating to the safety of blood and blood products.

1. Current data on E&A reports and establishments inspected every two years.

Enclosed at Tab A please find current data on the time between E&A reports and the initiation or confirmation of blood product recalls. This is in response to a request made at the June 5, 1997 hearing and in the July 1, 1997 letter from your subcommittee clerk. The enclosed pie charts provide an updated analysis of the E&A reports for Fiscal Year 1996 received and classified by the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER).

In preparing these updated charts, CBER also reviewed the testimony provided by the General Accounting Office (GAO). GAO testified that 25% of recalls were not undertaken by companies until the recommendation or classification was made by CBER and that such classification often took up to one year. CBER has attempted to verify this percentage value (25%) cited in the GAO report and mentioned during the June 5, 1997 hearing. To the best of CBER's knowledge, the figure is not based on a statistical assessment of CBER data.

The type of situation described by GAO may be when blood facilities act after FDA recommends that a recall is warranted. Often firms wait for an FDA inspection to identify an error or accident circumstance, and then the firm decides on an appropriate course of action such as a recall. CBER has not

maintained statistics of such situations. The staff responsible for the day-to-day review and assessment of E&A reports, however, indicates the percentage to be considerably less than 25% of the E&A reports

The following will assist in clarifying the process utilized by CBER and the time frames in which these actions are taken.

When CBER receives an E&A, a review and evaluation is performed within five working days. If the review shows that the firm's corrective actions included a product retrieval or some form of notification (or should have done so), the report is forwarded to the appropriate FDA District Office for follow up. Some reports, however, are not received from the company until 12 months after the event is detected. It is these situations to which GAO may be referring in its testimony.

The current 1996/1997 data indicate that the timeliness of any follow-up contacts FDA might have with reporting firms about the adequacy of their corrective actions is improved substantially. In addition, a far greater number of reports are being received in a shorter period of time from companies than that reflected in the GAO data. For example, the GAO data set (from 1993) shows that 14% of reports are received within one month and 73% within one to six months.

The 1996/1997 data show that over 40% of reports are received in one month and over 50% in one to six months. Over 90% of incoming reports are received by CBER in six months or less. The most significant gains are in the earlier category. It is anticipated that the proposed revisions to the E&A rule may further reduce the time frame from detection to submission with the clarification of the term "promptly." This time frame will be defined as a specific number of days.

At Tab B please find a chart entitled, "Statutory Inspection Coverage." This information is provided for the hearing record as promised by Mr. Ron Chesemore, Associate Commissioner for Regulatory Affairs.

2. Documents relevant to the May 22, 1997 document request.

At Tab C are additional documents provided in response to your document request of May 22, 1997. These documents were either located subsequent to FDA's May 30, 1997 response and not previously provided, or have been received by FDA subsequent to the request but are relevant to the original document request. The documents provided are in response to request number 8 and request number 14.

Some of the documents provided with this response are not publicly releasable under FDA's Freedom of Information Act regulations as they contain confidential information, including commercial trade secret information. We, therefore, request that the Subcommittee not publish or otherwise make public any of this information. We will be glad to discuss the confidentiality of any particular document with the Subcommittee staff.

We hope this information is helpful. If we may be of any further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosures

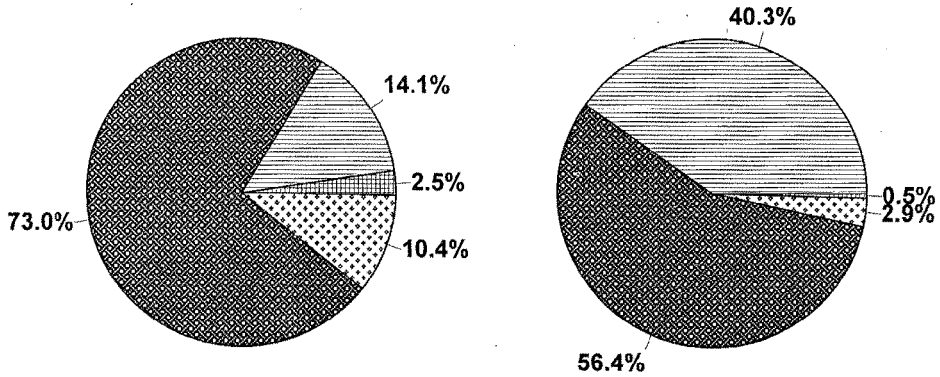
cc: The Honorable Dan Burton
Chairman, Committee on Government
Reform and Oversight

The Honorable Henry Waxman
Ranking Minority Member
Committee on Government Reform
and Oversight

The Honorable Edolphus Towns
Ranking Minority Member
Subcommittee on Human Resources
and Intergovernmental Relations

The Honorable Vince Snowbarger
Member, U.S. House of Representatives

DETECTION TO SUBMISSION



GAO AUDIT

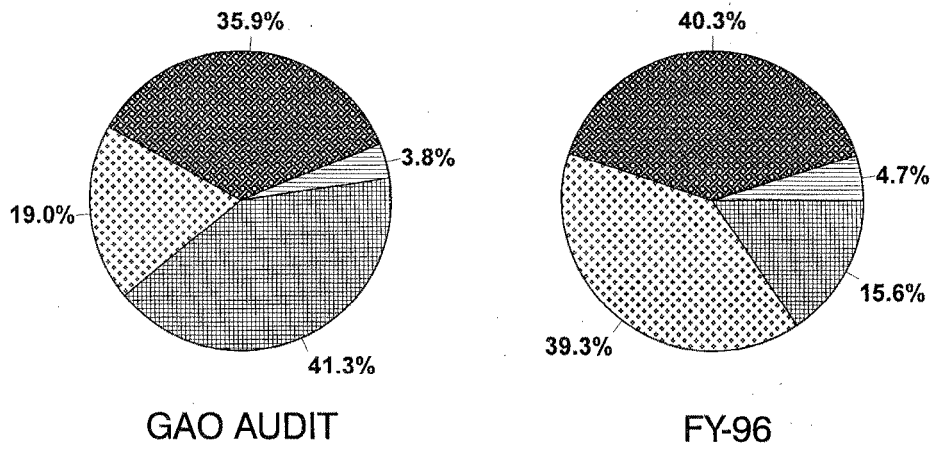
FY-96

TIME FROM DATE E/A DISCOVERED TO DATE FDA RECEIVED

UP TO 1 MONTH | 1-6 MONTHS | 7-12 MONTHS | 12+ MONTHS

GAO AUDIT: TOTAL REPORTS = 163 (RECEIVED 10/92 - 4/93)
FY-96: TOTAL REPORTS=10,942 (RECEIVED 10/1/95 - 9/30/96)

SUBMISSION TO RECOMMENDATION

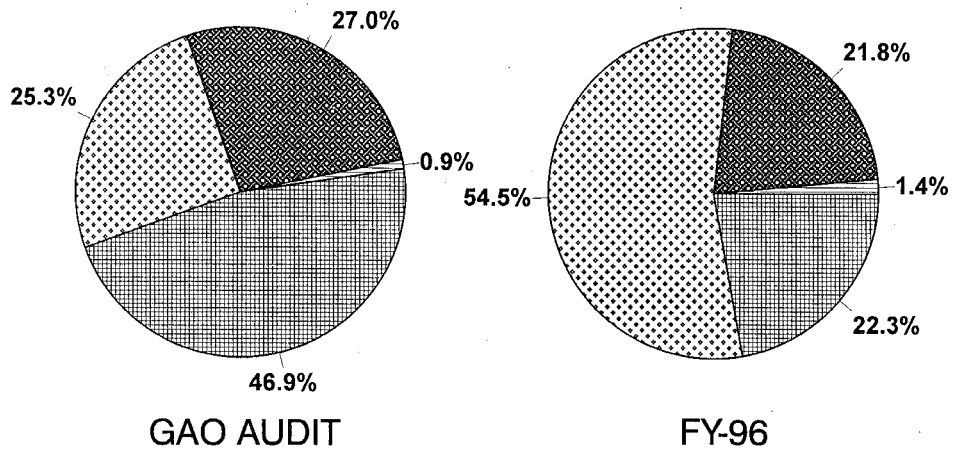


TIME FROM DATE FDA RECEIVED E/A TO RECALL RECOMMENDATION

UP TO 1 MONTH | 1-6 MONTHS | 7-12 MONTHS | 12+ MONTHS

GAO AUDIT = E/A REPORTS RECEIVED 10/92 - 4/93
FY-96 = E/A REPORTS RECEIVED 10/1/95 - 9/30/96
(FY-96 = 211 POTENTIAL RECALLS THAT WERE CLASSIFIED AS RECALLS)

SUBMISSION TO CONFIRMATION



TIME FROM DATE FDA RECEIVED E/A TO RECALL CONFIRMATION

UP TO 1 MONTH | 1-6 MONTHS | 7-12 MONTHS | 12+ MONTHS

GAO AUDIT = E/A REPORTS RECEIVED 10/92 - 4/93
FY-96 = E/A REPORTS RECEIVED 10/1/95 - 9/30/96
(FY-96 = 211 POTENTIAL RECALLS THAT WERE CLASSIFIED AS RECALLS)

Dr. FRIEDMAN. And I'm interested in that, as well.

Mr. SHAYS. OK. But walk me through the process of an accident report being submitted and how you respond.

Dr. FRIEDMAN. OK. I will begin with that, and then, again, I'll ask others to please——

Mr. SHAYS. Someone else can respond. You don't have to if you don't want to.

Dr. FRIEDMAN. No. There are a couple of general things that I'd like to say and then I'd like others to——

Mr. SHAYS. You want to take the easy stuff and have the hard stuff done by staff. I can relate to that.

Dr. FRIEDMAN. My staff calls me the warm up band for the real——

Mr. SHAYS. For the real stuff.

Dr. FRIEDMAN. Yes. That's exactly right.

Mr. SHAYS. OK.

Dr. FRIEDMAN. I'm told that there are approximately 12,000 error and accident reports that we receive each year and that these are a variety of different sorts of reports. As you recognize, there are the most serious kinds of life threatening reports, and then there are others which are technically noted but don't have any health significance either for the individual or for all people who might receive a product.

And we have mixtures of those sorts of things here. As I understand what is being described in this pie chart, there is a period of time that is being counted until we close our file or we show that there has been a complete audit of some activity. And so there are two important components here that I'd like to distinguish. One is: are we recognizing and acting in an appropriate and timely way when there is a health concern for an individual patient, the sort of individuals that you are talking about—a patient who wants to know whether he or she can inject yourself from material that's in her refrigerator or his refrigerator. Are we acting promptly on that?

There is a second concern which is—are we acting promptly there? And I think that's what the Inspector General was saying was their review of things. But there's a second component, which is, are we completing all the necessary classifications, and audits checks that are appropriate to be done—are we completing those in a timely and complete fashion. And I'm distinguishing between those two things.

This chart doesn't tell me either one. I can't be quite sure what it means. But what I am told—because we were—as this was being presented—furiously whispering questions back and forth—that in the most recent year and perhaps longer, there have not been class 1—those are the most life threatening or potentially life threatening kinds of recalls—there have been none of those kinds of events that have taken the length of time that is portrayed here, that those are being handled in a much more rapid timeframe.

As you pointed out earlier, in the Centeon situation, there was an unacceptable delay in a recognition of a problem. That, we believe, we've looked very hard at and have fixed. But those are the sorts of concerns—that I want to make sure that we don't have lapses where we can help an individual patient or group of pa-

tients. And we will become more efficient in terms of dealing with the paperwork that is required afterward.

Those are my general remarks. I would ask other people to please make specific comments, sir.

Ms. ZOON. Yes. The center does have standard operating procedures for handling error and accident reports. And if you would like, I could briefly summarize.

Mr. SHAYS. I'd like you to just walk me through. When a complaint comes in tell me how you deal with it.

Ms. ZOON. All right. The error and accident reports are received by the division of inspections and surveillance in our office of compliance. Once the action reports come in, they are reviewed and evaluated by a consumer safety officer and the error and accident coordinator within the division.

Mr. SHAYS. Are these just mailed in? Are they FedExed in? Are they sent in weeks and weeks after the event? From the moment a facility realizes that they need to send a report, do they send it in within 12 hours? Give me a sense of the kind of feeling of urgency that they might have?

Ms. ZOON. Right. May I ask Mr. Jim Simmons, head of the Office of Compliance to address that?

Mr. SHAYS. Yes. Were you sworn in, sir? Good. You can just sit over there. And just identify your name again. I'm assuming our transcriber has the names. And if not, you have a card that you'll be able to give him?

Mr. SIMMONS. I think that my name was provided to the party already.

Mr. SHAYS. Great. Thank you.

Mr. SIMMONS. You were asking about the manner in which they were submitted?

Mr. SHAYS. Right. I have no sense of how people deal with these and the sense of urgency or not. The one thing I do is I have people who know what it's like when they're taking the blood product and they hear many weeks after the fact that maybe what they took will be harmful to them. So they have a sense of urgency. I want to know how the urgency is felt within the Department.

Mr. SIMMONS. The situation is certainly variable from company to company. And I think you may recall the representative from the General Accounting Office indicate that the time lapse in average is in excess—or the time of their audit—was in excess of 4 months. And it ranges from a few days to longer than a year. And part of that was attributed to our regulation that currently says, promptly. And in the proposed revisions we will define promptly, and have used the recommendation from that audit of 45 days. I think in terms of——

Mr. SHAYS. Wait. The facility itself realizes that a—maybe I don't even have an appreciation of what we're talking about in terms of an accident. Maybe I need to have——

Dr. FRIEDMAN. May I just? Because I had the same question you do. There are several ways in which information is provided to the agency. Through the MedWatch system as you've heard, through adverse events, which may be phoned in by a company or by a facility where they see something very serious.

Mr. SHAYS. Right.

Dr. FRIEDMAN. That's a phone system that has 24-hour a day coverage 7 days a week. But there are also error and accident reports which can include things from—and I'll give you a couple of examples so you'll understand that it's not the sort of significance that you're speaking of. If a patient in a facility receives a unit of platelates—which is a portion of the blood—has an infectious disease—passes away, the question comes up whether there was any relationship between that unit of material and death.

Mr. SHAYS. Yes.

Dr. FRIEDMAN. It turns out that the unit was cultured, that the patient's blood was cultured, the urine was cultured and so forth. There wasn't a relationship between that unit. But it was reported as a perfectly plausible, possible thing that then required some followup. But the followup was that you had to wait for all those blood cultures and all those cultures to be competed, all the information to be assembled and so forth. It could be that a patient received the wrong unit in certain facilities.

I'm saying this—because many of these would not be reported in this way. But it can be something important for the individual patient, but from your point of view, not related to a systemic problem with how a product is made or processed or drawn. And there's this whole range of things. It could be a systems failure in an organization to an individual patient problem. And it encompasses a large number of different sorts of things, sir.

Mr. SHAYS. OK.

Ms. ZOON. If——

Dr. FRIEDMAN. Go ahead.

Ms. ZOON. Would you like me to continue to tell you how we deal with error and accident reports?

Mr. SHAYS. Sure. You can stay there. You need to speak clearly, though. Have you completed the point that you wanted to make to the committee?

Mr. SIMMONS. The point that you had asked I think I did.

Mr. SHAYS. Yes.

Mr. SIMMONS. I will respond further if you like.

Mr. SHAYS. The word "prompt" is going to be redefined to be 45 days? You are considering that?

Mr. SIMMONS. We have defined "prompt" in terms of numbers of days.

Mr. SHAYS. OK. Yes.

Ms. ZOON. Following the receipt of the error and accident report a determination is made—one, in terms of the completeness of the report. If there is insufficient information, it's followed up and the further information is obtained from the filer. And that's generally—can be—depending on the nature of the situation, direct contact by phone, or it could be in other forms of communication.

The data is entered into an error and accident reporting system. And this data can then be accessed by the field offices by the CBER's error and accident reporting system that we refer to as "CEARS." Those E&As are evaluated to determine if additional followup activities or alerts are necessary if not already initiated. Additional activities include but are limited to determining if a recall has been initiated and determining if any investigations were initi-

ated or on-going regarding significant adverse event reports were filed.

Then for error and accidents representing possible recall situations a copy of the error and accident report is forwarded to the district office as an alert to a possible recall. There also are quarterly and annual reports prepared by the division director. And these reports and trends are looked at with respect to those types of errors that are found.

Mr. SHAYS. What I'm going to do is I'm going to have both majority and minority staff ask some questions and I'm going to just respond to some of your responses.

Ms. FINLEY. Thank you, Mr. Chairman. Dr. Friedman, why didn't the FDA require patient labeling on the factor 8 product manufactured with the transferrin produced from the plasma of a CJD patient?

Mr. SHAYS. You've got to slow down a little bit. I'm going to have you start over again.

Ms. FINLEY. OK.

Mr. SHAYS. That's why I didn't ask this question.

Ms. FINLEY. Could you describe the procedures for biohazard labeling of products manufactured from the plasma of CJD patients? It's my understanding that you require it for CJD-derived products intended for research use only and the agency didn't require it for patient labeling on the factor 8 product manufactured—that was put on hold—I think—of January of this year?

Dr. FRIEDMAN. I'll ask Dr. Epstein or others to embellish my answer.

Mr. SHAYS. OK.

Dr. FRIEDMAN. I guess there are two important things to note about CJD which you appreciate. One is how little we understand about certain aspects of the biology of the diseases and how we don't have a really appropriate test for identifying potentially infectious material in either an organ or in a plasma or derived component. The second point is that although this has been looked for very vigorously—cases in which a human may have gotten CJD from a blood or blood product, it's been difficult, some say impossible to detect such a thing.

Nonetheless, we feel that there is reason to be cautious—because of the first point I made which is how large our ignorance is in certain important areas. And the policy, the guidance which has gone forward, tries to rank potential risks in a logical way so that if one has something that's directly derived from a donor who ultimately turns out to have CJD that might represent one sort of risk. If you have that unit of which one tiny fraction is removed, purified and then is further removed, purified, the risk begins as remote and progresses to exceedingly remote.

And that's the sort of general framework of risk that we try and utilize. The question you ask is a provocative one, and I'd like Dr. Epstein or others to please add more.

Dr. EPSTEIN. Yes. Thank you, Dr. Friedman. And thank you, Ms. Finley and Mr. Shays. In the case that you're describing the final product, which was a Factor 8 product, had been manufactured using a purification system that depended on a synthetic antibody—a monoclonal antibody. That monoclonal antibody had been

generated from an invitro culture in which the medium had been supplemented with a blood product. And it was that blood product which had been withdrawn on account of a contribution by a donor who later got CJD.

So we have a fairly indirect situation in which there was some exposure during manufacturing many, many steps removed from the final product. Now, the issue, of course, was whether the policy on withdrawal of plasma derivatives based on subsequent knowledge of a contribution by a donor who got CJD, or was later learned to even have risk factors for CJD, should be applied in this case. But it is distinct in that you're not dealing with potential contamination directly of the derivative due to the pool, you're dealing with potential contamination due to exposure to a reagent many, many steps removed from the final product.

What was done in this case is that first we charged the company, which did duly report this as an error or accident. We would view it as accident—it's all learned post hoc—to the FDA. We charge them with doing a risk analysis. The company provided the risk analysis to the FDA. FDA performed its own risk analysis and FDA requested that the CDC perform a risk analysis.

The bottom line of the risk analyses was, that the risk for any persistence of CJD infectivity in the final product was extremely remote based on effective removal of the additive—so-called transferrin—due to the many purification steps. Now, what we did in the face of that was have a dialog with the hemophilia community over the risk assessment.

We requested and the industry voluntarily complied with informing the hemophilia community fully of the events surrounding the incident and the analysis and the basis for the conclusion of a safe product. Therefore, as a result of the investigation, a determination was made that there was no significant added risk. And I'm sure you understand—and, indeed, your question suggests—that there always is some risk. And we appreciate that. But the conclusion of the analysis was no significant added risk due to the remote exposure to a reagent at an early stage of manufacturing. Therefore, the product did not require special labeling and it was permitted to remain on the market.

Let me just remark at a more general level that I believe you are aware that there has been an initiative since 1995 to work with the industry to develop more specific warning labels regarding viral risks or risks of unconventional agents in plasma derivatives. Let me stop there.

Ms. FINLEY. OK. Thank you, Dr. Epstein. Dr. Friedman, the blood safety committee report of December 1996 analyzed the FDA's management of the Centeon recall in the fall of 1996. They determined that the FDA had not inspected the albumin line at the Centeon plant in over 50 years since the license was approved for. I guess would have then been the Armour Co.—now Centeon—in 1947. Could you explain why when the Inspector General determined that albumin was listed in the top five of plasma products which help professionals report patient adverse reactions, why the FDA did not determine in the course of 50 years that it was necessary to inspect that line?

Dr. FRIEDMAN. Again, I'll ask Dr. Epstein to embellish on my answer. The individuals—patients who receive albumin are amongst the most ill, most fragile individuals who receive any blood product. These are often individuals who have suffered important trauma, major infection, and other overwhelmingly life threatening episodes. These individuals fall prey to a large number of concurrent infections or concurrent other physiologic problems. And they're the most fragile individuals. So the fact that these people have a great rate of illness, of morbidity and a high mortality rate indicates just how ill they are in the fact that they need this product.

I certainly cannot—because I don't know the answer to this—construct a coherent explanation for why this product was not inspected during that period of time. There has been—the number of cases in which this product has been poorly manufactured has been historically low. But I won't try and construct a defense of that. What I will say is, not only would I question the frequency of the inspections, I would question the quality of the inspections. And it's exactly concerns about that that led us to reinspect all of the plasma derived products over the last 6 or 7 or 8 months.

Because my concern was that we had not looked at those products either intensively enough or—in a situation like this—with sufficient frequency. Again, I cannot explain to you what the thinking was 30 or 40 years ago. I can tell you what our current interests and our current expectations are. Let me just ask if Dr. Epstein would like to add.

Ms. FINLEY. And then I have a followup question.

Dr. FRIEDMAN. Please.

Dr. EPSTEIN. Yes. Thank you. You really have asked two questions, one regarding prior inspections at Centeon for albumin. The other: what is our reaction to the fact that adverse event reports for albumin are among the top five reported for plasma-derived products. On the first question—FDA, as you know, inspected Centeon in June 1995 prior to the recall of albumin, and did examine general GMP including air and water handling systems, environmental controls, and related matters that would be applicable to all the products and would include the albumin as well as clotting factors.

In that sense—and that's limited—aspects of albumin production were inspected. However, there was no focused inspection on albumin. The basic reason that there was not an in-depth review of processed validation related to albumin was because of its extensive record of product safety of approximately 50 years.

I believe that it will be made clear that the new approach to plasma fractionator inspections does involve a more comprehensive review of process validation. And that is a shift of focus. And we acknowledge that had that been in place, there might have been a more effective inspection.

Ms. FINLEY. May I assume from both of your statements and from the report that the blood safety committee produced for Dr. Lee that FDA states that its position is to inspect plasma fractionators every 2 years? But in this particular case, it clearly didn't meet that goal.

Dr. FRIEDMAN. I'm not sure that's exactly accurate. I think the question you're asking is: Will each product line be individually in-

spected every 2 years. I don't know the answer to that. Will we inspect each facility at no less frequency than every 2 years? That is correct. And for cause or as a followup, it will be more frequent absolutely.

Ms. FINLEY. Bottom line: What assurance can you give the American people that you will not let a product line go for another 50 years without an inspection? What things have you put into place to ensure that you catch that situation?

Mr. SHAYS. And I'm going to just add: what kind of requirements are on FDA for inspection? Is there an every so many years or is there just a——

Dr. FRIEDMAN. May I ask Mr. Chesemore to please deal with the——

Mr. SHAYS. Sure.

Mr. CHESEMORE. The requirements, Mr. Chairman, are that for a drug or a biologic manufacturer, that we do a general GMP inspection at least once every 2 years. That's what the law states.

Mr. SHAYS. OK. And it gets around a problem I had with HCFA in terms of timeframes on HCFA and just rewriting rules. And also with the FDA on your licensing of products and your deciding that you were going to do it—you had this backlog and you were going to bring this backlog down and you did a sensible requirement of how you would get the backlog down, but it was not in conformance with the law. So we need to either change the law or get you to conform to the law. Let me ask this, and then I do want to make sure we—is it feasible for you to abide by the law of inspecting every 2 years? Is that a wish list on the part of Congress and the White House?

Mr. CHESEMORE. It's becoming much more difficult, Mr. Chairman. And the situation that Ms. Finely raised is, do we have the ability to cover every product that a firm manufactures once every 2 years. And the answer to that is clearly "no."

Mr. SHAYS. OK.

Mr. CHESEMORE. What we try to do is, at least try to inspect the process, whether it's biological or a tablet or an injectable. And we try to take a look at the firm's inspectional history. And all those things go into consideration in determining which firms we do need to inspect.

Mr. SHAYS. Now, the law requires you to do it every 2 years. What is your——

Dr. FRIEDMAN. Sir, it's very important to state—as far as I know, we're in conformance with that. We are doing inspections that frequently.

Mr. CHESEMORE. In the plasma fractionator industry.

Dr. FRIEDMAN. So that there's no misunderstanding about that.

Mr. SHAYS. No. You weren't doing it in the case of this.

Dr. FRIEDMAN. Yes, sir. That was the point I was trying to make, which is, this facility was actually inspected more frequently than every 2 years. But this particular product line had not been inspected as a particular product line.

Mr. SHAYS. Right. OK. Why don't you followup?

Dr. FRIEDMAN. Please.

Ms. FINLEY. I still believe the question that I'm asking—and perhaps I didn't phrase it properly—is what assurance can you give

us that another Centeon situation will not occur? In other words, how do you structure your inspections to ensure that you're not letting a product line like that slip by for 50 years? And the reason I'm concerned about this is that—according to your staff, Dr. Friedman—that is the largest plasma product recall in the history of the United States. For that not to have been caught at any point in 50 years is a very serious problem, as I'm sure you'll agree.

Dr. FRIEDMAN. I'm sorry. I don't mean to disagree. I think that it is a very important observation. I don't minimize it for a moment. I do think, though, there are two ways in which one would help to ensure the American public that these sorts of problems would be caught at the earliest possible time. On the one hand, there had been previous inspections at this facility that indicated certain kinds of problems that had occurred, certain concerns that had been raised, which we do not believe were adequately followed up on.

And had those been adequately followed up on, this problem potentially would not have occurred. I'm assuming the best case situation. The fact that we are much more rigorous, much more consistent and much more timely in how we do our inspections and how we followup on those inspections should give the American public some additional confidence in the quality of the product. The fact that there was a period of time—not when this manufacturing site wasn't inspected, but when these problems were not followed up on—is what I am concerned about and what I think needs further attention. I believe it's entirely credible that had we done more careful assessment of whether the recommendations that were being made were followed up on, that this particular occurrence might not have happened.

Mr. SHAYS. Let me do this, let me ask our minority staff, Cherri Branson, if she has some questions.

Dr. FRIEDMAN. Please.

Mr. SHAYS. But I just want to be clear as someone who is not the expert in this group up here—and I want the record to be clear—there is inspection of facilities and there's examination of product lines, and two separate issues? Am I'm mixing the two up? Is that what's happening here?

Dr. FRIEDMAN. Well, think of it this way, sir. If, for example, a drug manufacturing facility might make 10 or 20 products at different times of the year or different parts of the factory——

Mr. SHAYS. Right.

Dr. FRIEDMAN [continuing]. That factory will be inspected. And if it's a new product, before that new product is approved for use, that particular line will be inspected. But at subsequent visits, the air and the water and the general cleanliness—so there will be some general features of the facility that will be looked at. And then there will be specifics of specific manufacturing areas will be focused on. But not every product line in each facility will be looked at.

Mr. SHAYS. Now, Mr. Chesemore, I do want to make sure that we're clear on this, though, because this is under oath. Is it your testimony that every facility is inspected within the law, which I believe is a 2-year requirement?

Mr. CHESEMORE. Every plasma fractionator facility.

Mr. SHAYS. OK. And that's what the legal requirement is?

Mr. CHESEMORE. That is the legal requirement.

Mr. SHAYS. Now, other facilities, do you still have a 2-year requirement or do you have another?

Mr. CHESEMORE. We have a 2-year requirement on all human pharmaceuticals, all veterinary pharmaceuticals, many medical device manufacturers. There is a requirement within the Food, Drug and Cosmetic Act of a biennial or once every 2 years inspection.

Mr. SHAYS. OK.

Mr. CHESEMORE. There is no requirement, for example, for the majority of food firms that we regularly——

Mr. SHAYS. OK.

Mr. CHESEMORE. And that's where I'm coming from.

Mr. SHAYS. I'm frankly surprised that you can keep up with that. Are you able to do that every 2 years?

Mr. CHESEMORE. In all those product lines the answer is "no."

Mr. SHAYS. The answer is "no," not "yes?"

Mr. CHESEMORE. The answer is "no." We are unable to make an inspection once every 2 years in all areas that we're required to.

Mr. SHAYS. OK. If you were to figure out the average. In other words, I can relate it to roads. We figured out when we were in the State house that we should do a road every 7 years—repave it—and if we didn't, the roads would deteriorate. And the average was, we did every road every 50 years. What's the average for inspections?

Mr. CHESEMORE. It's going to the vary, sir, by commodity.

Mr. SHAYS. OK.

Mr. CHESEMORE. And I'm not sure that the once every 2 years is the most important thing. As a matter of fact, in our thinking, we think the risk is much more——

Mr. SHAYS. No, I understand that. But now we get into the evaluation and then we also get into law.

Mr. CHESEMORE. Right.

Mr. SHAYS. And the one thing you're not going to get from this committee on either side of the aisle, we're not going to throw bricks at you because you can't do something and we didn't appropriate the money for the people to do the inspections. But we are going to have the public record be clear. And then we're going to have an open dialog about it.

Mr. CHESEMORE. Sure.

Mr. SHAYS. And we can get into debate whether it should be every 2 years. Well, what is the average?

Mr. CHESEMORE. Well, if I could, I'd like to submit that for the record.

Mr. SHAYS. Yes.

[The information referred to follows:]

2 YEAR STATUTORY INSPECTION COVERAGE (JUNE 1995 THRU JUNE 1997)			
CATEGORY[1]	CYCLE OF COVERAGE	ESTABLISHMENTS INSPECTED[2] PER YEAR	STATUTORY INVENTORY[3]
Biologics[4]	2.3	1,204	2,810
Human Drugs[5]	4.2	1,473	6,243
Vet Drugs & Medicated Feeds[6]	3.6	481	1,747
Medical Devices[7]	4.2	1,135	4,805

[1] No food establishments are subject to the 2 year statutory inspection requirement.

[2] Some establishments may have been inspected by states under contract to FDA, primarily in medicated feeds and some medical gas repackers.

[3] Statutory Inventory limited to the number of establishments that are subject to the 2 year statutory inspection requirement. The total number of establishments which are FDA inspectional obligations is currently 110,000.

[4] Biologics--blood banks, source plasma operations and manufacturers (fractionators).

[5] Human Drugs--manufacturers, repackers, relabelers and medical gas repackers.

[6] Vet Drugs & Medicated Feeds--manufacturers, repackers and relabelers (drugs); manufacturers and growers requiring a Medicated Feed Application (MFA).

[7] Medical Devices--manufacturers, repackers and relabelers of class 2 & 3 devices.

Mr. CHESEMORE. But I can give you an approximation.

Mr. SHAYS. Approximate will do now.

Mr. CHESEMORE. In drugs and devices it's about once every 3 years.

Mr. SHAYS. OK.

Mr. CHESEMORE. In foods it's more like once every 5 to 10 years.

Mr. SHAYS. OK.

Mr. CHESEMORE. In veterinary products it's a little over once every 2 years as well.

Mr. SHAYS. Yes. But the once, once every 5 to 10 years, which is a big spread——

Mr. CHESEMORE. There is no requirement in the act for food firms.

Mr. SHAYS. There's no legal requirement.

Mr. CHESEMORE. So, we're close, but we're over.

Mr. SHAYS. OK.

Mr. CHESEMORE. With the exception of we have concentrated, really, in the last 5 to 7 years, in the biologics area, since the mid 1980's to make sure that that's where we at least did the biennial if not sooner inspections.

Mr. SHAYS. You're going to have to make choices given limited resources.

Mr. CHESEMORE. That's right.

Mr. SHAYS. Now we just have to know what the law requires and whether the law needs to be amended.

Mr. CHESEMORE. We'd be delighted to provide that information for the record.

Mr. SHAYS. Yes. Sure.

Dr. FRIEDMAN. That's very——

Mr. SHAYS. Ms. Branson?

Ms. BRANSON. On the issue of inspections, it's my understanding that the FDA has a Memorandum of Understanding with HCFA that allows coordination of certain inspections of facilities. Can you give me your impression on the advisability of that sort of coordination, whether an expansion of coordination would assist you with some of the inspection problems that have been noted? And basically tell me your thoughts on the agreement between FDA and HCFA.

Dr. FRIEDMAN. Mr. Chesemore, please.

Mr. CHESEMORE. We've had a Memorandum of Understanding with HCFA, I think, since the early 1980's. The HCFA inspections are primarily of the laboratory operations or the transfusion part of a hospital. It really doesn't go into—if you would—the blood and blood products area that the Food and Drug Administration does. Some of those inspections are done by HCFA employees. And it's my understanding that HCFA might contract some of those inspections as well. To the best of my knowledge, I'm unaware of any difficulties that we have with our coordination with HCFA. If there's others who know differently——

Ms. BRANSON. I think what I'm trying to ask you is whether or not that sort of coordination and MOU agreement would be possible with other agencies in order to ease some of the burden of the inspections that you just described?

Mr. CHESEMORE. What we're talking about here is making sure that whomever does the inspection is adequately trained and will conduct the same type of inspection the Food and Drug Administration does. At the present time I'm not sure that we could say that the HFCA inspection that is now currently done under the Clinical Laboratory Improvement Act is the same inspection that the Food and Drug Administration makes of manufacturers of blood and blood products.

So it's going to be very difficult for us, I think, to transition to someone else doing those inspections. And right now, I think, too, it continues to be a critical time that we make sure the agency continues to do those inspections. And we've started this team approach with the Center for Biologics Evaluation and Research. Dr. Epstein, you might have something.

Dr. EPSTEIN. Yes. I just wanted to make one point clear. If a blood establishment collects blood or plasma or processes blood or plasma, it must register with FDA and FDA inspects it. What we are talking about with the HCFA registered and HCFA inspected establishments are transfusion services which are engaged in storing blood, doing donor cross matching so you don't get a mismatched unit, and distribution. But they do not collect and they do not process. FDA regulates all collection facilities involved at that level.

Ms. BRANSON. It's my understanding that FDA has classified certain computer software that's used in blood facilities as medical devices. Can you tell me how this classification assists in the oversight process and whether or not the facilities we had talked about earlier as unlicensed facilities are required to use that same type of software?

Dr. FRIEDMAN. Please.

Dr. EPSTEIN. Yes. You are correct that FDA has promulgated a policy which requires pre-market approval as a device of software systems used in the blood bank. We believe that this step became necessary because of findings dating back to the early 1990's of failures of performance and failures of design validation involving the systems which play a critical role in the operation of blood centers. We have reviewed since approximately April 1996—approximately 40 or a few more applications—these are major systems used throughout the country—and have approved 7 of these at this time including some of the largest ones.

The problems that are encountered have mainly to do with design issues. Up until very recently there was not a regulation requiring validation of software design for software as a device, and, therefore, it was felt necessary to do pre-market approvals rather than review them simply under GMP. The policy at the FDA would encompass software used both in transfusion services as well as in establishments which collect and process.

However, it was recognized that the original policy was unclear regarding the obligations of the transfusion services and, therefore, there was a need for a clarification and a slightly different timeframe. However, it remains our intention to assure that all blood bank software is properly developed, properly documented, and meets its functional specifications. We continue to do this under pre-market approval. But now that new GMPs applicable to soft-

ware have been promulgated by the FDA there is the question whether we can shift some of that effort toward review of GMP at the time of inspection as opposed to pre-market. But that change has not yet occurred.

Ms. BRANSON. Can you just tell me whether the intrastate facilities—just "yes" or "no"—whether the intrastate facilities are required to use that same software?

Mr. CHESEMORE. If they use it, they are required to meet the same as the licensed facilities.

Ms. BRANSON. But they're not required to use it?

Ms. ZOON. If they develop their own software and they use it within the intrastate blood bank, then they are not subject to submitting a 510K. It is for those commercial software or those software that are being used in a large cohort of blood banks maybe perhaps under a single license but crossing State lines, that then would be subject to this filing.

Ms. BRANSON. And if they do develop and use their own software, is there any review on all of that?

Ms. ZOON. They would be covered under GMP inspections.

Mr. CHESEMORE. Right.

Ms. BRANSON. Mr. Chairman, I think that's all we have.

Mr. SHAYS. Let me just get to one last question. And I don't want to throw a curve ball here, but the Inspector General is concerned as well as we are on an issue dealing with the plasma industry and the fact that for 5 years the industry may have been aware that they were not properly testing saline contamination. And they notified FDA. I want to know how FDA responded to this.

Dr. FRIEDMAN. Yes. If I could ask Dr. Epstein to please deal with that specifically if he would?

Dr. EPSTEIN. Yes. The FDA became aware through a whistle blower complaint of the fact that at a particular fractionator—their testing laboratory—which dealt with the marker testing of donations intended for further use to make fractionated products, that some samples had been identified as improperly diluted with saline. In other words, a sample should be diluted with anti-coagulant if it's a plasma sample, but it should not have further dilution with saline. This implied that it would not be a valid sample for testing.

Mr. SHAYS. So it would distort all your testing?

Dr. EPSTEIN. Pardon?

Mr. SHAYS. It would distort the testing?

Dr. EPSTEIN. Yes, it would. If the sample were sufficiently diluted, such as more than 50 percent, then testing might become false negative.

Mr. SHAYS. And when was the FDA notified about this by the whistle blower?

Dr. EPSTEIN. I can get that in one moment.

Mr. SHAYS. Take your time.

Ms. ZOON. 1995.

Dr. EPSTEIN. Yes. It was February 7, 1995.

Mr. SHAYS. And so this whistle blower came forward. And was the whistle blower's complaint valid?

Dr. EPSTEIN. Yes. The FDA did a focused inspection to determine whether the allegation had merit, and determined that, in fact,

there was a documentary record supporting the allegation that some small number of samples submitted to the testing laboratory for infectious disease and other marker testing were saline contaminated and would not be valid.

Mr. SHAYS. Was this with one company?

Dr. EPSTEIN. Yes. The observation was made at only one company.

Mr. SHAYS. What was that company?

Dr. EPSTEIN. Am I permitted to disclose this?

Mr. SHAYS. Why not?

Dr. EPSTEIN. Yes. OK. This was Baxter Corp. And the laboratory was their Roundlake testing facility.

Mr. SHAYS. And then what was the response? Were they fined? Or how long did they know that this was taking place? Was this a 5-year problem that they weren't dealing with?

Dr. EPSTEIN. Well, there was evidence in their records that management was aware of this issue for a period of as much as 5 years. However, it was the conclusion of the FDA investigation that this was in fact a systemic problem which was due to a limitation——

Mr. SHAYS. Systemic throughout the industry?

Dr. EPSTEIN. Yes.

Mr. SHAYS. So, the problem didn't just exist there, it existed everywhere?

Dr. EPSTEIN. Yes. Although we have no documentary evidence from our own inspections, we do have statements from industry to the effect that other fractionators had made similar observations. And the underlying causes suggest to us that it must be a widespread problem because it has to do with use of the equipment by which the source plasma is made in the first place and a particular vulnerability related to that use, that equipment.

Mr. SHAYS. So, you have one company where you had a whistle blower come forward. You had other companies that were probably aware of the problem and didn't step forward. That invalidates some testing.

Dr. EPSTEIN. Well, let me say that when an improperly prepared sample was identified the unit to which it referred would not be used. The companies viewed their monitoring of the sample quality as an added quality control measure above and beyond standard requirements. In cases where they found diluted samples, the units were not used. And, therefore, there was no sense that final product had been compromised. However, the issue was failure to correct the problem at its source.

Mr. SHAYS. Let me ask you, what was their legal requirement if they knew there was a problem? Were they legally required to notify the FDA?

Dr. EPSTEIN. Well, the error and accident requirement is actually written to refer to reporting related to units which have issued. There is not obligatory reporting to the agency if a unit which was subject to an error and accident was never entered into distribution. That's not to say that they lack a requirement to investigate and correct error or to maintain a record of such an investigation. But they do not actually have a requirement to report to the agency in the event that an error and accident was for an undistributed unit or product.

Mr. SHAYS. So it's your testimony that this company—I'm a little confused.

Dr. EPSTEIN. Well, let me say it another way. We believe that they ought to have reported it as a matter of good sense.

Mr. SHAYS. Right.

Dr. EPSTEIN. However, their formal requirement since they never used an identified improperly tested unit, would not have been there.

Mr. SHAYS. Wouldn't it have been exactly helpful for them to report it to see if this was an industry-wide problem?

Dr. EPSTEIN. Yes.

Dr. FRIEDMAN. Yes.

Dr. EPSTEIN. I think that had we learned about it sooner, we would have acted sooner.

Dr. FRIEDMAN. That's right.

Mr. SHAYS. I'm unclear as to how FDA responded. How did FDA respond? You investigated, and what did you do?

Dr. EPSTEIN. First, we made a determination that the problem really lived at three levels. You had the devices that make the plasma. These are called apheresis separation machines. The problem that causes the saline dilution is a backflow of saline, intended to replenish volume in the patient from whom plasma was just withdrawn, instead entering not only the patient but the collection container.

Mr. SHAYS. Yes.

Dr. EPSTEIN. Now, that problem arises for two reasons. First, a lack of a safeguard in the device design. In other words, its software programming, its monitors, its alerts, its warning lights, et cetera. Second, it arises because the users of that equipment—namely the centers that collect the source plasma—may have been deficient in training of the operators so that the operators would know to adequately clamp off the tubing so that saline could not backwash into the collection.

Mr. SHAYS. OK. Did this company not know why the problem was being caused or they just didn't care about it?

Dr. EPSTEIN. They had understanding. They made efforts to inform the providers of the source plasma. However, they were inconsistent in that effort. They did not notify the providers in all cases, nor did they document any corrections. They simply continued to make these occasional observations of a diluted sample. And that, of course, is the third level involved, which is, why didn't the laboratory—which in this case was part of the fractionator licensee—but it isn't always—but why didn't the laboratory seek effective correction. And we see that as the failure at the third level.

But yes. They did attempt correction. They did notify many of their source plasma providers that they were finding this. But they did not demand correction or show evidence that correction was achieved. They simply continued to monitor and occasionally report dilution.

Mr. SHAYS. If the whistle blower hadn't stepped forward, what would still be happening?

Dr. EPSTEIN. Well, that's hypothetical, so I can't say. Could we have learned through some other route? Yes.

Mr. SHAYS. No. That's not what I'm asking. Let me ask you this: What was the effect over these 5 years of your not knowing about it and their continuing to tolerate this? I don't know. What was the impact on the public?

Dr. EPSTEIN. Well, we believe that there was no health impact on the public.

Mr. SHAYS. Let me ask you this: is this still happening?

Dr. EPSTEIN. Measures are in place that should have mitigated the problem. I think that perhaps Mr. Simmons would like to comment. I think that we have not completed the phase of auditing all corrections.

Mr. SHAYS. That's too long an answer for me.

Dr. EPSTEIN. We're not certain that all correction is in place. We know that steps have been taken to correct.

Mr. SHAYS. OK. Now, what I'm trying to understand is what is the impact to the public?

Dr. EPSTEIN. It has been our assessment that there is not health impact to the public because of the adequacy of viral inactivation of the plasma derivatives.

Dr. FRIEDMAN. Mr. Chairman, may I try and——

Mr. SHAYS. Can I ask you something before you try? I'm getting a little uneasy by this dialog.

Dr. FRIEDMAN. Please.

Mr. SHAYS. Because I feel there's something more significant here. And I——

Dr. FRIEDMAN. Please.

Mr. SHAYS. When the FDA finally inspected this Baxter plant—and that was on May 12, right? There was a class 3 recall that resulted in 26 million units of hemophilia products. Is that correct?

Dr. FRIEDMAN. Are you talking about just recently, Mr. Chairman?

Mr. SHAYS. Yes. I just don't know how we can say that there's not impact?

Dr. FRIEDMAN. Sir, I'm sorry, let me——

Mr. SHAYS. I don't want to blow this out of portion, but——

Dr. FRIEDMAN. I know you don't——

Mr. SHAYS. I just want to say. I don't want to blow it out of proportion, but I don't want to end this dialog until we have a full disclosure on the record.

Dr. FRIEDMAN. Right. Let me go through a couple of things, if I may, with you, sir?

Mr. SHAYS. Yes.

Dr. FRIEDMAN. The first thing that you're talking about has to do with how viral tests are performed on plasma samples. And Dr. Epstein has just said that it's our assessment that there was not a health hazard under those circumstances. Let me explain at least three reasons why that's the case. The first is that, the best estimates we can make, is that this occurred extremely rarely. And so there were relatively few collections where this was a problem.

The second is that even when it was a problem, there are those samples where testing was still appropriate and accurate because the samples were not sufficiently diluted. The third is, that even when there was an inappropriate false negative test—that is, there was too much dilution, the test wasn't accurate—those units were

subjected to the same viral inactivation that would have been successful under any circumstances.

So when he says he believes there is not a health hazard, I want you to understand what the levels are that document and provide confidence from that. The point that you're just making, sir, is something which is different, if I may just talk about that for a moment.

We have taken recent class 3 action—and, as you recall, class 3 is the lowest health risk class—at this Baxter facility because there was inadequate documentation that the plasma units or the material that was derived from the plasma had been maintained at the proper temperature for the proper period of time. And, therefore, there was a recall based upon that.

Now, when we went back and looked at other systems that were in place, such as a detergent system for inactivating virus—killing virus—those things all seemed to be perfectly appropriate. And so there wasn't a health risk to an individual. But the point you made earlier, sir, is that if you have a multi-layer system, the power in the system comes from having all the layers intact.

If you start to lose some of those layers, you start to lose not just the integrity of the system, but the confidence in the system. And so even though a particular lapse might not be associated with a health risk, I don't think we should tolerate that. Because each gap subjects the whole system to some risks. Therefore, we took this class 3 action because, even though there was not a health risk by any assessment that we could identify, we should not have those lapses. I don't know if that helps or not, sir.

Mr. SHAYS. It does. But let me read the testimony. One of the problems when we ask people to summarize their testimony is that they don't put it out on the public record verbally. "First, the ORA recommendation"—this is the IG's testimony to the subcommittee. "First, the ORA recommendation to conduct a followup inspection of viral inactivation procedures at Baxter's manufacturing plant was rejected by CBER. A regularly scheduled inspection conducted subsequently gave no indication that the viral inactivation procedures were reviewed. The FDA informed us that as of May 12, 1997, it had underway an inspection of Baxter's manufacturing plant and included examining the viral inactivation procedures. We subsequently learned that Baxter initiated a class 3, the least serious, recall of plasma product on May 24, 1997 due to the firm not maintaining specific temperature for the viral inactivation process."

Dr. FRIEDMAN. Yes, sir.

Mr. SHAYS. OK. Now, what's the significance of the last sentence—the temperature for the viral inactivation process?

Dr. FRIEDMAN. As I explained, when these units are treated to inactivate the virus, the operating procedures say that they should be held in a certain temperature for a certain period of time in order to most effectively kill the virus. That standard operating procedure can be breached in a couple of ways. Either you don't have the temperature documented or you don't have the time documented. And we were concerned that there was inadequate recordkeeping to assure us that all these systems had been done exactly as they should be done.

You asked a question earlier, sir, that's really important. And I know you're going to ask me at the end, what questions you wanted to ask us.

Mr. SHAYS. Yes.

Dr. FRIEDMAN. The question I want to put a marker down on is, the fact that we are seeing more recalls, more product withdrawals, is this something that should give us confidence or not? I'd like to speak to that later because I think this is actually relevant in that regard.

Mr. SHAYS. OK.

Dr. FRIEDMAN. I'm sorry. Others may want to add.

Ms. ZOON. I just wanted to let you know, some of the observations on the inspection were actually that the temperature range was 1 or 2 degrees below what the range was listed in their SOP.

Dr. FRIEDMAN. Standard operating procedure.

Ms. ZOON. I'm sorry. Standard operating procedure. And that was because it was outside of its operating procedures, that was a GMP deficiency. And that——

Dr. FRIEDMAN. They were cited and things——

Ms. ZOON. And an evaluation was made as to the impact of that deviation.

Mr. SHAYS. But was that related to the flawed testing?

Ms. ZOON. That was the viral inactivation procedure that was done at Baxter.

Dr. FRIEDMAN. Sir, that inspection was going on anyway. The Inspector General asked that we make sure that the evaluation of the adequacy of viral inactivation be conducted. That had been an intention of ours at the time, and we were happy to assure the Inspectors General that in fact we were in the process of doing that and that we did care about that as well.

Mr. SHAYS. Now, what I'm hearing from your testimony—and this is the laymen speaking—I'm hearing that this one line of defense that broke down, but the other lines of defense caught the problem. That's what I'm hearing. But is that an accurate first?

Dr. FRIEDMAN. Yes, sir. I just want to make sure I'm not misstating that.

Mr. SHAYS. But that says to me, OK, public, we think we caught the problem. But what it doesn't say to me is, that if I had five armies out there and all five were to protect me, and one army was asleep—one unit was asleep—then I'd say, not to worry, the other four protected me. I expect all five to work. And all hell is going to break loose if one of those parts breaks down. So I'm willing to have the public record reflect the fact that it's the comfort level of the FDA that the public was not threatened, but one of our lines of defense was broke and had been broke for a long time. And one company knew about it.

When you looked at that one company, because, thank God, a whistle blower stepped forward, your response was to look at it and realize that this same process was occurring throughout the industry, so this line of defense was broken down throughout the plasma industry. Where is my logic breaking down so far?

Dr. FRIEDMAN. Your logic is not breaking down. It's the association of these two things that isn't as accurate as you want it to be. Let me point out.

Mr. SHAYS. OK.

Dr. FRIEDMAN. There was a problem with this company.

Mr. SHAYS. Right.

Dr. FRIEDMAN. And the dilution and, hence, possible inaccuracy of the viral testing.

Mr. SHAYS. And the company knew about it for 5 years?

Dr. FRIEDMAN. The company knew about it for a considerable period of time and should have taken action and should have informed us.

Mr. SHAYS. For at least 5 years.

Dr. FRIEDMAN. Should have informed us. Should have taken action.

Mr. SHAYS. But for at least 5 years that knew about it?

Dr. FRIEDMAN. I don't know that. But that's what others are saying. And, yes.

Mr. SHAYS. But that's the idea.

Dr. EPSTEIN. Alleged.

Mr. SHAYS. It's alleged. OK. I'll accept that.

Dr. FRIEDMAN. But I want to be accurate about what we say. That's one problem. What we're talking about with the temperature is a different problem in a different situation.

Mr. SHAYS. OK. Let's leave the temperature aside. Let's talk about the problem—why the whistle blower contacted and——

Dr. FRIEDMAN. That's not so related to this recent withdrawal.

Mr. SHAYS. OK. I accept that. In the process of being in the plant you realized about the temperature problem, and that was——

Dr. FRIEDMAN. Yes, sir.

Mr. SHAYS. The withdrawal was related to that and not this problem?

Dr. FRIEDMAN. That is correct, sir.

Mr. SHAYS. OK. And that's important for the record to reflect. And so I'm sorry that I brought that up right now. Because I don't want to lose—I want to understand this issue.

Dr. FRIEDMAN. Your point is, that if viral testing is one of crucial components of our confidence in the safety of the blood supply and we identify something that compromises that, should it be tolerated.

Mr. SHAYS. Right.

Dr. FRIEDMAN. The answer is "no."

Mr. SHAYS. No. And that's one thing. Well, there we agree. But that should have happened. But it is alleged that this company knew for many years, whether it's 5 years or——

Dr. FRIEDMAN. That's right, sir.

Mr. SHAYS. And didn't choose to tell you. And you have stated for the record that, in the process of looking at it, you realize that it is an industry-wide problem?

Dr. FRIEDMAN. Yes.

Mr. SHAYS. Which raises questions in my mind, which this committee will look at, and bring these companies forward. Maybe not in a hearing but before—to answer some questions for the committee staff at the minimal—that other companies knew about this problem, as well. Correct? All the other companies did not know? Or did some other companies know they had a problem as well?

Dr. FRIEDMAN. I think a more accurate way to say it was that it was a kind of a machine and that this was a problem with the machine so that any company that used this machine might experience that problem.

Mr. SHAYS. Would have, not might.

Dr. EPSTEIN. We did inquire with the industry what it's level of knowledge was of problems of this sort. And we did receive a letter from the industry trade organization documenting awareness of a low frequency of saline contamination of samples for testing.

Mr. SHAYS. OK. And their point is, low frequency, not a serious problem. Low frequency—occurring infrequently or when it occurred, not to any major degree.

Dr. EPSTEIN. No. Occurring infrequently. I forget the exact numbers. But it's fractions of a tenth of a percent. You know, like 0.003 percent.

Mr. SHAYS. I've been here 10 years and I still don't know what six lights means. Would you find out? It scares the hell out of me. Something serious is happening. I don't want to be talking with you while I'm missing a vote, with all due respect.

Dr. FRIEDMAN. Nor do we want you to, Mr. Chairman. Thank you.

Mr. SHAYS. OK. I'm going to just end this, though. But I don't think I'm going to like the answer to this last question. What did you do about it?

Dr. EPSTEIN. The FDA did several things. First, we have ensured that the apheresis devices have been modified to prevent this problem. And there are several corrections that have been put in place for the two devices affected by the problem. Second, we have worked with the industry—and this was subject to the review in the OIG report—to assure that an information campaign would be developed to emphasize the adequacy of the training of the operators who use this equipment and to assure that the industry will be more responsive in reporting any further observed instances of saline contamination to the agency.

Mr. SHAYS. OK. If I had a staff member and a staff member didn't tell me that they had made a mistake, and a few weeks later I was confronted with that mistake by someone else, and the next time I interacted with that staff member I wouldn't have the same confidence level. It sounds to me like you just turned this over back to the trade association to deal with. Is that what you basically did? You just put it back on their laps?

Dr. FRIEDMAN. No.

Dr. EPSTEIN. No. I would say that the effort is to engage the assistance of the industry in getting the word out. However, FDA does not leave to the industry its monitoring of correction. FDA is examining on inspections whether there are further incidents of saline contamination, whether there is monitoring for it, whether centers that have had it documented are making correction, et cetera.

Mr. SHAYS. Yes. I would also have said to my staff, how can I trust you on something else if I couldn't trust you in telling me this. No, I don't think I have staff members that do that. In fact, I know I don't. Or if I did, we'd straighten it out.

Dr. FRIEDMAN. Mr. Chairman, may I just add one or two other things, because I understand the point that you're making?

Mr. SHAYS. Yes.

Dr. FRIEDMAN. This was not something that was left entirely to that particular industry. I understand your skepticism there. Some of the changes that needed to be made had to do with the equipment—software changes so that there wouldn't be this backup of saline into that part of the system. That's a different set of industries. Those are companies who have committed to fixing the software changes for that.

Mr. SHAYS. I'm really talking about fixing the problem which you feel you're addressing.

Dr. FRIEDMAN. You're talking about in general levels of confidence.

Mr. SHAYS. I'm talking about levels of confidence and I'm talking about integrity. I'm talking about a person who probably risked his or her job. And sees the FDA responded, it appears to me, in a pretty casual way, frankly. And the casual way is: any fines? Any penalties? And any riot act? Any letters to the individuals? Any public disclosure? You know, all those things that I'd like to think would take place. Did any of those things happen?

Dr. FRIEDMAN. The question that's been asked is, are there fines, are there other sorts of penalties that have been posed?

Mr. SIMMONS. Certainly, there have been no fines or no penalties. If I could try to address some of your concerns. This was deemed to be an industry-wide problem. Assessing fines or penalties against one company when you have an industry-wide problem while the other problems persisted would have little effect on public health. And our assessment of the situation was that the public was better served by working with the total industry to try to remedy the problem. And that's the approach we took to it.

Mr. SHAYS. Why would you have been encumbered from dealing with this problem? Why are they mutually exclusive? Why wouldn't someone have to pay a penalty when they are not honest and straightforward and come recognize it? That's what I'm missing.

Dr. FRIEDMAN. Sir, two things. One is that, to the best of our knowledge, none of these units were released to the public.

Mr. SHAYS. That's irrelevant to me.

Dr. FRIEDMAN. I'm sorry?

Mr. SHAYS. No. That's not irrelevant.

Dr. FRIEDMAN. No.

Mr. SHAYS. Thank God.

Dr. FRIEDMAN. No. I think that's the most important thing.

Mr. SHAYS. But it's irrelevant to the issue.

Dr. FRIEDMAN. I think the second thing is, in terms of—and I would ask our legal counsel to say what was—not what was the violation of trust or good sense, we've already spoken to that, and I think we've spoken clearly to that. The question you're asking is what's the violation in law.

Mr. SHAYS. Well, no. There's law. There's a lot of things here. First off, this was a problem that existed for years, not a few weeks, not a few months. And so they knew the system wasn't working properly. This one company was aware of it. It evidently is a problem based on equipment that therefore was an industry-

wide problem. It meant that one of our lines of defense was faulty and unreliable. And yet you had every reason to believe that it wasn't faulty or unreliable. But you were notified. The FDA was notified by a whistle blower.

If I was the whistle blower, I would feel that I had done my job, but I would say, I could lose my job over this if the company knew and yet nothing happened to the individuals involved in this. No one seems to have been held personally accountable or the company appears to be accountable.

Dr. FRIEDMAN. Well——

Mr. SHAYS. And so that just raised the question——

Dr. FRIEDMAN. Well, yes.

Mr. SHAYS. And I just want to say, and the fact that that wouldn't have helped necessarily solve the problem is another issue.

Dr. FRIEDMAN. As you know, sir, this is the subject of on-going litigation. I think that we've been told that there's only a certain amount that we can say publicly about this. Obviously, we're prepared in a private venue to answer other questions about this. This is an actively litigated matter. If I just may——

Mr. SHAYS. Does the litigation involve the FDA?

Ms. ZOON. Justice.

Mr. SHAYS. What?

Ms. ZOON. Government.

Dr. FRIEDMAN. The Department of Justice, I understand, sir.

Ms. ZOON. Justice is doing the case.

Mr. SHAYS. OK. You know what I'm going to say to you, this is—I feel like we're getting deeper into a hole and I'm getting more uncomfortable with your responses and more disheartened by your responses. I'm just going to suggest that maybe we'll just have a special hearing on this kind of issue. The IG is looking into this issue, correct?

Ms. FINLEY. That's the subject of their testimony.

Mr. SHAYS. Right. OK. What we're going to do—I am not comforted that because it's an industry-wide problem we're not holding a particular company accountable. That implies to me that because everyone is involved we'll hold no one accountable. You know, it does say that to me. And rather than make more statements that I may regret, I think we'll just leave on unfortunately a negative note.

Dr. FRIEDMAN. If I may, I'd like to change the tenor of that note?

Mr. SHAYS. Sure. OK.

Dr. FRIEDMAN. I would just point out a couple of things, sir. One is that lest you think there is some inherent inability or reluctance on the part of the agency to take strong action when we identify something that threatens the overall integrity of the safeguards. The matter that you were just discussing—the recent identification of inadequate recordkeeping and temperature control for these products, even though there was nobody that we could identify would be harmed by it, we imposed a restriction. We imposed a requirement on the company that is going to have a substantial financial impact on that company.

And the purpose of that is not to be punitive. The purpose of that is to demonstrate——

Mr. SHAYS. That was another issue.

Dr. FRIEDMAN. Right. But I'm pointing out—lest you think that we aren't interested in doing this or we have some reluctance in doing this, that is not a message that I would like to——

Mr. SHAYS. In the Civil War, if a sentry fell asleep they shot him. And they couldn't say, well, no one happened to break through out lines that evening. That sentry was there for a purpose. And, obviously, we wouldn't shoot someone today, but they would be held very strongly accountable.

Dr. FRIEDMAN. Right.

Mr. SHAYS. And if someone knew for years that sentry had been asleep and we said, well, no harm came because nobody ever attacked us. So that's why I'm feeling very uneasy.

Dr. FRIEDMAN. I understand. And what I'm saying is that the sentry——

Mr. SHAYS. And I don't want to get you deeply in a hole here.

Dr. FRIEDMAN. The sentry was dealt with in this latest episode in a manner that you've just identified, and that we would be very pleased to go over with you——

Mr. SHAYS. Can I ask you something? I just don't want to back you in a corner. Are you fully versed on this issue? Or is this an issue you need to take a look at?

Dr. FRIEDMAN. This is something that I have taken some look at, but I am not fully versed.

Mr. SHAYS. OK. I would like to leave it on that note.

Dr. FRIEDMAN. OK.

Mr. SHAYS. And I would like to hear how the FDA feels it should respond to this issue after you have—you may come up with the same answer. But I'm not looking to have you take an opinion as the person in charge without a full and——

Dr. FRIEDMAN. Thank you.

Mr. SHAYS. OK.

Dr. FRIEDMAN. I appreciate that.

Mr. SHAYS. OK. And I did hear you ask, had any penalties been levied. And, so, since you asked that question, I'm assuming you didn't know.

Dr. FRIEDMAN. That is correct.

Mr. SHAYS. And I would like you to. Do you have a point you want to make here? And just identify yourself.

Ms. MALONEY. My name is Diane Maloney. I'm in the Office of the Chief Counsel.

Mr. SHAYS. Yes.

Ms. MALONEY. With regard to the company's failure to report to the agency the fact that some units—there was this issue of saline contamination. If the company found it and did not made those products available for release, their system is working. That's what quality control is all about—quality assurance.

Mr. SHAYS. No. Another system caught it.

Ms. MALONEY. I'm sorry?

Mr. SHAYS. Another part of the defense system caught it. One part of the defense system broke down. Correct?

Ms. MALONEY. Right.

Dr. FRIEDMAN. No, sir. I'm not sure that's right.

Mr. SHAYS. OK. Well, I want to be corrected. That's why I'm stating it.

Dr. FRIEDMAN. What she's saying is that the company had what they said were other effective systems for identifying when a unit had too much saline in it, and that those units were put aside and never released. Those units were destroyed.

Mr. SHAYS. OK.

Dr. FRIEDMAN. And so she's saying the company had an additional built-in mechanism. And because those units weren't released the company—well, I don't want to make the point. Go ahead.

Mr. SHAYS. OK.

Ms. MALONEY. Well, I was just trying to make the point when you asked the question of whether or not fines or penalties were imposed.

Mr. SHAYS. Right.

Ms. MALONEY. There was not a violation to the extent the units—regarding the saline contamination—were caught before they were made available. I am referring to units not made available for distribution.

Mr. SHAYS. Right.

Ms. MALONEY. It is not a violation to not report that to the agency. So there could be no penalties imposed in that situation.

Mr. SHAYS. OK. For the record, what I'm hearing you saying is that no contaminated plasma blood supply came onto the market because they were able to catch it when there was—they were able to catch it.

Ms. MALONEY. No. I'm not saying that, because I don't know all the facts. And whether they absolutely caught every single unit I can't—and I'm not sure anybody could tell you that.

Mr. SHAYS. OK. Yes.

Ms. MALONEY. But I'm just saying, with regard to your specific question, why were penalties not imposed for failing to report this to the agency—what I'm saying, if they catch a problem before a unit is made available for release, and they do not make that unit available for release, then it is not a violation to fail to report it to the agency.

Mr. SHAYS. OK. And I would respond—and I feel like I'm beating a dead horse—I would respond by saying that one line of our defense was not working properly and couldn't be trusted. And this company seemed to know about it for a number of years. They felt they could catch it through another process, and chose not to notify the FDA. In the words of the chairman who preceded me in this subcommittee, that boggles my mind. And it's something that we'll just take a better look at.

Ms. MALONEY. Yes.

Mr. SHAYS. And I will say to you, if I were the FDA, I would say, well, what other areas of the plasma industry are there circumstances like this where you also haven't come forward? How can I trust you? How can I feel confident since you've known this for years? And I would also say, isn't it dumb that you didn't come forward, because if you'd come forward we could have solved this problem years ago. And you chose not to.

And, so, you're making a point, legally you may not be empowered to levy a fine. That's your point. Yes?

Ms. MALONEY. If I could just add to something Dr. Epstein said earlier. On the other hand, the company does have an obligation to investigate problems and come up with fixes. So that is something that I think we've been continuing to look at, and I'm not sure that the matter is closed at this point.

Mr. SHAYS. No. It can't be closed. But one of the things that the subcommittee will look at is to see why you can't penalize someone. Is there a need to make sure that there are requirements for companies to do logical things like notify you and to share it with other people in the industry. I have a high respect for the FDA. I have high respect for you, Dr. Friedman, and the rest of the people on your staff. And I'm sure there are some answers that will not make this look as bad as it looks. And I'm sure there are some things that will make me feel that more action or better action needs to be taken. So we'll split the difference and try to end on a medium note.

Dr. FRIEDMAN. And if I may, I beg your indulgence just for 60 more seconds, sir.

Mr. SHAYS. Sure.

Dr. FRIEDMAN. One is that I think that please look again at the number of inspectional findings that we are making with this more intensive, more aggressive, and, I think, more fine system of scrutiny that we're subjecting these individuals to. I take your point very seriously. How can one assume that every other part of the system is working well? We don't assume that.

You'll see the documentation. The inspections are longer. The number of findings is way up. We're taking action on these. So I don't want you to leave this room thinking that we think that there's no problem and you perceive a problem.

Mr. SHAYS. OK.

Dr. FRIEDMAN. That's No. 1. No. 2 is let me just quickly deal with your question to the other panel for this day's committee hearing. It's my view that several things have happened that contribute to the number of recalls or findings that are being made. One is the point that was made earlier. Scientifically, we're much more sophisticated. We're able to detect problems that were unheard of and unknown previously. I take great comfort in that. That's No. 1.

No. 2 is: the public is simply not tolerant of risks and problems. They deserve and they wish to know about these. And, therefore, that is making the system scrutinize all aspects of this industry much more carefully. I think that's a very positive thing. I really do.

The third is an area of personal responsibility, which we have not always given consistent, clear, uniform guidance and regulation to industry in this regard. Our expectations have not always been articulated as clearly as they should have been. And that is a responsibility that we have to the extent that we make our inspections and our regulations and our requirements and our guidances more clear and more comprehensive, we will, at first, have more adverse findings. Ultimately, things will get a lot better.

But I think that we share some of the responsibility there. I see that as a very positive thing because it means that we are bringing a greater discipline, a greater focus, a greater seriousness to how we perform our job. That's my quick answer, sir.

Mr. SHAYS. That's a nice way to end. The hearing is closed.

[Whereupon, at 1 p.m., the subcommittee was adjourned.]