BLOOD SAFETY: MINIMIZING PLASMA PRODUCT RISKS

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES

OF THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTH CONGRESS

SECOND SESSION

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CONTENTS

	Page
Hearing held on September 9, 1998	1
Statement of:	
Reilly, James, executive director, American Blood Resources Association; Jan Bult, executive director, International Plasma Products Industry Association; Brian McDonough, CEO, American Red Cross Biomedical Services; and John Boyle, Ph.D., Plasma Users Coalition	60
Steinhardt, Bernice, Director, Health Services Quality and Public Health Issues, Health, Education and Human Services Division, General Accounting Office, accompanied by Marcia Crosse and Kurt Kroemer; and Michael Friedman, M.D., lead Deputy Commissioner, Food and Drug Administration, accompanied by David Feigal, M.D., Jay Epstein, M.D., Center for Biologics, and Ronald Chesemore, Associate Commissioner of Regulatory Affairs	9
Letters, statements, etc., submitted for the record by:	
Boyle, John, Ph.D., Plasma Users Coalition, prepared statement of	122
Bult, Jan, executive director, International Plasma Products Industry Association, prepared statement of	72
Friedman, Michael, M.D., lead Deputy Commissioner, Food and Drug Administration, prepared statement of	25
McDonough, Brian, CEO, American Red Cross Biomedical Services, prepared statement of	114
Reilly, James, executive director, American Blood Resources Association, prepared statement of	63
Shays, Hon. Christopher, a Representative in Congress from the State of Connecticut:	
Prepared statement of	3
Report of the Expert Panel on Donor Pool Size Immune Globulin Products	142
Steinhardt, Bernice, Director, Health Services Quality and Public Health Issues, Health, Education and Human Services Division, General Accounting Office, prepared statement of	12
Towns, Hon. Edolphus, a Representative in Congress from the State of New York, prepared statement of	6

BLOOD SAFETY: MINIMIZING PLASMA PRODUCT RISKS

WEDNESDAY, SEPTEMBER 9, 1998

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, Snowbarger, and Kucinich.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley, professional staff member; Jesse S. Bushman, clerk; and Cherri Branson, minority counsel.

Mr. SHAYS. I would like to call this hearing to order. We will have other Members showing up, but I think we should get started, and I apologize for being late.

Two weeks ago, Surgeon General David Satcher decided to lift the precautionary hold on blood and plasma from donors who may have Creutzfeldt-Jakob Disease [CJD]. He did so, in part, because quarantines of CJD-implicated blood products were reducing already scarce supplies of lifesaving medicines, and because the proven, negative health effects of shortages far outweigh the theoretical risk of CJD transmission through blood.

The CJD decision illustrates many of the strengths and weaknesses of the system now used to protect an inherently risky but vital resource. Weighing, and minimizing, the risks of an uncharacterized threat like CJD challenges each layer of the interlocking blood safety complex: donor screening, unit testing, antiviral technologies and manufacturing standards.

While in place, the CJD exclusion policy had a far greater impact on those who collect "recovered" plasma from volunteer donors of whole blood than on those who collect "source" plasma from paid donors. That unexpected disparity, and contrary suggestions that the payments lure higher-risk donors, led us to ask the General Accounting Office [GAO] to assess the relative risks of plasma from paid and volunteer donors.

Three aspects of the GAO findings released today stand out: First, despite persistent questions whether paid donors have less incentive to disclose disease risks, neither the Food and Drug Administration [FDA] nor the blood industry have much useful data on the viral marker rates of blood donors. This points to a need for more effective, more consistent disease surveillance.

Second, while paid plasma donors are 1½ times more likely to donate potentially infectious units, recent safety initiatives by the fractionation industry greatly reduce the chance that an infected unit will be pooled for use in making a final product. This sustains our heavy reliance on source plasma from paid donors for most plasma-derived therapies.

Third, the success of those industry initiatives to inactivate or remove viral agents depends heavily on consistent compliance with strict regulatory standards governing manufacturing practices and procedures. In view of recent FDA inspections citing numerous violations of good manufacturing practices [GMP's] at plasma fractionation facilities, this GAO finding compels us to ask: What is being done to minimize the risks to blood product safety and blood product supply posed by widespread failure to comply with good manufacturing practices?

In May, we heard testimony that compliance-related production shortfalls, along with surging demand, have created chronic, critical shortages of immune globulins, the plasma-derived antibodies needed by some to fight disease. Both the FDA and the plasma industry described ambitious plans to strengthen regulatory policy and company compliance without compromising blood product safety or supply. Today we look to both for word of progress, not more plans, toward full regulatory compliance and timely production of needed plasma-derived products.

Our 3-year investigation of blood safety issues has included seven prior hearings, and full committee adoption of specific findings and recommendations to protect the safest blood supply in the world from emerging infectious agents. Our goal, shared by patients, regulators and the blood products industry is a vigilant, comprehensive, science-based system of safeguards that yields necessary medicines while avoiding the need to make false, potentially deadly, tradeoffs between product safety and adequate supply.

Toward that goal, we asked the GAO, the FDA, and representatives of blood banks, the plasma industry, and plasma patients to help us address the risks of paid versus volunteer donors and the importance of GMP compliance in minimizing those risks.

We welcome today's testimony. Mr. Snowbarger, the vice chair of this subcommittee has arrived, if he has an opening statement.

[The prepared statement of the Hon. Christopher Shays follows:]

[illegible]

ONE HUNDRED FIFTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

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WASHINGTON DC 20515–6143

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BERNIE SANDERS VERMONT
INDEPENDENT

SUBCOMMITTEE ON HUMAN RESOURCES
Christopher Shays, Connecticut
Chairman
Room B-372 Rayburn Building
Washington, D.C. 20515
Tel: 202 225-2548
Fax: 202 225-2382
E-Mail: hr.groc@mail.house.gov

Statement of Rep. Christopher Shays
September 9, 1998

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Toward that goal, we asked the GAO, the FDA, and representatives of blood banks, the plasma industry and plasma patients to help us address the risks of paid versus volunteer donors and the importance of GMP compliance in minimizing those risks.

We welcome their testimony.

Mr. SNOWBARGER. All I have to say is welcome, because you left that out. Of course, I wasn't here when you left that out.

Mr. SHAYS. If we don't have some good laughs today, we are in trouble because there is lots going on in this place and we need something to make us feel good about the world.

I will swear in a host of people, two of whom will address us: Ms. Bernice Steinhardt, Director, Health Services Quality and Public Health Issues, Health, Education and Human Services Division, accompanied by Marcia Crosse and Kurt Kroemer.

Did FDA just get the chairs first, is that what happened?

Dr. FRIEDMAN. We had a drawing and we lost.

Mr. SHAYS. I will ask you all to be sworn in. Dr. Michael Friedman is accompanied by Dr. David Feigal and Dr. Jay Epstein and Mr. Ronald Chesemore.

And I will ask all to stand and we will administer the oath.

[Witnesses sworn.]

Mr. SHAYS. The record should reflect that everybody has been sworn.

I ask unanimous consent that all members of the subcommittee be allowed to place any opening statement in the record, and the record remain open for 3 days for that purpose, and also that witnesses be permitted to include their opening statements in the record, and without objection so ordered.

[The prepared statement of the Hon. Edolphus Towns follows:]

OPENING STATEMENT

REP. EDOLPHUS TOWNS
RANKING MINORITY MEMBER

BEFORE THE
SUBCOMMITTEE ON HUMAN RESOURCES

SEPTEMBER 9, 1998

Mr. Chairman, thank you for holding this hearing on the safety of the blood supply. Today, we will hear the results of a new GAO report examining the effect of volunteer and paid donors on the blood and plasma industry. Additionally, we will hear the results of GAO's overview of industry compliance with current Good Manufacturing Procedures in the collection, processing and distribution of blood and plasma products. I want to commend you on your long-term interest and commitment to this issue and your efforts to keep the blood supply safe.

It is my understanding that the GAO found that paid plasma donors are one and a half times more likely to donate potentially infectious blood and plasma. Hopefully, these findings will not lead to a call for the elimination of paid donors. Such an action would further reduce critical supply without increasing overall safety.

I am encouraged by a number of recent initiatives by the industry that have greatly reduced the chance of using infected blood or plasma. These initiatives include the use of only repeat donors and a 60 day inventory hold on all units. The GAO found that viral inactivation techniques significantly lower the risk of receiving an infected product when manufacturers follow all the procedures in place to ensure safety, quality and effectiveness.

Good manufacturing practices require that plasma manufacturers operate in compliance with applicable regulations and principles of quality assurance. Good manufacturing practices must include standard industry-wide operating procedures, effective donor education and screening; and maintenance and consultation of donor deferral registries. Most importantly, GMP must include high quality viral testing and inactivation techniques and procedures that assure that products are held in inventory until they have been found to be safe.

In the previous year, the industry has increased quality assurance, quality control and production staff training. Additionally, they have undertaken capital investments to improve equipment. FDA has also taken several actions to ensure manufacturer compliance. Under a new program, FDA has designated two groups of specialized investigators for plasma fractionation and blood banks. GAO found that if properly

implemented, these actions by the industry and the FDA should help alleviate current problems. Mr. Chairman, I think that your interest in this area has led to these beneficial changes and I commend you.

Now, Mr. Chairman, I call upon you to look into another issue regarding the blood supply. Every year blood centers throw away an estimated 3 million pints of healthy blood donated by people who have hemochromatosis, also called iron overload disease. These discarded units represent almost 20 percent of the entire amount of blood donated on a yearly basis. The FDA does not prohibit the use of blood with excess iron content, the blood is not harmful and the condition is not contagious. Therefore, it is unclear why the industry does not use this blood. Mr. Chairman, I request that you look into this issue to determine whether the use of this blood is a way to combat blood supply shortages.

Again, I want to thank you for holding today's hearing. I look forward to the testimony of the witnesses.

Mr. SHAYS. It is wonderful to have both of you with your staff. Ms. Steinhardt, you may begin.

STATEMENTS OF BERNICE STEINHARDT, DIRECTOR, HEALTH SERVICES QUALITY AND PUBLIC HEALTH ISSUES, HEALTH, EDUCATION AND HUMAN SERVICES DIVISION, GENERAL ACCOUNTING OFFICE, ACCOMPANIED BY MARCIA CROSSE AND KURT KROEMER; AND MICHAEL FRIEDMAN, M.D., LEAD DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DAVID FEIGAL, M.D., JAY EPSTEIN, M.D., CENTER FOR BIOLOGICS, AND RONALD CHESEMORE, ASSOCIATE COMMISSIONER OF REGULATORY AFFAIRS

Ms. STEINHARDT. Thank you.

As you pointed out, our report to you discusses the risk of infection associated with plasma products. To sum it up, the risk of receiving a potentially infectious plasma product is extremely low if manufacturers follow all of the safety assurance procedures that they have put into place.

It is very important to stress the "if" here, though, because if these critical steps are not taken, the risks can be considerably higher, and this caution is especially important today in light of the recent performance of the industry.

Let me describe what our analysis found and what it means for the industry and FDA. The risks of infection in plasma products start out higher than where they ultimately wind up. About 85 percent is collected from paid donors who are more than 1½ times more likely to donate potentially infectious plasma than volunteers. About 1 in 3,800 units collected from paid donors is potentially infectious for hepatitis B, C or HIV, but particularly for hepatitis C where the rate of infection among paid donors is twice as high as among volunteers. Some of the recent initiatives that the plasma industry has adopted helped to lower this risk considerably. By using donations only from repeat donors which helps to reduce the likelihood of infected donors and by putting a 60-day hold on donations before using them to——

Mr. SHAYS. Ms. Steinhardt, if I may interrupt. I have no problem with the first three chairs being used. I don't want—if we have paid lobbyists here, I think it is more appropriate if we do have students. Do we have anyone who has no vested interest—someone like the press, they can sit up here. I would like to free up some chairs.

Thank you. Why don't you sit in one of the first three there? Either side. Does anyone else want to? Do we have any witnesses in our next group who are here? Why don't you—if you don't mind coming up front. I am sorry to delay the hearing a bit, but I would like everybody to be comfortable. Any witnesses sitting in the front row, maybe they can sit up here and we can free up some seats.

You can't say I didn't try. I am sorry. We have three chairs on this side also. OK.

Sorry.

Ms. STEINHARDT. That is OK.

I started to explain that the risks of infection in plasma products have been lowered considerably because of some recent initiatives that the industry has taken. By using donations only from repeat

donors which helps to reduce the likelihood of infected donors and by putting a 60-day hold on donations before using them to make sure that they don't subsequently turn out to test positive for infection, the risk of pooling an infectious unit is reduced to 1 in 11,000. This is still higher than the risk from volunteer donors which is roughly 1 in 16,000.

Another practice which has been adopted by the industry that helps to reduce the risks of infection for some users has been the limits placed on pool sizes. Larger pools mean that someone who receives the product is exposed to more donors and consequently to more potentially infectious units. For an infrequent user of plasma, somebody who is being treated for a burn, for example, lower pool size can significantly reduce the risk of receiving an infected unit. But for frequent users, like hemophiliacs, the decrease winds up making little difference.

By far the most important safety assurance is in the manufacturing process itself. We know that the viral inactivation and removal techniques that are used in manufacturing virtually eliminate enveloped viruses such as hepatitis B and C and HIV, and any other type of lipid-enveloped virus that hasn't been identified yet. These techniques are only partially effective against nonlipid-enveloped viruses like hepatitis A and human parvovirus, so it is important to recognize that manufacturing practices are much less of a safeguard.

But the promise of eliminating or reducing potentially infectious agents is only meaningful if manufacturers adhere carefully to good manufacturing practices. And recent experience tells us this hasn't been the case. In fact, we know that FDA inspections at the four major fractionation companies found numerous deficiencies in each company's adherence to these good manufacturing practices. Let me just run down the list.

At Alpha Therapeutic's facility, FDA inspectors observed 139 instances of potential problems, a finding that resulted in a recent consent decree. At Baxter Healthcare's facility, inspectors flagged 96 potential problem areas.

At one of Bayer's facilities they had 30 observations, and at another, 77.

Finally, an inspection of Centeon's facility last year found 87 observations and resulted in a consent decree that ordered the company to cease distributing all but two of its products while it brought its plant up to standards. Last month, after FDA reinspected the plant, the company was ordered to cease manufacturing most products because it was still out of compliance.

What are the kinds of problems FDA inspectors found? In a number of instances, manufacturers were relying on processes that hadn't been validated or fully tested to make sure that they perform predictably. In one case the company wasn't correctly following its viral inactivation processes and hadn't detected or corrected the problem. In some cases, the final product did not meet specifications. More than half of one company's albumin lots failed final container inspection because they were contaminated.

Since these deficiencies were found, the manufacturers have all taken some corrective actions, in many cases slowing production in order to address problem areas. Undoubtedly this is playing some

part in current plasma product shortages. In fact, at this committee's hearing last May, FDA estimated that over 60 percent of the IVIG shortage was attributable to the GMP problems.

FDA has also made some changes in its inspection practices, following recommendations that we and the IG's office made last year, but the key will be sustaining the commitment to improvement on the part of both the industry and the FDA. On that note I will conclude my remarks, and I look forward to your questions.

[The prepared statement of Ms. Steinhardt follows:]

Mr. Chairman and Members of the Subcommittee:

We appreciate the opportunity to be here to discuss blood plasma safety. In the 1980s before the mechanism of human immunodeficiency virus (HIV) transmission was understood, many hemophiliacs used plasma products made from donations by HIV-infected individuals, which consequently infected 63 percent of all hemophiliacs in the United States. Many more such patients contracted hepatitis B (HBV) and hepatitis C (HCV). Although the introduction of antibody tests and viral inactivation and removal processes has reduced the number of people contracting these diseases from plasma products, some safety concerns remain.

One of these concerns relates to plasma donors, who may be paid or unpaid. A long-standing concern exists that paid donors might have higher infectious disease rates than those of volunteer donors because paid donors may have a financial incentive to conceal risk factors that would prevent them from donating. Concerns have also been raised about the number of donors to whom a recipient is exposed because manufacturers of plasma products pool donations from many donors. Furthermore, the efficacy of viral clearance procedures manufacturers use and the manufacturers' safety record can clearly affect the ultimate safety of plasma products.

Because of these concerns, you asked us to discuss the results of our recent report on blood plasma safety.[1] In that report, done at the Subcommittee's request, we (1) compared the risks of incorporating a plasma unit infected with HIV, HBV, and HCV–from donations from volunteer donors with those from paid donors–into the manufacturing process; (2) examined the impact on frequent and infrequent plasma users when pooling large numbers of plasma donations into manufactured plasma products; (3) assessed the safety of end products from plasma after they have undergone further manufacturing and inactivation steps to kill or remove viruses; and (4) examined the recent regulatory compliance history of plasma manufacturers.

In summary, viral clearance techniques have made the risks of receiving an infected plasma product extremely low when manufacturers follow all the procedures in place to ensure safety. Although paid plasma donors are over one and a half times more likely to donate potentially infectious units (1 in every 3,834 units), several recent initiatives by the paid plasma industry have greatly reduced the chances (to 1 in every 10,959 units) of these units being included in the plasma production pool. These initiatives include using only repeat donors (who have been found to have lower rates of viral infection than first-time donors) and a 60-day inventory hold on all units to allow manufacturers to retrieve units from donors who subsequently test positive for disease or are otherwise disqualified. Nonetheless, even with these initiatives in place, plasma units

[1] Blood Plasma Safety: Plasma Product Risks Are Low If Good Manufacturing Practices Are Followed (GAO/HEHS-98-205, Sept. 9, 1998).

donated by paid donors pose a somewhat higher risk of infection than those from volunteer donors (in which 1 in every 15,662 units are potentially infectious).

Limiting the number of donors whose plasma is pooled for production into plasma products helps to reduce the risks of viral transmission for recipients of these products. Currently, the industry has a limit of 60,000 donors for each finished plasma product. This effort has minimized infrequent users' exposure to a certain number of donors for the few times they would receive a plasma product. For frequent users of plasma products, such as hemophiliacs, however, this donor limit has little impact because such patients receive a large number of infusions and are therefore exposed to a large number of pools during their lifetimes.

A more significant step in reducing risk of infection tales place in manufacturing, during which all plasma products undergo viral removal or inactivation procedures, which virtually eliminate enveloped viruses such as HIV, HBV, and HCV. Epidemiological data on the transmission of viruses through plasma products since the introduction of viral removal and inactivation procedures in the late 1980s support the value of these procedures as do laboratory data characterizing the effectiveness of viral clearance through these procedures. The effectiveness of these processes is limited, however, in reducing transmission of nonlipid enveloped viruses, such as hepatitis A (HAV), and human parvovirus.

Voluntary initiatives by the commercial plasma industry, technological advances from increasingly sophisticated screening tests that close the "window period" (the interval between when a donor becomes infected and when a particular laboratory test becomes positive), and viral removal and inactivation procedures are only effective if manufacturers of finished plasma products adhere to current good manufacturing practices. Not all of the major manufacturing companies producing plasma products adhere to these practices, however. In fact, recent FDA inspection reports highlight many instances of noncompliance with current good manufacturing practices. This has led to consent decrees between FDA and two manufacturing companies, temporary suspensions of production at one manufacturing company's facility, and shortages of some plasma products. Although no known cases of HIV, HBV, or HCV from plasma products have been transmitted during the time FDA identified these problems, instances of companies' noncompliance with current good manufacturing practices have been many. A lack of strict adherence to these practices related to viral removal and inactivation procedures could compromise the safety of plasma products. Actions being taken by FDA and the plasma manufacturers since these problems were identified should help to alleviate some of these problems.

BACKGROUND

Plasma is the liquid portion of blood, containing nutrients, electrolytes (dissolved salts), gases, albumin, clotting factors, hormones, and wastes. Many different parts of

plasma are used in treating the trauma of burns and surgery and for replacing blood elements that are lacking due to diseases such as hemophilia. According to estimates, each year about one million people in the United States receive products manufactured from human plasma.

Plasma-derived products are purified from plasma pools by a process known as fractionation. This procedure involves a series of steps so that a single plasma pool yields several different protein products such as albumin and immune globulins.

Plasma used for plasma-derived products manufactured and distributed in the United States may only be collected at facilities licensed and registered with the FDA. Centers require donors to provide proof that they are in the United States legally and have a local permanent residence. About 85 percent of plasma comes from paid donors in a commercial setting and is known as source plasma. The remaining 15 percent of plasma comes from volunteer donors and is known as recovered plasma. Units of plasma collected as source plasma contain approximately 825 milliliters; recovered plasma from whole blood donations contains approximately 250 milliliters. Thus, more than three times as many donated units of recovered plasma are required to make up a plasma pool equal in volume to one comprising only source plasma.

Approximately 370 paid plasma collection centers collect about 11 million liters of plasma from 1.5 million donors annually, involving a total of approximately 13 million separate donations each year. Four companies process the vast majority of source plasma: Alpha Therapeutic Corporation, Baxter Healthcare Corporation, Bayer Corporation, and Centeon LLC.

An additional 1.8 million liters of plasma are collected from approximately 8 million volunteer (not paid) donors, who contribute 12 to 13 million whole blood donations each year. These donors give blood at American Red Cross blood centers and independent blood centers represented by the trade group, America's Blood Centers, and the plasma is recovered for further manufacturing. Plasma collected by the American Red Cross is fractionated under contract by Baxter Healthcare and the Swiss Red Cross and returned to the American Red Cross for distribution. Plasma collected at centers represented by America's Blood Centers is sold only to the Swiss Red Cross, which manufactures the various plasma products and sells them through U.S. distributors.

Paid donors typically receive between $15 and $20 for the 2 hours of time required to remove whole blood, separate the plasma from the cells and serum, and reinfuse the latter back into the donor. Source plasma donors may donate once every 48 hours but no more than twice a week. Whole blood donors may only donate once every 56 days because their red cells are not reinfused as they are with paid donors.

All donors are tested for certain viruses known to be transmitted through blood, including HBV, HCV, and HIV. The specific screening tests check for the presence of

hepatitis B surface antigen (HBsAg), antibodies to hepatitis C (anti-HCV), HIV-1 antigen, and antibodies to HIV types 1 and 2 (anti-HIV).[2] Donors with positive test results are rejected from making further donations. The positive unit and all previously donated plasma units not pooled for manufacture in the preceding 6 months are retrieved, and those professional services that receive the plasma products are notified according to federal regulations (21 CFR 610.46).[3]

RISK OF INFECTIOUS UNITS ENTERING PLASMA POOLS IS SOMEWHAT HIGHER FOR DONATIONS FROM PAID PLASMA DONORS THAN FOR DONATIONS FROM VOLUNTEERS

The risk of incorporating a potentially infectious plasma unit into a plasma pool for HIV, HBV, or HCV is somewhat higher for donations from paid donors than for donations from volunteer donors. Information we obtained on viral marker rates for volunteer donors from the American Red Cross and from paid donors from the American Blood Resources Association (which represents paid plasma collection centers) showed viral marker rates among individuals who offer donations to paid plasma centers to be one and a half times higher than rates among those who come to volunteer blood centers.[4] This is due to higher HCV rates among paid donors.

In addition, incidence rates of HIV, HBV, or HCV are higher among paid donors than they are for volunteer donors, according to our review. These rates include donors who pass the initial screening tests and donate but who subsequently seroconvert and whom a screening test later detects during another donation as being positive.[5] Thus, potentially infectious units from these donors could be incorporated into a plasma pool for manufacturing. HIV incidence rates are 19 times higher for paid donors than for volunteer donors; HBV and HCV rates are 31 times and 4 times higher, respectively.

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

[3]In addition, tests are performed to examine the level of the liver enzyme alanine aminotransferase (ALT). ALT may be an indicator of liver disease or a viral infection. Units with unacceptable ALT levels are not used. Donors with elevated ALT levels are also deferred from donating in the future. In addition, whole blood donations are tested for antibodies to human lymphotropic virus types I and II, but source plasma is not screened for this because it is cell associated and not found in plasma.

[4]The term "viral marker rates" refers to the rate at which a particular group has confirmed-positive tests for particular viruses, in this case for HIV, HBV, and HCV.

[5]Seroconverting donors are recently infected donors who test negative on a currently licensed test.

Finally, the residual risk of incorporating an infectious plasma unit into a plasma pool is somewhat higher for donations from paid donors than for donations from volunteer donors, according to our review. The residual risk represents the incidence rate and other factors that, in the final analysis, could result in a potentially infectious unit being incorporated into a plasma pool. The overall residual risk of incorporating an infectious HIV, HBV, or HCV plasma unit into a plasma pool is about 43 percent higher for donations from paid plasma donors than for donations from volunteer donors (1 in every 10,959 donations compared with 1 in every 15,662 donations, respectively).[6] This difference is statistically significant. Thus, we calculated that about 3.8 infectious units would be included in a plasma pool of 60,000 donations if the pool were made exclusively from donations from volunteers; however, 5.5 infectious units would be included in that pool if it were made exclusively from donations from paid donors.

MANUFACTURER REDUCTIONS IN PLASMA POOL SIZES TEND NOT TO BENEFIT FREQUENT USERS

Concerns have been raised about the size of plasma pools because larger pools expose recipients of plasma products to more donors, raising the risk of infection. Manufacturers have recently taken steps to reduce the size of the plasma pools they use for producing plasma derivatives. Modeling techniques indicate that this effort can affect infrequent users of these products by minimizing their exposure to a certain number of donors. Frequent users of plasma products, such as hemophiliacs, however, tend not to benefit from these techniques because of the large number of different pools to which they are exposed during their lives.

As recently as a year ago, FDA believed that initial fractionation pools contained 1,000 to 10,000 source plasma units or as many as 60,000 recovered plasma units. In response to inquiries from your Subcommittee, however, FDA obtained information from plasma manufacturers showing that after adjusting for the combination of intermediates, pooling of material from several hundred thousand donors for single lots of some products sometimes took place. For example, albumin can be added during intermediate processing steps or to a final product, such as factor VIII, for use as an excipient or

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[6]The calculations for the volunteer sector are based on the possibility that donors infected with HBV may have transient antigenemia, of which a portion would be found positive by the HBsAg test. If this calculation is not made, the risk of incorporating an infectious HIV, HBV, or HCV unit into a plasma pool becomes 1 in 20,872. This would mean that donations from paid donors would be about twice as likely to be potentially infected with HIV, HBV, or HCV and incorporated into a plasma pool as units from volunteer donors (1 in 10,959 compared with 1 in 20,872, respectively).

stabilizer.[7] This albumin often comes from another plasma pool containing donations that are not in the original pool.

Because of concerns about pool size, the four major plasma fractionators voluntarily committed to reducing the size of plasma pools, measured by total number of donors, to 60,000 for all currently licensed U.S. plasma products, including factor VIII, factor IX, albumin, and immune globulin intravenous. This measurement takes into account the composition of starting pools, combining of intermediates from multiple pools, and use of plasma derivatives as additives or stabilizers in the manufacturing process. Prior production streams are still being processed and distributed, however, so that products distributed through the end of 1998 may still be produced from pools that exceeded the 60,000-donor limit.

The American Red Cross has also voluntarily reduced the size of the plasma pools from which its products are manufactured. As a policy, the American Red Cross has a 60,000-donor limit for plasma products that are further manufactured by Baxter Healthcare. Seventy-five percent of all American Red Cross plasma manufactured by the Swiss Red Cross is now at the 60,000-donor limit, with plans for all production to adhere to the limit in the near future.

In a study employing the modeling technique noted above, researchers found that limiting the number of donors in a pool may only be marginally beneficial for infrequent recipients, who might be exposed to an emergent unknown infectious agent with a low prevalence in the donor population, which current manufacturing processes did not inactivate or remove.[8] As an example, the researchers calculated that for an agent with a prevalence of 1 in 500,000 (for example, a rare or emerging virus), a pool comprising 10,000 donations would yield a 2 in 100 chance of exposure to that agent for a one-time recipient. For frequent users of plasma products (that is, 100 infusions during a lifetime), however, this same pool size of 10,000 would yield an 86 in 100 chance of exposure to that agent, assuming that the products would come from different pools. Reducing the number of donors in a pool does not significantly decrease this effect. Thus, these modeling data suggest that smaller plasma pool sizes will reduce the likelihood of transmission of viral agents to infrequent users of plasma products but will have only a minor impact on frequent recipients of such products.

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[7]Excipients are additives, other than the active ingredient of a drug, that confer a desired property on the final dosage form. This may include a preservative to prevent microbial growth or a stabilizer that maintains potency. A stabilizer maintains the integrity of the active ingredient against chemical degradation or physical denaturation.

[8]Thomas Lynch and others, "Considerations of Pool size in the Manufacture of Plasma Derivatives," Transfusion, Vol. 36, No. 9 (1996), pp. 770-75.

In addition, risk of exposure does not always equate with risk of infection. In fact, risk of exposure is always greater than or equal to risk of infection. For example, the recent transmission of HCV by a plasma derivative that had not undergone viral inactivation procedures showed that the risk of seroconversion for recipients of this product increased with the number of positive HCV lots infused and the quantity of HCV viral material infused. Not all recipients were infected, however, because the highest percentage of seroconversions seen with the highest levels of HCV virus infused did not exceed 30 percent. Not all recipients experience seroconversions because of two factors: (1) each recipient's dose and (2) the reduction of infectiousness due to steps in the manufacturing process in addition to viral removal and inactivation.

RISK OF INFECTION REDUCED THROUGH VIRAL INACTIVATION AND REMOVAL TECHNIQUES

As mentioned, certain infectious units could make it through the donor screening, deferral, and testing process. Manufacturers have, therefore, introduced additional steps in the fractionation process to inactivate or remove viruses and bacteria that may have gotten into plasma pools. These techniques virtually eliminate enveloped viruses such as HIV, HBV, and HCV. They are only partly effective, however, against nonenveloped viruses such as HAV and human parvovirus.[9]

All types of plasma derivatives undergo viral inactivation or removal.[10] The two main methods of inactivation are heat treatment and solvent-detergent treatment. To be effective, inactivation techniques must disrupt the virus, rendering it noninfectious. Heat treatment is accomplished either by exposing the freeze-dried product to dry heat or suspending it in a solution. Another technique heats the completely soluble liquid product with the addition of various stabilizers such as sucrose and glycine. The second technique, solvent-detergent washing, exposes the product to an organic solvent to dissolve the lipid coat of viruses, rendering them inactive without destroying the plasma-derived products. The lipid membrane contains critical viral proteins needed for infection of host cells. Disrupting the viral lipid envelope renders the virus noninfectious. Solvent-detergent inactivation is only partly effective, however, in eliminating nonlipid-coated viruses such as HAV or human parvovirus.

Assessing the amount of viral clearance obtained through a particular inactivation or removal process determines the effectiveness of these different procedures. This

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[9]Parvovirus is the cause of Fifth disease, a common childhood illness, which is usually mild and brief. Approximately 50 percent of the population has been infected by parvovirus at some time.

[10]Currently, only two immune globulin intramuscular products are manufactured without the use of viral inactivation procedures.

assessment is based on the amount of virus that is killed or removed and therefore the extent to which these processes eliminate viruses through manufacturing. Individual manufacturing steps can be specifically designed for viral clearance, or they may be intended primarily as a purification process that will also help in killing or removing viral agents. To meet FDA approval of their particular inactivation or removal technique, manufacturers must separately validate each clearance step.

The viral inactivation and removal steps now in use have all been demonstrated to reduce the levels of virus and, in many cases, most likely eliminate them. Even if the virus is not completely eliminated, reducing it significantly is of value. Although theoretically even a single virus can cause infection, research has shown that infection is much more likely to occur with higher concentrations of virus. Proper viral inactivation and removal steps have resulted in no documented cases of HIV, HCV, or HBV transmission from plasma products since 1988.

RECENT NONCOMPLIANCE WITH CURRENT GOOD MANUFACTURING PRACTICES COULD JEOPARDIZE PLASMA PRODUCTS' SAFETY

Although viral inactivation and removal techniques have proven to be highly effective, they are only useful if the steps in the manufacturing process are carried out properly. Recent FDA inspections of plasma fractionation facilities have found many violations of current good manufacturing practices. The lack of strict adherence to these practices could compromise the safety of plasma products.

The objective of good manufacturing practices is to ensure that plasma products are safe, effective, adequately labeled, and possess the quality purported. Plasma manufacturers should operate in compliance with applicable regulations, which require adherence to current good manufacturing practices and quality assurance principles. In addition, each manufacturer must adhere to the standard operating procedures it has established for its facilities.

To ensure that manufacturing processes, including inactivation procedures, follow current good manufacturing procedures, FDA is authorized to inspect plasma fractionation establishments. If the inspectors identify problems, FDA has a range of actions it may take. For violations deemed serious, these actions can include issuing warning letters, seeking a consent decree, or suspending a facility's license.

When an inspection reveals deficiencies, FDA may issue a warning letter to the facility, which does not suspend operations but gives the facility an opportunity to correct deficiencies. A warning letter notifies a firm that FDA considers its activities to be violating statutory or regulatory requirements and that failure to take appropriate and prompt corrective action may result in further FDA action. For some serious violations, FDA may seek a consent decree against a firm or individual--a court-ordered action that

either mandates corrective actions that must be taken or prohibits the firm's operation unless and until such actions are taken. FDA may pursue an action to suspend a facility's license if the agency has documented deficiencies that constitute a danger to health, necessitating immediate corrective action. In such instances, the manufacturer would not be conforming to the standards in its license or the regulations.

Recent FDA inspections conducted at the four major fractionation companies found many potential deviations in each company's adherence to current good manufacturing practices. A recent inspection by FDA of Alpha Therapeutic's facility observed 139 potential deviations from current good manufacturing practices or standard operating procedures; this has recently resulted in a consent decree with FDA. An FDA inspection of Baxter Healthcare's fractionation facility observed 96 potential deviations. Bayer Corporation's Berkeley, California, facility was cited for 30 potential deviations, and an inspection of Bayer's Clayton, North Carolina, facility observed 77 potential deviations. Finally, an inspection of Centeon's facility observed 87 potential deviations, which resulted in a consent decree filed in January 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. In May 1997, FDA authorized the distribution of Centeon's products from the facility, but, in a subsequent inspection completed in July 1998, FDA found that Centeon had failed to fully comply with the consent decree, and the company was notified to immediately cease manufacturing, processing, packing, holding, and distributing all biological and drug products manufactured at that facility. The company may, however, manufacture products deemed medically necessary.

Examples of potential deviations from current good manufacturing practices found by FDA inspectors include the following:

- in-house-developed software that had not been validated being used for performance of finished product testing;
- often incomplete and sometimes inaccurate calibration and preventive maintenance records;
- reports of problems with plasma products after distribution not being reviewed and investigated in a timely manner;
- undetected or not corrected deviations found in viral inactivation processes used on several lots of factor VIII;[11]

[11]Factor VIII is the antihemophilic factor concentrate used to treat hemophilia A bleeding episodes.

- no validation of reprocessing steps used for repooling of albumin product lots that failed final container testing for sterility;

- no validation of the cleaning process and removal of cleaning agent residues from fractionation kettles, bulk tanks, buffer tanks, or centrifuge bowls; and

- no validation of albumin manufacturing processes and final products that did not consistently conform to the release specifications. In 1997, 54 percent of albumin lots for one company failed final container inspection because of visible evidence of protein material.

To overcome these problems, the major fractionation companies have taken certain steps, such as increasing quality assurance and quality control and production staff and training, implementing capital investments at the fractionation facilities, and validating equipment processes. Many of the facilities slowed production as the firms reallocated resources to work on their corrective actions.

In addition, FDA has taken several actions within the last year to better ensure manufacturer compliance with current good manufacturing practices. In a previous study examining the safety of the blood supply, we found inconsistencies in FDA's inspection practices. As a result of this and an Office of Inspector General study examining FDA's regulatory role in the field of biologics, FDA adopted a new inspection program Under this program, FDA has designated two groups of investigators: one to focus on blood banks and source plasma collection centers and another to focus on plasma fractionation and manufacturers of allergenic products, therapeutics, licensed in vitro diagnostics, and vaccines. This approach is intended to ensure that all FDA current good manufacturing practice inspections are conducted by a single agency unit using a similar approach. If properly implemented, these actions by plasma manufacturers and FDA should help alleviate the problems related to adherence to current good manufacturing practices and quality assurance.

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.

(108384)

Mr. SHAYS. Thank you.

Doctor? You don't always wear your uniform. What is going on?

Dr. FRIEDMAN. Two things. It is Wednesday; and the second is, since I have accompanied Dr. Satcher last time in uniform, it seemed consistent.

Mr. SHAYS. I treated you better, that is what happened.

Dr. FRIEDMAN. Mr. Chairman and members of the committee, with me today is Mr. Ron Chesemore, our Associate Commissioner of Regulatory Affairs; Dr. David Feigal and Dr. Jay Epstein from our Center for Biologics Evaluation and Research.

We appreciate this opportunity to once again come here and discuss these important issues. We are prepared today to focus on three main topics.

First, the serious issue of continuing shortages of immune globulin, intravenous preparation, IGIV; and second, to update the FDA compliance program, that program that helps assure the safety of blood and plasma derivatives; and, third, to cooperate with the General Accounting Office in discussing their report on blood plasma safety and plasma donors. These are all important and complex issues, issues which have garnered the attention of this committee on previous occasions.

As you well recognized in your opening remarks, FDA must balance the need to assure the quality of blood and plasma products with a need to maintain an adequate supply of these life-sustaining therapies. The tension created by these two interests can be a formidable challenge, and while I recognize at this time there continues to be shortages, I believe very strongly that the agency must maintain a comprehensive regulatory approach that assures that the industry follows the good manufacturing practices that are necessary to produce high-quality products. Only in this way can future supplies of high-quality products be assured.

There is a shortage of a number of plasma derivatives, particularly IGIV, but not exclusively IGIV. A contributing factor has been the production problems encountered by several plasma manufacturers that have resulted in the compliance actions that we have just heard about.

One of the more recent and concerning problems has been with Centeon Corp., headquartered in Pennsylvania, a major manufacturer of plasma products. In a consent decree last year, Centeon agreed to sharply curtail production and distribution of most of its plasma products until it came into compliance with good manufacturing practice.

This spring, FDA testified that it expected the shortage of IGIV to be alleviated once Centeon resumed full production at its previous capacity. Despite the agency's belief that the company was making important steps on the road to compliance, the latest comprehensive FDA inspection revealed concerns that have just been enumerated. The company failed in several critical GMP areas, including quality assurance investigations, laboratory controls, equipment and process validation and production and process controls.

Consequently on August 13, 1998, FDA presented to Centeon a letter requiring it to take specific action under the consent decree to correct these violations. We met with the company leadership in a very serious and sober and I think a very thoughtful discussion.

The agency is now evaluating the company's response. We are permitting the company to continue producing, on a selective basis, medically necessary products, including IGIV. This action is consistent with FDA's policy of carefully considering the impact of its regulatory actions on product availability. We will exercise the discretion, balancing all of the factors, permitting the manufacturer of a medically necessary product to continue manufacturing.

Under some circumstances, the FDA will permit the continued manufacture of the critical product even while regulatory action against the firm proceeds. And again I want to stress the seriousness of the commitment that was given to us by the leadership of the Centeon company.

Despite this exercise of discretion, FDA is aware of IGIV shortages as well as possible future shortages with several other plasma derivatives. FDA anticipates that the IGIV shortage will continue as long as production levels do not meet or exceed previous years' levels.

Since May, when Dr. Satcher and I described the IGIV shortage as it existed at that time, FDA has taken a number of actions to try and address and, if possible, alleviate it. FDA is working with the plasma industry to alleviate shortages, including expediting lot release for IGIV, monitoring the shortages, working with health professionals to identify needed supplies. We continue to feel that the plasma industry needs to aggressively comply with good manufacturing practices standards in order to meet the medical demands.

In April the department's Advisory Committee on Blood Safety and Availability made several recommendations that may help alleviate the shortages.

You, sir, have discussed the impact of the Creutzfeldt-Jakob Disease restrictions that had been in place. Those restrictions Dr. Satcher announced will be relaxed in the future. We are also looking at ways in which we can work with the industry to better foster the necessary supplies.

On August 27, Dr. Satcher made his announcement concerning CJD. We hope to see the effects of that in the future. This policy change was deliberated very carefully and extensively within the Health and Human Services, and was the subject of two meetings of the Public Health Services Blood Safety Committee. Epidemiologic studies of humans over the past two decades have failed to demonstrate even a single case of blood transfusion causing CJD infection. Based upon that, the risk is thought to be very low and possibly even nonexistent.

Conversely, we recognize that removing plasma products because of CJD has caused shortages with real medical consequences. Our policy regarding CJD has been a contributing factor to the shortage of IGIV. Multiple lots have been quarantined or withdrawn because of donors who, after donation, were identified of being at risk of or having developed CJD. This new recommendation, once fully implemented, should help the present supplies of CJD and other derivatives.

Let me briefly turn to the GAO report. There has been concern that there may be an increased risk of infection from plasma collected from paid donors compared to unpaid donors. GAO evaluated

the risks of infectious agents, including human immunodeficiency virus, hepatitis B and C, and found that paid and unpaid donor populations have different viral marker rates. We generally agree with these findings. As the GAO has shown, viral marker ratios for both paid and unpaid donors are such that some viral contamination is possible with all plasma lots, both from paid and unpaid donors.

We believe that GAO's analysis shows that the risk of contamination of plasma pools from paid versus unpaid donors is very similar, although there is a slight increased risk from the paid donors. The implications of viral marker rates in paid donations have been considered by FDA for a number of years. We believe that direct comparison of viral marker rates does not adequately or fully measure the risk of contamination in the final product since, as was just discussed, the techniques for clearing these products of infectious units can be enormously effective.

In the end, it is critically important that plasma fractionators adhere to good manufacturing practices, for exactly the reasons that have been mentioned by both previous speakers, that eliminate or inactivate viruses. In addition, we believe that it would be counterproductive to further restrict the donor pool to unpaid donors entirely when such a restriction would unlikely improve the safety or even the availability of products. This same conclusion was reached independently by experts in 1993 and 1996 at national and international workshops.

The safety of the blood supply and products from blood and plasma remains one of FDA's highest priorities. Working with this committee, Mr. Chairman, the agency has significantly improved and continues to address the need for increase in its vigilant oversight of good manufacturing compliance by the plasma fractionators, and the agency is doing everything within its power to help alleviate product shortages.

As the industry moves toward aggressively implementing the quality improvement and quality assurance programs, shortages and occasional disruptions may continue to occur but will, I think, be addressed ultimately when these good manufacturing practice are completely complied with.

We appreciate being here again, sir, and I look forward to answering your questions.

[The prepared statement of Dr. Friedman follows:]

I. INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Michael A. Friedman, Acting Commissioner of Food and Drugs (FDA or the Agency). I appreciate this opportunity to discuss the General Accounting Office (GAO) report: "Blood Plasma Safety: Plasma Product Risks Are Low If Good Manufacturing Practices Are Followed" which reviewed the viral marker rates of paid versus unpaid donors. As requested, I also will update the Committee on the status of FDA's regulatory compliance program which helps assure the safety of blood and plasma derivatives through the application of good manufacturing practices (GMP) as well as the continuing shortage of immune globulin, intravenous (Human) (IGIV), the subject of the subcommittee hearing on May 7 of this year.

II. BACKGROUND

For the millions of Americans with certain medical needs, whole blood and plasma derivatives are essential for preserving their life or for maintaining a normal quality of life. These patients expect that the products will be free of infectious disease and effective for their intended use. Fundamentally, it is the role and responsibility of industry to provide adequate and safe products. FDA has a responsibility to help ensure that these patients' expectations of safety and availability are fulfilled

by our oversight of blood and plasma collection, processing and manufacturing facilities, as well as through product approvals and surveillance.

While the United States is recognized as having one of the safest blood supplies in the world, assuring the safety and availability of blood products still poses formidable challenges. While humans are the source of plasma, humans also are potential carriers of many transmissible diseases. From the collection of source and recovered plasma from donors, through the fractionation and manufacturing process, to the quarantine and retrieval process, there are numerous points at which safety measures are in place to minimize the risk of exposing recipients of blood products to infectious agents. FDA views the entire process as a continuum of interrelated steps. At each one of these steps, the Agency has recommended or required safety mechanisms to decrease the risks associated with the use of blood products.

The technology associated with disease detection in blood and plasma donors is continually improving, but is not perfect. The number of blood and plasma donors, while adequate to meet present needs, is not unlimited. Further improvements in efficiency, capacity and quality in the manufacturing process are possible, but often take significant time to accomplish and the commitment

of major resources by an industry that often is resistant to change.

In this process, the Agency deals with competing interests in effecting its regulatory compliance program. Product safety must be maximized, but an adequate supply of lifesaving blood products needs to be available. The balance of these two interests can be very difficult to achieve and is often precarious at best.

There is no question that a shortage of plasma derivatives still exists, particularly of IGIV. This shortage situation was described in detail this past May 7 before the Committee by Dr. David Satcher, Assistant Secretary for Health and Surgeon General, Department of Health and Human Services (DHHS) and myself. Since that hearing, FDA has taken a number of actions to try and alleviate the shortage. Simultaneously, however, FDA continues to demand the highest level of compliance from the plasma industry. Actions taken by the industry have had, and will continue to have, an impact on product availability.

III. UPDATE ON FDA INSPECTIONS AND REGULATORY OVERSIGHT

Since 1996, FDA has strengthened its oversight of the fractionation industry. As elaborated upon last year in the June 1997 hearing held by your subcommittee, FDA transferred lead responsibility for periodic inspections of fractionators

(manufacturers who further process plasma and other blood derivative products) from The Center for Biologics Evaluation and Research (CBER) to the Office of Regulatory Affairs (ORA) in 1996. Along with that transfer of the lead responsibilities in inspections and field emergency response, FDA also adopted a new model and approach, called Team Biologics, to the inspection of plasma fractionators.

Under Team Biologics, FDA has established a partnership between ORA and CBER which utilizes the diverse skills and knowledge of both ORA and CBER staffs to focus Agency resources on inspection and compliance issues in the biologics area. The goal of Team Biologics is to assure the quality and safety of biological products and bring product manufacturers into compliance. To accomplish this a cadre of investigators has been created that is more specialized and technically prepared to inspect fractionated product facilities and other biologics establishments. This specialized investigator cadre has access to a similarly specialized group of compliance officers for guidance, support and counsel on evidence development and assistance in drafting any required administrative or regulatory action documents. Likewise, a specially trained cadre of investigators has been established to inspect blood banks and plasma collection facilities.

This new approach emphasizes a more complete assessment of compliance with GMP. In addition, the approach includes a more detailed assessment of the manufacturer's procedures in handling and investigating reports of adverse experiences and subsequent FDA notification of these adverse experiences. FDA has taken strong steps to assure compliance of the plasma industry with GMP through court injunctions and warning letters.

A. PRODUCT AVAILABILITY/SHORTAGES

As part of the FDA enforcement program, FDA carefully considers the impact of regulatory actions on product availability. FDA takes regulatory action when it believes that products are violative and could compromise the public health. FDA will exercise enforcement discretion when appropriate. For example, if the Agency determines, after balancing all the factors, that halting the manufacture of a "medically necessary product" could cause harm to patients, FDA can permit continued manufacture of the critical product even while regulatory action against the firm proceeds. Each case has to be evaluated on its own merits weighing the need for the medical product versus the risk of use of a product manufactured outside the parameters of GMP. In no instance, however, would FDA authorize release of a product known to be contaminated or potentially unsafe.

In the case of plasma manufacturers, FDA faces a very difficult task. In many cases, the plasma industry lags behind the drug industry in compliance with GMP. As FDA has acknowledged over the past year, and in testimony before this committee, past regulatory efforts with the plasma industry were not as rigorous and exacting as they could have been with respect to GMP. Not all plasma fractionators have accepted FDA's increased surveillance and oversight. Until the plasma industry accepts that GMP are essential to safe, high quality products, the manufacturing operations will continue to be out of compliance, often necessitating enforcement actions that potentially threaten product supply.

In May, I testified that FDA anticipated some relief in the shortage of IGIV based on the assumption that Centeon would resume production of IGIV at its previous capacity. Centeon is subject to a court order in the form of a consent decree with FDA that requires significant improvements in GMP. Pursuant to the consent decree, the company resumed production based on its initial efforts to comply with the consent decree, which required improvements to quality assurance, including the hiring of third-party consultants to evaluate and improve Centeon's quality assurance programs. Despite FDA's belief that the company was on the road to compliance, the first comprehensive inspection of the company to determine compliance with the consent decree revealed otherwise. The inspection revealed inadequacies in several

critical areas including: quality assurance, failure investigations, laboratory controls, equipment and process validation, and production and process controls.

Consequently, it was necessary for FDA to require Centeon, by notice dated August 13, 1998, to take specific action under the consent decree to correct these violations. As this testimony was being prepared, the Agency was evaluating the company's response to FDA's August 13 letter and the plans to address the specified violations.

Although Centeon continued to be out of compliance, FDA has advised Centeon that it can continue to produce medically necessary products for the time being, including IGIV, under certain conditions. At this time, FDA is still working with the company to determine the company's final response to FDA's August 13 letter and the ultimate impact on the availability of the products it produces.

B. IGIV SUPPLY

At the present time, FDA continues to be aware of IGIV shortages as well as shortages and possible shortages of several other plasma derivatives, including albumin and clotting factors. FDA anticipates that the IGIV shortage will not be alleviated and will continue as long as production levels do not meet or exceed

previous years' levels. FDA has acted affirmatively to assist the plasma industry to alleviate shortages and is exploring other alternatives to address shortages. FDA has continued to expedite lot release for IGIV; monitored the shortages through data submissions; and worked with health professionals to identify needed supplies.

FDA believes that the plasma industry also needs to act more aggressively to comply with GMP while maintaining adequate production to meet medical demands. FDA will not and can not relax GMP standards for this industry. While FDA would prefer not to allow products manufactured under inadequate GMP to be distributed in the marketplace, the Agency appreciates the risk to patients of not obtaining product and, where the safety of the product can be assured, will exercise enforcement discretion in a manner that accommodates both priorities.

On April 28, 1998, the DHHS Advisory Committee on Blood Safety and Availability (Advisory Committee) considered the issue of shortages of plasma derivatives and issued a number of recommendations. One recommendation was that FDA and industry should collect and disseminate standardized information on production, distribution and demand for a number of plasma derivatives. FDA has asked industry for monthly data on product supplies, although there has not been final agreement about the terms and extent of data collection and sharing. Another

Committee recommendation was for FDA and industry to explore the possibility of importing supplies of IGIV and Immune Globulin Intramuscular (IGIM). FDA has explored this issue and various concerns need to be resolved involving GMP and plasma collected abroad.

The most important action, however, has been the recommended change in policy on plasma derivative product withdrawals because of concern regarding transmission of Creutzfeld-Jakob (CJD) disease. On August 27, Dr. Satcher announced at the DHHS Advisory Committee that he supported a modification of the current recommendation on quarantine and withdrawal of blood and plasma derivatives due to the theoretical risk of CJD. The new policy recommends withdrawal of plasma derivatives only if the blood or plasma donor develops new variant CJD (nvCJD). FDA presently recommends the withdrawal of blood and plasma derivatives when there is any evidence in a donor of classical CJD or CJD risk factors. The policy change was deliberated carefully and extensively within DHHS and was the subject of two meetings of the Public Health Service (PHS) Blood Safety Committee. The scientific deliberations considered a number of factors before recommending the policy change. Most importantly, epidemiological studies of humans over the past few decades have failed to demonstrate a single case of blood transfusion causing CJD infection. Based upon that, the risk is thought to be very low, and possibly non-existent. Conversely, withdrawal of plasma

derivatives has caused harm to the public health due to product shortages.

FDA's policy regarding CJD has been a contributing factor to the shortage of IGIV. Multiple IGIV lots have been quarantined or withdrawn because of donors who, after donation, were identified as being at risk of, or as having developed, CJD. Substantial amounts of intermediate product, not yet processed into final products, also were affected by the withdrawals and placed in quarantine.

The Agency anticipates that this new recommendation, once implemented by industry, should help minimize the present shortages of IGIV and other plasma derivatives, although the change will not resolve the shortage situation.

III. VIRAL MARKER RATES/DONOR SCREENING

Although the final safety step of viral inactivation/removal is the most important mechanism which assures the safety of plasma derivatives, the initial step in the process, namely donor collection, also plays a critical role in product safety. GAO evaluated this first step to determine the risk of infectious agents including human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) from unpaid versus paid donors being incorporated into the manufacturing process. The

Agency generally agrees with the findings relating to the viral marker rates of donors made by GAO in its report. In particular, FDA agrees that the data presented demonstrate that the paid and unpaid donor populations, whose plasma is used for manufacture of fractionated products, have different viral marker rates. FDA believes, however, that GAO's analysis shows that within the error of estimation, the risk of contamination of plasma pools from paid versus unpaid donors is comparable as a result of donor screening and testing, and inventory hold procedures implemented by the source plasma industry.

There have been various studies[1] conducted to assess the extent of the differences in the viral marker rates of paid versus unpaid donors. As might be expected, the studies show different results depending upon the design of the study, the region where the study was conducted and other variables. Various differences between procedures for collection of source plasma versus recovered plasma make direct comparison of marker rates difficult. For example, the differences in frequency of donation

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[1] California Department of Health Services, Office of AIDS (various studies analyzing data from California Blood Banks and Plasma Centers on HIV-1 and HIV-2 prevalence rates of California blood donors in 1995 and 1996); Schreiber, Busch, Kleinman and Korelitz, *The Risk Of Transfusion-Transmitted Viral Infections*, The New England Journal of Medicine, Vol. 334, No. 26 (June 27, 1996); Kleinman, Busch, Korelitz and Schreiber, *The Incidence/Window Period Model and Its Use To Assess The Risk OF Transfusion-Transmitted Human Immunodeficiency Virus and Hepatitis C Virus Infection*, Transfusion Medicine Reviews, Vol. 11, No. 3 (July 1997).

of whole blood versus plasma affects the calculation of the viral marker rates. While the various studies are instructive, none should be interpreted as an absolutely accurate measure of viral marker rates nationwide.

The implications of viral marker rates in paid donations have been considered by FDA for a number of years. On June 28, 1993, FDA sponsored a Workshop on Safety of Plasma Donation as part of the June 28 and June 29 Blood Product Advisory Committee (BPAC) Meeting. FDA asked committee members to review whether source plasma and recovered plasma were comparable with regard to the safety and efficacy of plasma derivatives produced. The safety of plasma derivatives also was reviewed at the International Conference on the Virological Safety of Plasma Derivatives in November 1996. FDA again brought the issue of viral marker rates to the BPAC on March 19 and 20, 1998, and asked for a similar review based upon additional data and changes in the plasma industry, including implementation of PCR testing and new donor management practices.

Direct comparison of viral marker rates, therefore, does not measure either the differences in the underlying donor populations or the residual risk to plasma pools. FDA concurs with GAO's models for estimating the incidence of infections in the populations and the risk after donor selection and screening.

It needs to be recognized, however, that these calculations have a wide margin of error.

The Agency believes that management and analysis of viral marker rates should be considered in the broader context of implementing strategies for reducing risk, including developing improved donor screening processes, additional and more sensitive testing methods, improved viral clearance procedures, and reducing pool size. If an opportunity exists to make the ultimate product safer by addition of tests in the initial stages of plasma collection these tests should be utilized. More importantly, plasma fractionators must adhere to GMP to ensure the safety of products. Presently, however, it makes no sense to further restrict the donor pool to unpaid donors given the need for plasma for manufacturing needed products when there is no evidence that safety of the products would be enhanced. This same conclusion was reached independently by experts in 1993 and 1996 at national and international workshops.

It is, of course, highly desirable to collect plasma from disease-free individuals, whether paid or unpaid. Collection establishments assess for risk factors for blood borne diseases by interviewing potential donors for high-risk behavior and for symptoms of disease. Based on this information, donation facilities eliminate individuals with higher risks for disease, although this process also eliminates many healthy potential

donors. Donor screening criteria identify behavior that correlates with higher risk for disease and higher risk of contaminated blood. For example, FDA has recommended that prisoners not be used as donors because it has been found that a high percentage of all prisoners are drug users. Thus, although in the past blood and plasma were allowed to be colleted in prisons, that is no longer the case. It is difficult, however, to identify and isolate other large segments of society that may be high risk, thus selection must be done on an individual donor basis.

IV. PLASMA POOLS

In order to manufacture sufficient quantities of plasma derivatives, most manufacturing facilities are designed to work on a large production scale, using large plasma pools. These plasma pools are derived by combining units from thousands of individual donations. The number of units combined into a common mixture for processing is known as "pool size."

A major recent advance in assuring safety of plasma derivatives is gene amplification based testing by polymerase chain reaction, or PCR. After individual units are collected and the marker positive units eliminated, the plasma industry now combines several hundred units into mini-pools for further testing by newer methods that are not yet feasible to use on individual

donations. These mini-pools are tested with a very sensitive means of detecting infectious agents -- nucleic acid techniques. While there are a variety of nucleic acid techniques, the most promising is PCR testing. This technology can detect very minute levels of nucleic acids, which are genetic building blocks for infectious agents such as HIV and HCV and for all organisms. If this testing detects the presence of an infectious agent in the mini-pool, the individual positive unit can be identified and eliminated from further processing. Units that are marker negative based on testing in mini-pools are then combined into a larger pool. This larger pool is used as the starting material which will be separated, or fractionated, into various components that will eventually become finished products such as albumin, clotting factors, immune globulins, among others. Because this technology is more sensitive than some current screening, PCR testing leads to better detection and elimination of most window period donations from the plasma pool. This greatly decreases, if not eliminates, the viral load, or the number of infectious virus particles, in a plasma pool. Although current viral inactivation/removal techniques have a capacity that greatly exceeds the anticipated viral load in a plasma pool, further reductions in viral load only can be viewed as positive measures, which add to assurance of safety.

Another means of managing risk is to limit the pool size. The potential benefit of limiting pool size is that the infectious

risk for infrequent users would be reduced in instances where the prevalence of the infectious agent is low. Reduction in pool size also might lessen the impact of recalls and withdrawals on supply of the products. In setting upper limits on pool size, however, potential adverse consequences also must be considered. With small size batches, quality monitoring and release testing could consume a large portion of the batch. Smaller pool size, and therefore smaller batch size, in existing plants may result in sub-optimal processing and decreased overall product availability.

This Committee has considered issues related to plasma pool size in its ongoing oversight activities concerning blood safety issues and recommended limitations on pool size. FDA is now developing guidance on limitations to plasma pool size which is expected to be issued in the near future.

V. VIRAL INACTIVATION

Since the initial safety steps of eliminating blood possibly contaminated with infectious agents is imperfect, the most critical safety step remains viral inactivation. The risk to a patient from any particular agent may vary with the particular plasma derivative. Thus, FDA believes that all human plasma derivatives should undergo viral inactivation or removal procedures to ensure safety. FDA has been moving progressively

toward this goal even for products that never have been documented as transmitting viral agents. Most plasma derivatives already are processed specifically to inactivate or remove many viruses. There are highly effective mechanisms for removing or inactivating lipid enveloped viruses such as HIV, HBV, and HCV. The technology to inactivate heat stable, non-lipid enveloped viruses, such as the Hepatitis A virus, or agents such as CJD while preserving the functions of plasma proteins, however, currently is not available.

While all the above safety measures enhance the reduction of risk, without adequate viral inactivation, the other safety measures will not provide the measure of assurance that is necessary for public safety. The application of GMP to this process is particularly important. If viral inactivation and removal processes are not carried out in accordance with GMP standards, the companies will not be able to provide the necessary level of assurance that the finished product is safe.

VI. EMERGING INFECTIONS PLAN

The greatest threat to the blood supply is posed by unknown or emerging agents that may not be inactivated or removed during processing. Realizing that there constantly will be emerging infectious agents which pose threats to the safety of the blood supply, FDA is committed to developing a strategy for each

identified emerging infectious agent. The Agency is engaged in the scientific investigation of emerging infectious agents, which includes surveillance, methods and standards development and regulatory controls.

In 1997, DHHS organized a Committee on Emerging Infectious Diseases (Committee) comprised of representatives of the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and FDA. The Committee has developed a plan for evaluating and managing any emerging infection with the potential to threaten the blood supply. The Committee also has developed a database of known emerging infectious agents that might threaten the blood supply. This database is updated as new information is obtained. The response to a potential threat falls into four phases. First, epidemiologic characteristics of the agent will be identified and its transmissibility by blood ascertained. This process may involve field investigations, seroprevalence studies (if it is a known agent) using banked and acquired specimens, literature reviews and consultations with outside experts. Second, the Agency will undergo extensive laboratory investigations, including, as necessary, attempts to grow the agent, to infect laboratory animals, and contribute towards the development of serologic and gene based amplification assays. In addition to the laboratories of the PHS agencies, assistance may be requested from outside laboratories that have the appropriate expertise either through collaborations or by supplementation of

existing grants. Third, FDA will issue recommendations to blood establishments for donor screening and deferral. Fourth, PHS will establish emergency communications to enhance coordination and interact with State and local health departments and blood organizations.

The Committee has been holding regular quarterly teleconference meetings and ad hoc meetings. The FDA BPAC and PHS Blood Safety Committee have been informed on a regular basis of updates and initiatives undertaken by this Committee. FDA also regularly interacts with patient groups, academicians and industry scientists to remain current with outstanding issues of concern and technological advances.

There are a number of examples of emerging threats for which FDA has been actively involved in developing a response. For example, Chagas disease, caused by the parasite *Trypanosoma cruzi,* while endemic in South and Central America, has become an emerging threat in North America. This parasite is transmitted through blood transfusion, although fortunately there only have been four cases of this disease caused by transfusions in North America. FDA is monitoring several large-scale clinical trials being conducted in blood banks in the United States using experimental assays to detect infection of the parasite.

Some emerging threats do not come from newly characterized infectious agents, but rather from variations of well known infectious agents. An example of this is HIV-1 Group O that was identified for the first time in 1996. In July 1996, FDA requested manufacturers of HIV test kits to modify their kits for enhanced sensitivity to Group O. Later that year, FDA advised blood and plasma establishments to add to their donor deferral criteria histories of risk factors associated with geographical areas in which Group O is endemic.

Identification of a new emerging infection will depend heavily on the recognition by the epidemiology community of new trends in data. While it is possible that viral marker rates may assist in identifying certain trends there is no present identifiable correlation that will assure that certain viral marker rates will lead to the identification of presently unknown infectious agents. It is just as possible that there will be no correlation. Populations at increased risk for known agents, however, are appropriate to monitor for emerging agents.

VII. CONCLUSION

FDA maintains as one of its highest priorities assuring the safety of the blood supply and blood and plasma derivatives, including vigilant oversight of GMP compliance by the plasma fractionators. The Agency also will continue to do everything

within its power to help alleviate product shortages. Unless industry moves forward aggressively with its quality improvement and assurance efforts, however, shortages and occasional disruptions in the distribution of needed products will continue to occur. We will continue our efforts to assure the safety and availability expectations of patients who need these critically important products.

Mr. SHAYS. Thank you.

Dr. Friedman, the first hearing I think we had on blood safety dealt with HIV and an infectious agent that we really didn't know much about at the time, but we all realized that once we had indications that we had a problem, we didn't deal with it quick enough, and a number of people became infected. In the process of that hearing, we also learned about concern about hepatitis B and this hepatitis strain that we now name C.

At one of the hearings, we thought there were 400,000 that were infected with hepatitis C, and now we know it is somewhere close to a million, through the blood.

I feel like in the 3 years, that there has been movement but rather slow. And I am just interested, since you brought hepatitis C up, before I get to my other questions, if you would tell me where we are at.

Dr. FRIEDMAN. I will be happy to. I will ask my colleagues to help me address this as well.

As you recall the commitment given by Dr. Satcher, not just on the part of FDA but on the part of the entire Department of Health and Human Services, indicated a serious organization-wide commitment and a look-back campaign.

Mr. SHAYS. Is that sputtering?

Dr. FRIEDMAN. No. If I implied that——

Mr. SHAYS. I am not aware, after the major announcement by Dr. Satcher, what we have been doing since then.

Dr. FRIEDMAN. I can say that he has assigned several activities to different portions of the Department of Health and Human Services. I can't speak definitively about all of that, but let me give you a sense of the global nature of that. For example, there is a serious effort ongoing, which I believe is more than halfway complete, of providing physicians in the United States with educational materials about hepatitis C and activities associated with the diagnosis and treatment. If I am correct, roughly half of the physicians have been mailed a full educational packet.

Mr. SHAYS. That part was done. What about the hospitals? What information—are they going over their records?

Dr. FRIEDMAN. Yes, sir. My understanding, and I will ask Dr. Epstein to please fill in on this, is that medical facilities have largely completed record reviews to identify the banks of patient names who would be considered for the look-back policy. Maybe I can ask you to elaborate.

Dr. EPSTEIN. FDA published a guidance in March of this year which directed the blood organizations to identify the units where the donor subsequently was learned to seroconvert to hepatitis C. The process of tracing those records, we believe, has been ongoing since that time. The notifications to the recipients——

Mr. SHAYS. Why do you believe that?

Dr. EPSTEIN. We have been told that by the industry.

Mr. SHAYS. What documentation have they provided?

Dr. EPSTEIN. I don't believe that we have any such statement in writing. We will follow with enforcement oversight after we publish regulations. In the meantime, we have issued a guidance.

Mr. SHAYS. When will regulations be published?

Dr. EPSTEIN. I am not sure that I should be answering that. Perhaps Dr. Zavagno can.

We are in the process of developing a proposed rule that will have to be cleared by the Department, by OMB before it can be published for comment, and we would follow with a final rule. We are trying to achieve a timeframe of publishing a final rule within about a year's time.

Dr. FRIEDMAN. That formal rulemaking process is necessary, but we are moving forward with other parts of the Department and with the industry to identify these individuals, to begin the educational effort, because this notification doesn't need to wait for that activity. It is my estimation that that will begin relatively quickly.

Mr. SHAYS. Has any blood recipient yet received a letter informing him or her of possible infection?

Dr. FRIEDMAN. Not that I know of, sir.

Mr. SHAYS. It seems to me that we are moving rather slowly.

Dr. FRIEDMAN. I would like to take that as a question that we will respond to you with. I will have the Department provide an overview of that.

Mr. SHAYS. To move on, what is the current compliance rate of the plasma fractionation industry with what we call the good manufacturing practices requirements? What is the compliance rate?

Dr. FRIEDMAN. I would ask Mr. Chesemore to please respond to that.

Mr. CHESEMORE. Mr. Chairman, this fiscal year the compliance rate of those firms which we have inspected, which is approximately 20 firms at this time, has been—55 percent have been within compliance; 45 percent we would classify as out of compliance.

Mr. SHAYS. That seems like a low compliance rate and a high noncompliance, but are we straightening out gnats and swallowing camels? If it is a technicality, is that called noncompliance?

Mr. CHESEMORE. I would say two things, Mr. Chairman. One is if you look at a similar percentage in fiscal year 1997, the out-of-compliance rate was approximately 60 percent. So now it is 45 percent. That is an improvement.

The other thing is, we are talking here about what I would characterize as serious deviations from good manufacturing practices. They are not small, technical violations.

Mr. SHAYS. With the drug industry, what would your compliance rate be expected, what would you expect it to be?

Mr. CHESEMORE. I would like to provide a more accurate statement for the record, but it is approximately, I would say, about 15 percent out of compliance.

Mr. SHAYS. So 85 percent in compliance?

Mr. CHESEMORE. Eighty-five percent in compliance.

Mr. SHAYS. I just get the feeling that the relationship with FDA—the way that it comes across to me is that you all seem to have a lot of confidence in the industry, and so if they say they are doing something, even if it is not in writing, you accept it, and I don't know why.

Dr. FRIEDMAN. If I may respond, I am not sure that is an entirely accurate portrayal. I do think—and there is a tension that I would like to describe. The tension is that working with the regulated in-

dustry, for whatever product it is, we think that a collaborative, cooperative, disciplined, serious relationship is the kind of relationship to have. It is not what has sometimes been described as a cozy relationship or a blind-eye relationship, but it is not an adversarial relationship unless it need be. I think the best way that we can accomplish what the American public wants is to work cooperatively.

Having said that—and there are dangers in oversimplifying and generalizing, and I don't mean to do that—but this is an industry where we have had difficulty reaching agreement on the importance of good manufacturing practices in the past. What impresses me is the point Mr. Chesemore made, which is, if you look at particular firms, you will see that their inspection—that the success of the inspections has moved up for selected firms; that individuals have understood the importance of GMP's, and their subsequent inspections have been better and better.

We believe that this is a trend that is moving forward. It is not moving forward as speedily as you or we would like. It is not as complete as you or we would like, but we think that there is important progress that is made. We accept the word of the companies, but I don't think that has diluted at all the intensity of our inspections.

Mr. SHAYS. Let me ask GAO's response to a 50 percent compliance.

Ms. STEINHARDT. Well, I was actually very interested in the rates. But let me share with you, I read over the inspection reports which accompanied these findings, the ones that I cited in my statement, and these were not minor paperwork kinds of infractions. These were very serious and systemic. They described problems across the board in manufacturing, in a series of manufacturing processes—and these are not the kinds of problems that could be corrected overnight. I mean, it was not difficult to understand why, following an inspection report like the one that was prepared after the—or during the Centeon inspection—it was not difficult to understand why the company might choose to shut down its whole operation to try and address some of those problems. So it is not just the compliance rate or noncompliance rate. I think it is important to understand that in this industry, the kinds of violations that FDA inspectors observed were very, very serious.

Dr. FRIEDMAN. If I may add one other thing, it was very interesting to me that the new chief operating officer of the Centeon Corp. came and spoke to us. He described the problem that he was encountering was a cultural problem. I am reinforcing what GAO is saying here. It was nonattention to important details.

Mr. SHAYS. Let me recognize Mr. Kucinich, and maybe he can ask you that question he asked under his breath.

Mr. KUCINICH. Thank you, Mr. Chairman. What do you mean by cultural problem?

Dr. FRIEDMAN. By that I mean it is the—what I understood him to mean—it was the attention to details, the viewpoint in doing everything possible to investigate problems, to resolve problems and to prevent problems from occurring.

If I may give you an example, in a certain piece of equipment, a residue was found on the bottom of that piece of equipment. That residue was cleaned up and nobody asked the question, where did

it come from? Did a vial break? Is there something wrong with this equipment?

That is the sort of cultural issue. You don't want somebody to just clean it up. You want somebody to say, did a problem occur? How did it arise? How can I prevent it and how can I fix it?

It is a more aggressive, overall commitment to quality. This chairman gave us his personal commitment to wanting to instill that sort of a culture. We told him that we thought that was entirely appropriate. But until that is done, the kinds of issues that GAO is talking about won't be addressed. We are not talking about a paper checklist.

Mr. KUCINICH. Thank you, Doctor. I am just wondering, since this shockingly low rate of compliance is at issue here, it occurs to me that in order to come to compliance, it would be expensive for these companies. I just wonder if profit motive is one of the cultural problems that we are talking about here.

Dr. FRIEDMAN. I can say that I think the most appropriate thing for me to say is that is a question that you should address to the industry. That concern has not escaped us. We have been told that considerable investments have been made, but the thing that influences me in this, sir; is that these are products that we are talking about that are in sometimes desperately short supply, where the price has risen progressively, where if a company were motivated by profit, then having the largest production because the need is a very substantial one——

Mr. KUCINICH. I can see that the FDA is concerned about addressing supply issues. I looked at your statement. Centeon is out of compliance despite repeated efforts. They keep operating. You relaxed restrictions on CJD, so obviously you are very concerned about supply. I congratulate you about your concern about supply.

I do not congratulate you about your concern about safety, because it seems when you decouple the issues about safety, the public has plenty of reasons to be concerned about the blood supply.

Dr. FRIEDMAN. I don't think any of our actions have compromised safety. We have carefully looked at all of the products currently being released. If we have any concerns about the safety of those products, those products are withdrawn and not released.

Mr. KUCINICH. I wish you would have footnoted your testimony with respect to the statement that says, "More importantly, epidemiological studies of humans over the past few decades have failed to demonstrate a single case of blood transfusion causing CJD infection."

That is a remarkable statement because it suggests a pathway for a cure for CJD. Whose studies were they? When were they done? Who did them? I would be very interested.

Dr. FRIEDMAN. I will be happy to supply that. That is information which comes to us from Dr. Schoenberg and others at the Centers for Disease Control. These are studies which have been presented nationally and internationally. If I may, I would be very happy to have them provide to you those data.

May I add one other thing, sir; and that is, we take no comfort from an individual point analysis such as that, and the commitment that we all have made is that we will continue to scrutinize very carefully the people who receive the most blood donations to

see whether any illness, either CJD or some other illnesses, occurred. This is a commitment that Dr. Satcher has made, and one that we strongly agree with.

Mr. KUCINICH. That is interesting. I want to go back over that statement, Mr. Chairman. "More importantly, epidemiological studies of humans over the past few decades have failed to demonstrate a single case of blood transfusion causing CJD infection."

I just wonder what part of the curve you are looking at because, Doctor, as you well know, this particular disease has not been a matter of major public health concern except for the last few years. And for you to talk about the last few decades, I am just wondering how aggressively the medical community and the scientific community was pursuing studies of that, because if you are comparing the last few decades as opposed to perhaps a curve that may not have even begun to peak, you may be looking at the wrong part of the study projectory.

Dr. FRIEDMAN. I think your concerns are very appropriate, sir. Let me answer, and then I will ask Dr. Feigal to amplify.

First of all, there has been real scrutiny of Creutzfeldt-Jakob Disease for a considerable period of time because unfortunately the injection of human pituitary growth hormone did result in cases in people both in the United States and abroad. Additionally, neurosurgical procedures done with the lining of the brain from donors who had CJD have resulted in other countries of Creutzfeldt-Jakob Disease. Luckily in the United States we had good manufacturing practice in place for dura mater. Those have not occurred here. There was a tragic outbreak of more than 60 cases in Japan.

But our Centers for Disease Control have been carefully tracking this for close to two decades. We have looked carefully at those patients with HIV disease and with classic fact rate hemophilia because those individuals received large amounts of blood donations to see if there were any illnesses detected there.

Dr. FEIGAL. I would add to that, the other way that they have looked at this, they have worked backwards. They have taken a look in many countries at patients who have had CJD disease to see if they were more likely to have any type of blood exposure. So the combination of not finding frequent or excessive blood use in patients with CJD, of not finding the disease in patients who frequently get blood products, and the knowledge that we have been able to detect it when it has been transmitted through medical problems in the past, at this point leads to the overall statement that we are unable to find documented cases despite a fairly intensive effort.

Dr. FRIEDMAN. We are committed to continue to look for this, and I can't adequately portray to you the soberness and the intensity of discussions which have taken place within our Department and at various Blood Committee meetings dealing with exactly the kind of concerns that you raise. We do not have all of the information about CJD, and the responsibility that we bear is to be especially careful.

Mr. KUCINICH. I yield back to the Chair but I would like to continue this line of questioning when we come back.

Mr. SHAYS. You can finish up.

Mr. KUCINICH. You have a fact of noncompliance and sloppy manufacturing techniques. How can the public be assured that there is not symmetry between that and the practices which investigate the transmission of viruses such as CJD?

Dr. FRIEDMAN. Your question is a really good one and it is a little complicated, so let me break it into two parts. The first is the confidence that the public should have in the manufacturing processes that exist now. As the chairman has pointed out and as GAO has pointed out and as we agree with, the safety that accrues to the American public is built upon multiple layers of different activities beginning with the screening of individuals who donate the material to the very finished end product. Any one of these steps may be flawed, and yet the overall product may be entirely safe because there is considerable redundancy and fail-safe mechanisms put in place. I am not comfortable with that and you are not comfortable with that.

Mr. KUCINICH. Let me tell you further why I am not comfortable, because you testified earlier about what you called a collaborative, cooperative, disciplined, not adversarial relationship. Now, there is a certain logic that flows from that, Mr. Chairman, a concern logic which suggests that the regulators and the community being regulated may be too cozy; that in effect the one paragraph in your testimony, "Although Centeon continued to be out of compliance, FDA has advised Centeon they can continue to produce medically necessary products for the time being, including IGIV under certain conditions. At this time FDA is still working with the company."

Now, it seems to me that if you have a consistent lack of compliance—excuse me, I am not a doctor, I am not a scientist, just a public servant from Cleveland, OH—why don't you shut them down?

Dr. FRIEDMAN. I think, sir, that it is a question that we have seriously considered. If we believed that the product that was being produced was risky or harmful, if we had evidence of that, it would not be released. There are patients, ill, sick, and dying because of lack of material. For the theoretical risk of a patient receiving something which may not have been produced under the highest quality, to say to that patient, "You will die because we believe that it is more important to keep records straight than it is to care for you," I think fundamentally moves away from our public health mission.

Mr. KUCINICH. I am touched by your concern for dying people, but I would be more touched if there was a stronger statement from the FDA in support of blood safety.

Dr. FRIEDMAN. Sir, I think it would be a misstatement to say that the agency is anything less than committed to full GMP compliance. We are currently engaged in two consent decrees. These are court orders where we have gone to court to make sure that companies don't do this voluntarily, but that we have the power of the legal system behind us to order third-party inspections, them to hire consultants and do extra special checks.

The reason that we are permitting Centeon to release some materials that are medically necessary is because we have imposed upon them extra layers of inspection, extra layers of third-party in-

spection, not by the company, but by consultants that they must hire that we will then inspect.

I do appreciate your concern, but I think it is very important to understand how committed we are to good manufacturing practice and that we are putting considerable pressure on the industry right at this time.

Mr. KUCINICH. Thank you, Mr. Chairman.

Mr. SHAYS. Mr. Snowbarger.

Mr. SNOWBARGER. I want to go back to the original topic of the report. Ms. Steinhardt, you keep saying that these are not just paperwork kinds of mistakes, and Dr. Friedman indicated they are not that serious because they are paperwork kinds of mistakes.

Dr. FRIEDMAN. If I said that, it was not my intention.

Mr. SNOWBARGER. I didn't think it was, but you said it.

Dr. FRIEDMAN. These are serious mistakes. I said this is not merely a checklist. I think GAO and FDA are in exactly the same place here. These are serious concerns, and I apologize for interrupting.

Mr. SNOWBARGER. That is fine.

Dr. FRIEDMAN. This is so important, I wanted to make it clear.

Mr. SNOWBARGER. Ms. Steinhardt, I would like to know the kinds of violations that were found. I don't care that you identify them with a particular company or anything of that nature. We heard about the residue problem that no one had traced the source for. What are the kinds of issues that to a layman are going to be real significant?

Ms. STEINHARDT. Right. And I read them as a layman. While our report gives the kinds of problems in general terms, I want to give you a flavor of reading a whole inspection report that is not captured in just a summary.

There could be hundreds of different processes that are used to produce a final finished product; am I right? These are hundreds of processes. There were inspection reports that looked at every single one of these processes, and in every single one or at least many of them—I don't know whether it was the universe of processes—there were problems with how well tested those processes were, how well qualified the personnel were who were operating, who were conducting those processes, how well trained they were to carry them out, whether they had ever been validated and proven effective to do what they were supposed to be doing.

And they're—you know, some of the inspection reports are this thick, and they were very to the point. These weren't sort of rambling inspection reports. They weren't about, you know, something that hadn't been checked off. I mean, they were very focused, very disciplined, very structured, and they covered dozens and dozens and dozens of problems, and it was the total effect of these problems that I think is—you know, rather than what each one was, but the total effect of all of these problems that I think led to the kinds of concerns that led FDA to seek court orders for fixes.

Dr. FRIEDMAN. If I may? One of the things Mr. Snowbarger—I'd like to correct a mistake that I made. I said there were two consent decrees. In fact, my staff has correctly pointed out to me there are currently three consent decrees for fractionation facilities. We take these very, very seriously.

Mr. SNOWBARGER. Let me go back and kind of followup on a question that the chairman asked earlier about compliance rates, and, again, I don't necessarily need to know the name of the company, but what's the highest compliance rate that we have within the industry, for a company?

Mr. CHESEMORE. Could I address a couple of issues in responding to this question, and I think perhaps some other issues that Ms. Steinhardt raised? About a year and a half ago, the agency made a collective decision to change the way that we would inspect plasma fractionators by having a group of approximately 15 or 16 of our best investigators who are making these inspections. One of the reasons we wanted to do this was to better ensure consistency of our inspectional approach. And I think that's working quite well. I think it's also one of the reasons that the compliance rate of the industry is what it is. One of the comments made was that we're taking things for granted. My investigators would be very upset with me if they didn't know that just because a firm tells us they will do something, we want to see the data to show that they did that. The compliance rate is established really by not just the number of deviations or violations, but the seriousness of them.

And so there are approximately 26 firms that fractionate products within the United States and abroad, that produce products, that ship products to this country. Three foreign firms are not shipping any products. So that leaves about, you know, 22, 23 firms to inspect. There are four major manufacturers of plasma fractionated products that produce the most. Two of those, as Dr. Friedman indicated, are under consent decree. Very few, I would say maybe 2 of those 20-odd inspections that we made did we find situations so good that we classified that report as no action indicated, in other words, that firm was totally in compliance.

Then you have a range of serious violations, some of which the firm needs to improve, but it's not serious enough where we're going to either send the firm a warning letter or we're going to seek an injunction or some other serious action.

Then at the far end you have these firms that are totally out of compliance as far as we're concerned. They really have major, serious violative situations. We either send them a warning letter that says, basically, if you don't improve your GMP's, then we will possibly seek a court-ordered injunction or perhaps a suspension of your operations.

The other thing with this particular product is simply that the features of fractionation are such that the viral inactivation is very strong. That's fortunate. But still how you make that product day in, day out, lot by lot, that's the thing that our investigators look at, and that's what the GAO has described in their report.

That's a little bit of a long answer. I apologize.

Mr. SNOWBARGER. There ought to be a longer way to ask this question, but I'll ask it very shortly, and if you're not addressing it the way I had in mind, I'll let you know.

Where are we getting the GMP's? I guess I need a little history. I mean, this is an industry that has a history, that's been around a while, that's been making blood products, and I presume that as we got into an era where there seems to be more blood-borne pathogens, that we began to look at it more seriously, and all of

a sudden we are measuring these companies against some industry standards that obviously didn't come out of this industry, or they would have been following those kinds of things all along.

I guess I'm trying to figure out where those standards came from and how we are making that measurement.

Mr. CHESEMORE. There are standards for drug manufacturing, and there are standards for biological products. Biological products are considered drug products, and they should follow the GMP's for drugs as well as biologicals. The set of standards as published in the Federal Register have been around probably since the 1970's.

Mr. SNOWBARGER. But were those for—this is for drugs as a whole, and then we classified——

Mr. CHESEMORE. And they're very general, they're very broad. You should have these types of systems, these types of processes, you should validate that type of thing. Since that time, since the 1980's and in the 1990's, we've added a number of guidances for the industry, both the blood industry and the plasma fractionation industry, because the GMP's are called the current GMP's, and things change. We now know about situations in the 1990's with HIV, et cetera, that we did not know in the 1970's. So these things are taken into consideration, and we do provide then updated compliance guides for the industry to follow.

The other thing I would simply state is that we have changed our inspectional approach in that the same people who inspect the drug plants for GMP's are now inspecting the plasma fractionators for GMP's. So from that standpoint, I think we're getting a more focused view of how the industry complies with GMP's.

Mr. SNOWBARGER. When were the biological products brought under the same standards as the drug manufacturing, or has that always been the case?

Dr. EPSTEIN. Yes, the biological products are subject to the drug GMP's and always have been. The issue has been regarding the inspectional approach. We operate under two acts, and historically the Public Health Service Act, which governed the biologics, had its own structure for dealing with inspections.

What has happened since 1996 is a careful merger of the two systems, taking advantage of the virtues of both, namely the product expertise in the biologics center and the GMP expertise in the field force, which historically had the sole role for inspecting the drugs. So whereas the biologic products were subject to the biologic GMP's in the Code of Federal Regulations as well as the drug GMP's, it's the shift of balance and focus that has changed.

The particular points of importance are the fact that the lead responsibility for the periodic inspecting has been transferred since October 1996 to the field, and as Mr. Chesemore stated, that means that the people who had been doing the pharmaceutical drug inspecting are doing the fractionation inspecting. So there has been a shift of orientation, a shift of leadership and a merger of expertise.

Mr. SNOWBARGER. Not to suggest that we're not using the proper standards, but when we go back to low compliance rates, how much of the low compliance rate is attributable to the fact that we've now, in effect, upped the standards by following them more strictly since 1996 and had the field inspectors—I mean, there was a sig-

nificant drop from 1997 to 1998. I think—I can't remember who mentioned it, but what, a 60 percent noncompliance in 1997 and 45 percent noncompliance in 1998, and how much of this is a matter of the industry catching up to at least new enforcement if not new standards?

Dr. FRIEDMAN. I think a lot of it has to do with the industry's more serious attention to the standards. I think that the standards—in addition to what's been said, the standards were not as clearly defined and articulated for the biologic products as they have been over the past several years. We've changed our means of checking and enforcing compliance. We've put new emphasis on that.

I think that the question that you're really asking is are these the right standards. We constantly re-evaluate them based upon new emerging scientific information. We strongly believe and have advisory committees that have told us that these are the right standards, that this is what the American public expects in terms of a quality product. We know that in the 1970's, for example, there were similar problems with drug manufacturers, where it was difficult to ratchet up their compliance, but they have done so very successfully.

We have seen movement on the part of this industry. We have heard a commitment on the part of this industry. We're going to keep up the strong discipline, the clear message here, and we expect that there will be the same high level of compliance not to our standards, but what the right standards should be.

Mr. SNOWBARGER. I'm not so sure that I'm questioning changes in standards which may be occurring, but it sounds like there has been a significant change in enforcement.

Dr. FRIEDMAN. There has been.

Mr. SNOWBARGER. We allow the industry to get lax, and then all of a sudden we decide to enforce it pretty stringently, and all of a sudden they're surprised that very few are in compliance. I mean, it's the way my kids treat me all the time if I don't make them toe the line, they're going to get away with as much as they can and then move on. And if I say, no, you can't do that, they won't do it.

Dr. FRIEDMAN. I think it's fair to say we paid much more attention over the past 2 years, that we have been much clearer, that we have been much more consistent about this, and that does contribute to the out of compliance rate, you're correct.

Mr. SHAYS. If the gentleman would yield?

The one challenge though is that you're kind of between a rock and a hard place because you need the product, I don't know—well, you do need your kids, but——

Mr. SNOWBARGER. Only for 1 more year.

Mr. SHAYS. I'd like to get to the next panel, but I would like, Ms. Steinhardt, to ask you the question of how the GAO views FDA's information collection practices with regard to the availability of critical plasma products. What's your take on their process today?

Ms. STEINHARDT. I want to answer that question. I want to say something more generally, though, on the way to the answer to that question which struck me in the line of questioning here, and that is that in the risks, looking at the overall risks presented to the product that this industry produces—in the product that this

industry produces, I think it's really important to note the salutary effect that oversight has played here.

And I admit to having an institutional bias. I am the GAO, and we are the watchdogs, so we believe in oversight. But when we first testified on the safety of the blood supply before you in this room 1 year ago in June, we talked about risks associated with the plasma products industry specifically, and we had—there were a lot of unknowns. I mean, there was very little known about it then. And if we had—and that was in part why you asked us to do the study that we have just completed. If we had done that study, if we had done the analysis right then in June 1997, we would have had different numbers to report to you, because right after that hearing, the industry adopted two very important practices which reduced the risk of potentially infectious agents sixfold. The 60-day hold, inventory hold, alone has—plays a very big part in reducing the risks associated with plasma products.

The next big—the layers of safety that Dr. Friedman talked about, which we discussed at great length in the whole blood industry, there were no layers of safety or very few layers of safety at the time of that hearing. The industry adopted them voluntarily, but I think in large part because of concerns that were raised, practices, to help reduce the risks.

The residual risks, the risks of infectious agents that now go into the pool, are reduced dramatically by the viral inactivation and elimination processes associated with manufacturing, but it's because of the increased attention that FDA has paid to safety practices, to the integrity of the manufacturing processes and the industry—the increased attention of the management of the industry to those practices that I think changes are now coming about. I think that's undeniable, and I think all of those things together, the result of oversight, will have contributed to a safer product all around.

That same kind of oversight—and this returns to your question—that same kind of oversight also has to be paid to the consequences of these safety concerns for the supply of what is indeed a very critical material to many people whose lives depend on it, and I think there we are still concerned about the amount of attention that's paid to the consequences of all these actions on supply, too.

When we testified before you last May, we were trying to gauge—at your request we were trying to gauge the impact of withdrawals on the amount of intravenous immune globulin supply, and doing that we tried to get from FDA information about the amount of product that was actually in distribution. And when we asked for it, we were able to get information actually, although it came a little too late for us, but we were able to get information on immune globulin. But FDA told us that they couldn't give us any information on any of their other plasma products because even though the information was reported to them every 6 months by manufacturers, they hadn't analyzed the data.

Now those same manufacturers who have shut down production and whose compliance situation raises concerns about immune globulin supplies, those same manufacturers produce other plasma products. And so it remains a concern to us, the extent to which FDA is looking at the data it has and keeping an eye on the con-

sequences of changes in production for the supplies of other important plasma products.

Mr. SHAYS. Mr. Snowbarger asked his point, but let me just state to you I stayed up all night last night wall-boarding my recreation room to get it ready for the tapers today, so I'm going to ask the question and then I'm going to give the answer that's shorter than the one you gave me and ask you to tell me if my answer is accurate or not.

Ms. Steinhardt, how does the GAO view FDA's information collection practices with regard to the availability of critical plasma products? GAO, this is your answer, I want to know, GAO believes the FDA receives important information about supply of plasma-derived therapies in quarterly reports submitted by manufacturers to the agency. GAO has found that FDA does not review these data in a timely manner, resulting in lost opportunities to identify potential product shortages in advance of critical impact on patients who need these products.

Would that be an answer you would give in the shorter version?

Ms. STEINHARDT. Yes.

Mr. SHAYS. Thank you.

Mr. SNOWBARGER. Mr. Chairman.

Mr. SHAYS. We're going to allow you to respond, and I also say, Dr. Friedman, you have been a wonderful participant in a whole host of our hearings, blood supply and others, and I've always, including today, found you to be very forthright and frank and thorough and thoughtful, and appreciate that you came today because you do have—Dr. Henney is close to a confirmation and it's just nice that you're here. And so I do want to make sure that you all have a chance to respond to that.

But on the table right now is a concern that for whatever reason, the FDA may have information that it's just not—maybe staff or whatever taking advantage of the information. That's the thing that's on the table. And notwithstanding my love and affection for you, I wanted to make sure that that was on the record.

Mr. Snowbarger.

Mr. SNOWBARGER. Do you want him to answer now or respond?

Dr. FRIEDMAN. I'd like to bask in that for a few moments.

Mr. Snowbarger, please go ahead, sir.

Mr. SNOWBARGER. Well, Mr. Chairman, I want just to comment, and that is that any time that we have found a problem and are moving toward solutions, you can write reports in two different ways. One can be a report that says we're not there yet, and certainly we want to get to 100 percent compliance; where the other way you can write the report is, look how far we've come in a few short years, and it seems to me that we have a little bit of both of that.

We don't want to get complacent about things, but it's not like we're sitting still and that things haven't happened, that the industry is not responding. Again, we can all wish for more speed in the process and obviously are concerned about the quality of the product they put out, but I appreciate the fact that it's a difficult balance trying to make sure quality and availability mesh and in some degree, and I appreciate your statement earlier, Dr. Friedman, about that patient that may lose their life because the product just

isn't available even though the risk of some contamination would be fairly minor. But I want to thank the panel.

Dr. FRIEDMAN. Thank you, sir.

I would like to respond to your point, Mr. Chairman. I'll ask Dr. Epstein to please begin, and then let me add just a couple of words at the end if I may.

Please go ahead.

Dr. EPSTEIN. Yes, Ms. Steinhardt correctly states that there is product distribution information which comes into the agency routinely as required by regulation, however we get that at all times on all products, and I think that there has been a need for the FDA to focus its fairly limited resources wisely and to try to do further analyses where we think the problems lie.

Now, the problem with respect to the immune globulin shortage really was recognized only late in 1997. Since that time we have mounted a very focused effort to, first of all, improve the information coming into the agency, namely reporting monthly instead of 6-monthly data. The first monthly reports were, in fact, received only in the last 2 months. Industry periodically provided us monthly data prior to that reporting, but the ongoing reporting on a monthly basis is, in fact, new.

The second point is that the modeling process itself is quite complex, and it has taken the agency some time to figure out just how to model these data. Let me just say that there are a lot of parameters. It could be presumed, for example, that since we have lot release data, we should know what product is going out there, but it's, in fact, not so. Not every product is under lot release. The lot release report may not contain the production size of the lot, only the vial size, et cetera, and products that are lot-released may not always be distributed for a plethora of reasons.

So we've recognized, first of all, the need to focus on distribution data. Second, distribution data doesn't tell you the whole story, because there's supply and demand factoring into shortage. We do not have data coming into the agency regarding demand, and we are only now trying to figure out ways to create surveillance systems that could bring that information to light.

So I would answer Ms. Steinhardt that whereas it's correct that data were available to the agency which had not yet been utilized, it's because of the fact that we have needed to create systems to look appropriately at data where needed and then to try to model the data in a constructive way. And this we are doing now very aggressively, and we are expanding our scope of activities to look at other plasma derivatives, again judiciously. We're trying to look at where the problems are.

And let me just make one final point which is that the data that you look at retrospectively are not always predictive. If you look at month-by-month trends, you find that there can be very erratic swings, and you can be grossly misled thinking that you can trend past data. Furthermore, it requires an effort on top of that to try to figure out what's in the pipeline, not just to look at what was previously distributed.

So all I can say is that the apparent lag or lapse in analyzing available data is really due to mounting the appropriate effort; that we are attempting this now for the appropriate plasma derivatives.

Dr. FRIEDMAN. If I might take a page from your book, the short answer to that question is it's true in the past we didn't look at these data very carefully. It is not true now. Currently we're engaged in doing exactly what Dr. Epstein said. It's a little like economic modeling. You have to understand not just what's coming in, but what's going out, and we found that a formidable challenge, but we are committed to doing that.

I've made the invitation to Ms. Steinhardt previously, and do so again here, that if there are any suggestions that they have about ways we can do this, we've called you, we've talked, we're committed to working with them in that regard.

Mr. SHAYS. We'll be asking the next panel the same questions.

Dr. FRIEDMAN. Fair enough, sir.

As a closing, and I know you want to get on to the next panel, and we don't want to keep you, I personally appreciate the chance to come before this committee. I think that we have focused very intently on improving standards and making the quality of the blood supply and the information about the blood supply better and better. It is a never-ending challenge because of new science and new information that we learn.

I think it's fair to say that through the hard efforts of these people here and hard efforts in the industry and others outside, and certainly of this committee, that there's really been a sea change in how manufacturing practices have been looked at in this industry over the past several years. We are not satisfied with that. We're pleased that some progress is being made. We see considerable work to do in the future, and we're committed to doing that.

Thank you, sir.

Mr. SHAYS. I thank all of you, and I do think we've seen significant progress, and I do think that we've worked well together in this effort. So I thank you all.

Our second panel is James Reilly, executive director, American Blood Resources Association; Jan Bult, executive director, International Plasma Products Industry Association; Brian McDonough, chief executive officer, American Red Cross Biomedical Services; and Dr. John Boyle, Plasma Users Coalition. I think Mr. Boyle is the only new participant in these hearings. Do we have an initiation in cases like that?

You know, why don't you stand because I'll swear you in. Is there anyone that you might turn to as well on your staff that you want sworn in? If so would you ask them to stand, and they only need to identify themselves if they are asked to come forward. But if there's anyone else, you can sit in the back, you know, or sit up in the first two seats on the side there or behind, wherever you want. But I want whoever we need to swear in to swear in now and not later.

Anyone else? I see others standing and I know they want to be sworn in, so we'll wait.

I am assuming that whoever is standing is a potential witness there. If you would all raise your right arms, please.

[Witnesses sworn.]

Mr. SHAYS. Thank you very much. I appreciate you doing it this way just so we don't have to swear in someone later.

We have four people who will be giving testimony, and we'll just go right down the list: Mr. Reilly, Mr. Bult, Mr. McDonough; is that how we say your name? Thank you. And John Boyle. OK, thank you.

STATEMENTS OF JAMES REILLY, EXECUTIVE DIRECTOR, AMERICAN BLOOD RESOURCES ASSOCIATION; JAN BULT, EXECUTIVE DIRECTOR, INTERNATIONAL PLASMA PRODUCTS INDUSTRY ASSOCIATION; BRIAN McDONOUGH, CEO, AMERICAN RED CROSS BIOMEDICAL SERVICES; AND JOHN BOYLE, Ph.D., PLASMA USERS COALITION

Mr. REILLY. Thank you, Mr. Chairman.

My name is James Reilly. I'm the president of ABRA, the trade association representing the Nation's source plasma collection industry.

I'll ask—I will summarize our written testimony in the interests of time and would ask that the complete testimony be entered into the record.

ABRA members collect roughly 11 million liters of source plasma annually.

I appreciate the opportunity to speak to the subcommittee regarding the GAO report on plasma safety. I believe the message that can be taken from the report and today's testimony, and what we would like to reinforce, is that sound scientific analyses demonstrate the overall safety of source plasma.

Almost since its inception, ABRA has served as a vehicle for industry self-regulation through publication of industry guidelines and recommendations that go over and above existing Federal, State and local requirements. In the written testimony are several examples from our past experience.

One of the most significant examples of industry self-regulation is the Quality Plasma Program. QPP is a certification program that sets a baseline of industry standards. The program began in 1991, and today is a de facto requirement throughout the industry to maintain certification. To maintain certification, facilities must adhere to QPP standards and undergo inspections by third-party inspectors. Any facility found in noncompliance is immediately notified and given 60 days to respond with corrective actions or risk losing its certification.

QPP has had a dramatic affect on source plasma safety. Standards put in place through the program have resulted in more effective selection of low-risk donors, more skilled collection center personnel, better facilities and lower marker rates among the donor population. However, one of the greatest benefits of QPP is that it has served as a vehicle for effecting continuous improvement throughout the industry.

In 1997, the source plasma industry publicly committed to four voluntary initiatives. Two of these initiatives, the qualified donor standard and the inventory hold, have already been implemented, and are having a positive effect on plasma safety. Two of the initiatives are by necessity still work in progress. The initiatives that are still work in progress include PCR viral testing and a revised viral marker rate standard. We anticipate that the revised viral marker rate standard will take effect during 1999. PCR testing is

still under development, is being performed pursuant to Food and Drug Administration regulations for investigational new drugs.

Over the past year ABRA and its member companies have committed extensive resources to the collection of data to accurately characterize the safety of plasma. To date, ABRA's data collection has focused on viral marker rates among qualified donors. This is because only donations from qualified donors are used for further processing.

Donations from applicant donors are not used for further manufacture unless the qualified donor criteria are subsequently met. As such, ABRA believes that the data pertaining to viral marker rates among applicant donors are not meaningful in terms of assessing the safety of plasma for further manufacturing. Despite this strongly held belief, ABRA has begun a data collection effort to respond to requests for applicant donor data. The applicant donor data that have been collected to date are incomplete. Inclusion of these data in the GAO report would have been misleading.

ABRA provided GAO with the data needed to perform its analysis. These included prevalence rates for all donors, incidence rates on qualified donors and residual risk rates on qualified donors. Inclusion of the California Department of Health Services data in the GAO report was unfortunate, particularly in light of significant limitations of the data set and the lack of data verification acknowledged by GAO. The ABRA-supplied data represented the most comprehensive, complete and accurate data set available for the industry.

What the ABRA data show is that source plasma is extremely safe. For the HIV virus the probability that an undetected but potentially infectious window period donation may enter a manufacturing pool is 1.47 per million donations. All HIV window period donations are known. All HIV window period donations from known seroconverting donors are interdicted under the inventory hold standard. The 1.47 per million probability represents the remote likelihood that a nonreturning qualified donor's last donation may be in the window period despite the fact that it does not test positive using current testing technologies.

The data for HCV and HBV are also profound. With the promise of PCR testing within reach, the probability of a potentially infectious window period donation entering a manufacturing pool for HCV will fall from approximately 36 per million donations to only 3.32 per million donations. Like HCV, with PCR in place, 100 percent of all the HCV window period donations from known seroconverting donors would be removed under the inventory hold. For hepatitis B, currently 91 percent of all window period donations are removed under the inventory hold.

As the GAO report points out, these source plasma data are comparable to those reported from the American Red Cross. The only discrepancies between the two data sets exist for hepatitis B, and the GAO report notes this is partially due to the transient detectability of hepatitis B virus and the fact that source plasma donors donate more frequently than do whole blood donors.

The comparability of these two segments of the industry is not news. The comparability of source plasma and whole blood industries was demonstrated as early as 1985 in an article published in

the journal Transfusion. In that article the repeat reactive rates from nationwide screening for blood and plasma for antibodies to HTLV–III, currently known as HIV, were 0.34 percent for whole blood donations and 0.15 percent for plasma donations.

More recently, as Dr. Friedman noted, a 1993 FDA workshop on the safety of plasma donations concluded, "Plasma pools derived from compensated donors are at least as safe as comparable plasma pools recovered from whole blood donations from volunteer donors." The viral marker rates reported at that workshop were strikingly similar. Thus the comparability of residual risk rates for whole blood and source plasma donors reported in the GAO report should come as no surprise.

Given this history of comparable safety profiles, we have begun to question whether continued comparisons of viral marker rates between whole blood and source plasma are the best use of limited government and industry resources. We are focusing future resources on continuous quality and safety improvements measured against our own baseline of past performance.

In conclusion, I would like to thank the subcommittee for bringing these important issues to light and for giving me the opportunity to address them. ABRA and its members are committed to continuous improvement of the industry through the voluntary initiatives outlined previously and a number of planned enhancements to the QPP. We would welcome the opportunity to discuss our plans for enhancing QPP and the safety of source plasma with you and the subcommittee at any point in the future.

Mr. SHAYS. Thank you.

[The prepared statement of Mr. Reilly follows:]

ABRA

The International Authority for the Source Plasma Collection Industry

Statement of James P. Reilly, President

September 9, 1998

Good morning, my name is James Reilly. I am the president of the American Blood Resources Association (ABRA). ABRA is the trade association representing the nation's Source Plasma collection industry. ABRA members include approximately 375 community-based Source Plasma collection centers across the United States. These centers collect roughly 11 million liters of Source Plasma annually from approximately 1.5 million donors. Source Plasma donors are valued members of society whose donations provide the raw material used to manufacture an impressive list of live saving and life enhancing medical products. These donors make an important contribution to the healthcare community in the form of the products manufactured by the member companies of the International Plasma Products Industry Association (IPPIA).

I appreciate the opportunity to speak to the subcommittee regarding the General Accounting Office (GAO) report on plasma safety. I believe the message that can be taken from the report, and what we would like to reinforce today, is that sound scientific analyses demonstrate the safety of Source Plasma. ABRA and its members are committed to continued science-based analyses of the Source Plasma industry and its many voluntary safety initiatives.

This hearing and the GAO report represent the latest chapter in the subcommittee's oversight of the blood and plasma industries. We welcome this oversight and recognize the important role the subcommittee serves in maintaining the safety of the nation's supply of blood and blood products. We view ourselves as working in partnership with the subcommittee to provide the greatest possible assurance of Source Plasma and plasma product safety to the public and patient communities we all serve. Safety is not the responsibility of one subcommittee, one company, or one regulatory agency -- it is the collective responsibility of us all.

Before turning to specific aspects of the GAO report, I would like to take just a few minutes to describe how ABRA meets its responsibilities in assuring Source Plasma safety. Almost since its inception, ABRA has served as a vehicle for industry self-regulation through publication of industry guidelines and recommendations that go over and above existing federal, state and local requirements. The following are just a few examples of these industry policies and practices:

- Recommendation on AIDS and Plasma Donor Deferral (1983)
- Recommendations on Infectious Waste Management (1986)
- Guidelines for HIV Infection Control at Plasmapheresis Establishments (1987)
- Recommendations for Shipment of Biological Samples and Etiologic Agents (1988)
- Recommendations for Laboratory Standards (1989)
- Policy Regarding Hepatitis B Vaccine Usage by Plasmapheresis Establishment Employees (1989)
- Guidelines for anti-HCV Screening in Plasmapheresis Facilities (1991)
- Guidelines for Training, Supervising, and Evaluating Physician Substitutes (1991)
- Precautionary Measures to Further Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease: Recommendation for Donor Suitability (1995)

Beyond these recommendations and guidelines, one of the most significant examples of industry self-regulation and commitment to safety is the Quality Plasma Program (QPP). QPP is a certification program that sets a baseline of industry standards. The program began in 1991 and today is a *de facto* requirement throughout the industry. To maintain certification, Source Plasma collection facilities must adhere to QPP standards and undergo biennial inspections by third-party inspectors. Any facility found in non-compliance is immediately notified and given 60 days to respond with corrective actions or risk losing its certification.

QPP encompasses a broad range of industry standards including, among other things:

- use of a National Donor Deferral Registry (NDDR),
- adherence to a viral marker rate standard,
- conformance with additional donor screening, education, and testing requirements,
- compliance with formal employee training requirements,

- maintenance of certain facilities standards, and
- fostering community based donor groups (through the exclusion of individuals who do not have a local address).

A few of these standards deserve special attention. The NDDR, for example, is a nation-wide computer database that allows Source Plasma collection facilities to instantaneously check donors to assure that they have not previously tested positive on a viral marker screening test. The viral marker rate standard was established in 1991 and set an upper limit for the number of positive donations at any given collection center. In 1993 the standard was revised downward and is currently under revision once again to reflect recent industry safety initiatives. The QPP donor screening criteria include, among other things, an increased emphasis on donor education of high-risk activities and drug testing. In fact, QPP was instrumental in establishing FDA criteria for exclusion of donors for incarceration.

Since its implementation, QPP has had a dramatic effect on Source Plasma safety. The standards put in place through the program have resulted in more effective selection of low risk donors, more skilled collection center personnel, better facilities, and lower marker rates among the donor population. However, one of the greatest benefits of QPP is that it has served as a vehicle for effecting continuous improvement throughout the Source Plasma industry. This has been borne out by a number of recent voluntary industry initiatives.

In 1997 the Source Plasma industry publicly committed to four voluntary initiatives or standards. Two of these initiatives, the Qualified Donor standard and the Inventory Hold, already have been implemented and are having a demonstrable effect on Source Plasma safety – two of the initiatives are by necessity, still work in progress. The initiatives that are still work in progress include polymerase chain reaction (PCR) viral testing and the previously noted revised viral marker rate standard. PCR testing is still under development and is being performed pursuant to the Food and Drug Administration (FDA) regulations for Investigational New Drugs (IND). With respect to the revised viral marker rate standard, we had hoped to sit before you today and explain the full impact of an already implemented revised standard. However, after attempting to revise the standard, we quickly learned that a revised standard could not be established without first assessing the impact of the Qualified Donor standard.

The Qualified Donor standard takes advantage of the repeat donor population that is unique to the Source Plasma industry. Under the standard, no unit of plasma may be accepted for further processing unless the donor has successfully passed at least two health history interviews and two panels of all required screening tests within a six-month period. Thus, even regular donors that go for a period of six months without donating must once again become Qualified Donors. In this way, the Qualified Donor standard fosters a community-

based donor population by accepting only those donors that have shown a commitment to repeat participation in the program.

The Qualified Donor standard was implemented in July 1997. Concurrent with its implementation, ABRA began collecting data on the prevalence of positive viral marker test results among the Qualified Donor population. It was anticipated that these data would form the basis of the revised viral marker rate standard. While this remains true, in the year since the implementation of the Qualified Donor standard, we have learned a great deal about the resources needed to effectively collect, manage, maintain, and analyze data on roughly 1 million Source Plasma donations per month. As a result of these data collection efforts, we believe we now have the data necessary to proceed with the establishment of a revised viral marker rate standard. We anticipate that the revised standard will take effect during 1999.

It is also worth noting that the data collected in connection with the Qualified Donor standard forms the basis of the GAO report insofar as it pertains to the Source Plasma industry. However, before moving ahead to discuss ABRA's data collection activities in greater detail and viral marker rates in general, I would like to briefly outline the Inventory Hold standard. Implementation of the Inventory Hold began in July 1997 and was phased-in over a six-month period. This standard requires that each individual unit of Source Plasma be held in inventory for a minimum period of 60 days from the date of collection before it is used for further processing. This hold period provides a large window of opportunity to retrieve previous donations if a Qualified Donor seroconverts on a subsequent donation or if new health history information is discovered. The Inventory Hold is a powerful tool in terms of preventing so-called "window period donations" (potentially infectious but nonreactive) from entering a manufacturing pool.

Over the past year ABRA and its member companies have committed extensive resources to the collection of data to accurately and meaningfully characterize the safety of Source Plasma. Although ABRA initially believed that it would manage the data collection and analyses in-house, the sheer volume of data and the complexity of statistical assessments made this impracticable. Consequently, one of the milestones in the process was the retention of an independent research organization to assist with data collection and management activities and to ensure objective data analyses. Now, with the first round of data collection and analyses behind us, ABRA is committed to continue sound scientific assessment of the Source Plasma industry. This includes continued data collection and ongoing evaluation of statistical models to accurately depict our industry.

To date, ABRA's data collection has focused on viral marker rates among Qualified Donors. This is because, as noted, only donations from Qualified Donors are used for further processing. Donations from Applicant Donors are not used for further manufacture unless and until the Qualified Donor criteria are

met. As such, ABRA believes that data pertaining to viral marker rates among Applicant Donors are not meaningful in terms of assessing the safety of Source Plasma for further manufacturing into therapeutic products. Despite this strongly held belief, ABRA has begun a data collection effort targeting Applicant Donors to respond to requests for such data. The Applicant Donor data that have been collected to date are incomplete and thus, inclusion of these data in the GAO report would have been inappropriate and potentially misleading.

Notwithstanding the current unavailability of the Applicant Donor data, ABRA provided GAO with the data needed to perform its analyses. These include prevalence rates for all donors, incidence rates on Qualified Donors, and residual risk rates for Qualified Donors. Inclusion of the California Department of Health Services data in the GAO report was unfortunate, particularly in light of the significant limitations of the data set and the apparent lack of data verification as acknowledged by GAO. In contrast, the ABRA-supplied data represent the most comprehensive, complete, and accurate data available for the Source Plasma industry.

What the ABRA data show is that Source Plasma is extremely safe. For example, for the Human Immunodeficiency Virus (HIV), the probability that an undetectable but *potentially* infectious (HIV) window period donation may enter a manufacturing pool is 1.47 per million donations. Moreover, all HIV window period donations from known seroconverting donors are interdicted under the inventory hold standard. The 1.47 per million probability of a potentially infectious window period donation entering a pool represents the remote likelihood that a non-returning Qualified Donor's last donation may be in the window period despite the fact that it does not test positive using current testing technologies.

The data for hepatitis C virus (HCV) and hepatitis B virus (HBV) also are profound. With the promise of PCR testing within reach, the probability of a potentially infectious window period donation entering a manufacturing pool will fall from approximately 36 per million donations to only 3.32 per million donations. Like HIV, with PCR in place 100% of all HCV window period donations from known seroconverting donors would be interdicted under the inventory hold. For HBV, currently 91% of all window period donations are interdicted under the hold and the probability of a potentially infectious window period entering a pool is approximately 54 per million donations.

As the GAO report points out, these Source Plasma data are comparable to those reported for the American Red Cross (ARC). The only discrepancy between the two data sets exists for HBV and, as the GAO report notes, this is likely due to the transient detectability of the hepatitis B virus and the fact that Source Plasma donors donate more frequently than do whole blood donors. The safety profiles for these two sources of plasma are comparable.

The comparability of these two segments of the industry is not new news. In terms of viral safety, the comparability of the Source Plasma and whole blood industries was demonstrated as early as 1985 in an article published in the journal *Transfusion*[i] addressing the prevalence of HIV (know then as the human T-cell lymphotrophic III virus) in Source Plasma and whole blood donors. In that article, the repeat reactive rates resulting from nationwide screening of blood and plasma for antibodies to HTLV-III were 0.34% for whole blood donations and 0.15% for Source Plasma donations.

More recently, a 1993 FDA workshop on the safety of plasma donation concluded that "plasma pools derived from compensated donors are at least as safe as comparable plasma pools recovered from whole blood donations from volunteer donors."[ii] The viral marker rates reported at that workshop are strikingly similar. Thus, the comparability of the residual risk rates for whole blood and Source Plasma donors, as reported in the GAO report, should come as no surprise.

Given this history of comparable safety profiles, we have begun to question whether comparisons of viral marker rates between whole blood and Source Plasma are the best use of limited government and industry resources. Source Plasma donors provide an essential life giving material without which many Americans would suffer and/or die. Rather than expending valuable resources comparing one industry segment to another, we are focusing future resources on striving for continuous quality and safety improvements against our own baseline of past performance.

In conclusion, I would like to thank the subcommittee again, for bringing these important issues to light and for giving me the opportunity to address them. ABRA and its members are committed to continuous improvement of the Source Plasma industry through the voluntary initiatives outlined previously and a number of planned enhancements to the QPP. We would welcome an opportunity to discuss our plans for enhancing the QPP and the safety of Source Plasma with you and the subcommittee.

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[i] Kuritsky et al., Results of Nationwide Screening of Blood and Plasma for Antibodies to Human T-cell Lymphotropic III Virus, *Transfusion* (1986) 24, 205-7.
[ii] Meeting Report: Workshop on Safety of Plasma Donation, *Biologicals* (1994) 22, 269-283.

Mr. SHAYS. Jan Bult, please.

Mr. BULT. Thank you very much.

Good morning, Chairman Shays and honored distinguished committee members. My name is Jan Bult, and I'm executive director of International Plasma Products Industry Association, IPPIA.

Mr. SHAYS. Where are you based?

Mr. BULT. I'm based in Washington, DC, sir.

Our members include the four largest commercial fractionators, Alpha Therapeutic Corp., Baxter Healthcare Corp., Bayer Corp. and Centeon. I would like to thank the committee for inviting us here today to discuss the safety and supply of plasma-based therapy.

Our industry is committed to producing safe, high-quality plasma products, which are used by millions of people each year in fighting diseases and treating a variety of medical conditions. IPPIA members are working to continuously improve the safety of our products, and we appreciate the opportunity to brief the committee on our efforts. My testimony today will focus on three areas, an update on previous commitments from our industry, a discussion of the compliance issues and how we are addressing those issues, and our efforts to understand and respond to shortages of plasma products.

During testimony before this committee on July 31, 1997, the IPPIA announced a commitment to develop a comprehensive safety plan for the plasma products industry. We have made considerable progress in this area.

First, in response to a challenge from you, Chairman Shays, IPPIA promised that we investigate a system that would allow consumers to verify the regulatory status of a particular product lot.

Mr. SHAYS. Sorry to interrupt you. If you just put that mic a little closer.

Mr. BULT. Is this better, sir?

Mr. SHAYS. Yes, a little closer, too. I realize it gets in the way of your talking, but that will help.

Mr. BULT. OK, thank you.

In response to a challenge from you, Chairman Shays, IPPIA promised that we would investigate a system that would allow consumers to verify the regulatory status of a particular product lot. IPPIA is in the final stages of implementing a system that will do just that.

A second part of the industry comprehensive safety plan is the voluntary pool size limitation announced at the same hearing last year. We anticipate that all lots released after January 1999 will adhere to this limitation.

The association is currently developing a comprehensive plan to address current good manufacturing practices, compliance issues, which I will discuss in more detail later.

Our industry is continually striving to update our quality systems and other processes so that we can provide an adequate supply of safe products. In the last 4 years our members have spent in excess of $380 million of planned upgrades in compliance enhancements. Spending for these improvements increased by more than 20 percent in 1997 alone.

As you are aware, the FDA has changed its process for inspecting biological establishments through the introduction of team biologics. Recent inspections by the FDA have led to warning letters and in some cases to consent decrees being issued to our members. I want to assure this subcommittee that our members are working around the clock to institute facilitywide enhancements to address these findings.

Mr. Chairman, I would like to state for the record that we are proponents, not critics, of a new approach to enforcement. We agree with the FDA that this process has led to a greater assurance of quality conditions for product manufacturing.

We believe, however, several factors need to be considered to completely understand the potential implications on safety and supply. One must understand the nature of GMPs and how the FDA enforces these ever-changing requirements. Four hundred eigthy three observations need to be viewed in a proper context. Observations may reflect a range of seriousness. A significant amount of resources, including personnel, capital and time, may be necessary to meet the challenges of operating in this evolving regulatory environment. And 4, an increased focus on compliance has an effect on supply of these products.

CTMP's regulations are not static. Rather, they require a firm to maintain good manufacturing practices in light of current technology and other capabilities. Being current tomorrow is different than being current today. As technology and information capabilities change, so do the requirements for maintaining good manufacturing practices.

We want to assure this committee that the products we produce continue to be safe and effective. Quality systems of multiple tests and reviews provide a redundancy of systems to check and crosscheck that any released product meets its approved safety, purity and potency. In the short term this evolving regulatory environment has affected our members' ability to provide an adequate supply of several products. Consistent, stable and well-communicated requirements, with reasonable timetables for implementation, will help our industry to meet the expectations of this committee, the FDA and the general public. Our members have made and will continue to make the necessary investments in capital, personnel and training to meet this obligation.

I would like to focus my remaining testimony on the industry response to shortages of plasma products. First I would like to say that we recognize the importance of our products to those patients who depend on them to live healthy and productive life. We are doing everything we can to resolve the shortage as quickly as possible.

During this subcommittee's May hearing, IPPIA provided IVIG data. We also committed to providing updated data on a quarterly basis. I'm happy to report today that together with the American Red Cross and Novartis, we have been able to expand this effort to include data initiatives that will contain even more timely indicators of the U.S. supply situation. We will now be able to see the complete picture for the U.S. supply of IVIG and changes to that supply.

The good news is that the supply levels have remained stable and actually show a slight increase over the 6-months period. We will continue to monitor the situation and provide monthly updates of this information to this committee, FDA, consumer groups and other interested parties.

In addition to the collected data on IVIG, we have also started an initiative to collect information on the supply of Factor VIII. Our members have consistently made additional quantities of recombinant Factor VIII available to the U.S. market as this therapeutic has gained in its use.

The trend from the recombinant data factor shows a decreasing inventory-to-consumption ratio. One could expect tight supply versus demand margins in the near future. The tight supply-to-demand—tight supply-to-demand margin of recombinant Factor VIII may have an impact on consumption of the plasma-derived Factor VIII. As with the other products, we have started to look at this ratio as well, and we will continue to monitor the situation very closely, again on a monthly basis.

Our industry is taking several actions to address any potential supply issues for Factor VIII similar to those taken to address the IVIG supply. Short term our members are working with FDA to expedite lot releases for products as they become available. Additionally, an emergency supply of recombinant Factor VIII is being developed for patients in critical need.

In conclusion, I would like to reiterate that our members are working in cooperation with the FDA to address issues associated with continued cGMP compliance. All of us are committed to continuing to provide access to adequate supplies of these—therapies.

The IPPIA members together with the American Red Cross and Novartis have already started to collect data and plasma products to better understand current and potential future shortages. We will continue to collect and make available supply data on a monthly basis. We look forward to working cooperatively with patient groups, Government agencies and others to develop workable solutions to this critical shortage.

Thank you, and I will be happy to respond to any questions from the committee.

Mr. SHAYS. Thank you very much.

[The prepared statement of Mr. Bult follows:]

Good morning Chairman Shays and other distinguished committee members. My name is Jan Bult, and I am Executive Director of the International Plasma Products Industry Association (IPPIA), the trade association representing the commercial producers of plasma-based therapies. IPPIA members produce approximately 80% of the plasma products for the U.S. market, and include the four largest commercial fractionators: Alpha Therapeutic Corporation, Baxter Healthcare Corporation, Bayer Corporation, and Centeon. I would like to thank the committee for inviting us here today to discuss the General Accounting Office (GAO) report on the safety and supply of plasma-based therapies.

Our member companies are deeply aware of the critical role that the plasma derivatives we manufacture play in the lives of patients who depend upon them. We applaud the efforts this committee has made in helping to ensure the continued safety and availability of these therapeutics. Your efforts have assisted us in achieving the highest levels of safety for the plasma derivatives that we manufacture.

Our industry takes pride in the current safety record of our therapies, and we appreciate the opportunity to discuss our efforts to continually increase the margin of safety for these therapies. While the progress in further developing safer plasma therapeutics has been remarkable, we recognize that improving quality is a continuous process. We are also aware that there are compliance issues that need to be addressed.

My testimony today will focus on four areas:

- An update on previous commitments from our industry;
- Our comments on the GAO report;
- A discussion of the compliance history of our industry; and
- Our efforts to understand and respond to shortages of plasma products.

I will summarize my written testimony and request that a copy of my entire testimony be included for the record.

Industry Update

During testimony before this committee on July 31, 1997, the IPPIA announced our commitment to develop a comprehensive safety plan for the plasma products industry. As you may recall, our plan was based on the multiple layers of safety in the fractionation process, with an industry action plan to enhance the margin of safety for each of those layers. We presented a more detailed discussion of this plan to the FDA's Blood Products Advisory Committee in September 1997, and a copy of that presentation is included with my written testimony as Attachment 1. I would like to give you an update on the considerable progress we have made on several fronts of this plan.

Direct-to-Patient Notification System

In response to a challenge from you, Chairman Shays, IPPIA promised that we would investigate a system that would allow plasma-based therapy users to verify the regulatory status of a particular product lot. I am happy to report that, in cooperation with patient groups, IPPIA is in the final stages of developing a system that will do just that.

As you are aware, consumers and other interested parties were not always notified of recalls or withdrawals through the current regulatory system. Your suggestion to provide an 800 number for patients to verify the recall status of plasma products provided the encouragement necessary to bring about this unprecedented achievement. Our new system, when fully operational, will provide plasma product consumers, health care workers, and parents with the added piece of mind of knowing that they will receive timely notification in the event of a plasma product recall or withdrawal.

The industry system being developed, scheduled for release in early October, will include all major manufacturers and distributors of plasma products. This system will allow the industry to directly notify end users with a two-fold approach. First, individuals interested in receiving notification will register with an independent third party administrator of the system. These individuals are able to choose the method of notification most convenient to them, such as telephone, fax, e-mail, or overnight package. In the event of a recall or withdrawal, the individual will be directly notified via their chosen method. This outbound notification portion of this system will be launched in early October.

The dial-in section will allow the user to call a toll-free number to hear a list of the most recent recalls and withdrawals. A second option will allow the user to verify the regulatory status of a particular lot number before infusing the product. We anticipate that this section will be online by the first quarter of 1999. In order to ensure that this system meets the needs of its users, we have enlisted the help of patient groups in a recently created advisory panel.

Pool Size Limitations

A second part of the industry comprehensive safety plan is the voluntary pool size limitation announced at the same hearing last year. As we explained then, IPPIA members pledged to limit the total donor exposure to 60,000 for the major plasma-based therapies. Our intention to initiate this limitation for currently U.S. licensed products was communicated to the Food and Drug Administration (FDA) in January 1998. Our members began constructing manufacturing pools to meet this standard during the first quarter of this year. We anticipate that all lots released after January 1999 will adhere to this limitation.

cGMP Element
The association is currently developing a comprehensive plan to address cGMP compliance issues, which I will discuss in more detail later.

GAO Report
Both the American Blood Resources Association (ABRA) and the IPPIA provided extensive assistance to the GAO for the preparation of their report on the plasma (products) industry. IPPIA agrees with the comments provided by ABRA on the comparison of volunteer and remunerated donors. Regarding compliance with current Good Manufacturing Practices (cGMP), we agree with the GAO that compliance with cGMPs is important to ensure the safety of plasma-based therapies. We also agree with the GAO that FDA and the plasma fractionation industry have taken steps to address the concerns related to cGMPs and quality assurance. At this time, I would like to speak to the compliance history of our industry and the actions taken to help to ensure continual compliance with cGMPs.

Industry Compliance with cGMPs
Mr. Chairman, our industry takes its responsibility to manufacture an adequate supply of safe products very seriously. Adherence to all regulatory requirements is a part of this responsibility, and we are continually striving to update our quality systems and other processes to meet these requirements. An example of our efforts includes increases in capital expenditures. In the last four years alone, our members have spent in excess of $380 million on plant upgrades and compliance enhancements. Details are in the next table:

	1994	1995	1996	1997
Capital Expenditures (x1000)	$61,828	$99,749	$99,676	$120,287
% Increase	-.-	61.3	0	20.7

However, as you are aware, recent inspections by the FDA have led to warning letters and in some cases to consent decrees being issued to our members. I want to assure you, Chairman Shays, that our members are working around the clock to institute facility-wide enhancements to quality systems and manufacturing processes to address these findings, while at the same time continue to manufacture safe products for patients whose lives depend upon them. Additionally, the association comprehensive safety plan addresses efforts associated with cGMP compliance on an industry-wide level. The safety of our therapies is of the utmost importance, and we will take whatever measurers necessary to continue to assure their continued safety and quality.

With safety as our primary focus, one might be tempted to ask how this current situation arose. According to the FDA, the agency has placed increased enforcement scrutiny on the biologics sector, with a primary focus on the plasma

fractionation industry[1]. As you are aware, the FDA has changed its process for inspecting biological establishments through the introduction of Team Biologics. The Office of Regulatory Affairs has taken lead responsibility for these inspections, emphasizing a complete assessment of cGMP compliance. Under this new inspectional process, as documented by the Health and Human Services Inspector General (IG)[2], the inspections have lasted three times as long, reported four times as many observations, and resulted in five times as many enforcement actions as inspections under the old system. It is important to note that both types of inspections were conducted under the same regulatory requirements, and while the manufacturers were increasing quality systems and personnel as discussed earlier.

The IG reported several reasons for these changes, including more inspectors and longer inspections. Additionally, the reporting system changed. Items that in the past would only have been discussed with the firm are now reported on Form 483s. Another significant change was the inspectors themselves, scientists under the old system with primary focus on scientific or technical issues versus full time inspectors with greater attention to cGMP and documentation issues under Team Biologics[3].

Mr. Chairman, I would like to state for the record that we are proponents, not critics, of a new approach to enforcement. We agree with the FDA that this process has led to a greater assurance of quality conditions for product manufacturing. A larger number of inspectors spending more time on inspections are more likely to find areas needing further improvement. Our members are committed to working in cooperation with the FDA to address each of these issues in order to ensure production under the highest safety and quality standards possible.

We believe, however, several factors need to be considered to completely understand the potential implications on safety and supply from this increased scrutiny.

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[1] Statement by Michael A. Friedman, M.D., Lead Deputy Commissioner, Food and Drug Administration, Department of Health and Human Services before the Subcommittee on Human Resources Committee on Government Reform and Oversight, U.S. House of Representatives, May 7, 1998.

[2] "Review of the Food and Drug Administration's Inspection Process of Plasma Fractionators" Department of Health and Human Services Office of Inspector General, June 1997.

[3] Ronald F. Tetzlaff, "Preparing for Team Biologics Inspection", BioPharm August 1998, 18-28

1. One must understand the nature of cGMPs, and how the FDA enforces these ever-changing requirements.
2. 483 observations need to be viewed in a proper context: observations may reflect a range of seriousness.
3. A significant amount of resources, including personnel, capital, and time, may be necessary to meet the challenges of operating in this evolving regulatory environment.
4. An increased focus on compliance has an effect on supply of these products

Plasma fractionators must conform to cGMPs as defined under 21 CFR parts 210-211. These regulations are not static, rather they require a firm to maintain good manufacturing practices in light of current technology and other capabilities. What is considered current tomorrow will be different than what is considered current today. As technology and information capabilities change, so do the requirements for maintaining good manufacturing practices.

The FDA has varied and potentially significant authority to ensure compliance with these regulations and protect the public health. Following an inspection, the inspectors report observations of objectionable conditions and practices on the Form FDA 483, Inspectional Observations. The agency classifies observations as Voluntary Action or Official Action Indicated. Under official actions, the FDA may take advisory actions, such as issuing an untitled or warning letter. An untitled letter notifies the firm of circumstances that do not violate FDA regulations, but may nonetheless call for corrective action. Warning letters, a more severe regulatory action, notify a firm that a product, process, or other activity violates FDA regulations, but there is not an imminent public safety threat as a result of the violation. In certain circumstances, the FDA may seek to have a firm operate under a consent decree to ensure that products continue to be manufactured under quality conditions and that corrective actions are undertaken within an agreed timeframe.

Form 483 observations noted in the plasma fractionation industry have risen over the previous five years due to intensified inspectional practices by the FDA. This is indicative of the change in the direction and emphasis of FDA inspections in recent years

Once a 483 observation is communicated to the firm, the observation is analyzed to determine how to address it. It is important to note that 483 observations may reflect a range of seriousness. Regardless of the significance of the observation, all are treated very seriously. Some observations reflecting noncompliance may represent minor deviations, such as a simple error in documentation. Many observations such as these can be addressed immediately. For the more significant observations, those that could represent a serious systemic deviation in GMP compliance, a corrective action team comprised of individuals familiar

with the area of concern will be assembled. Depending on the nature of the issue, external consultants may be employed to provide additional expertise.

Following an analysis of the affected process or product, the team will formulate a plan to correct the deviation and submit the plan, with suggested timetables, for FDA review. In some circumstances the corrective action team may conclude that the nature of the deviation will require a temporary shutdown of part or all of the facility to implement the necessary corrective action. In many instances, personnel normally involved in manufacturing must be shifted to other areas in order to address these issues. Both of these actions have an impact on the firm's ability to produce these products. For these more serious observations, a significant amount of time may be required to develop and implement this corrective action plan.

The production of plasma derivatives is a very complex process and manufacturers recognize the importance of cGMP compliance. Therefore, to ensure product safety, purity and effectiveness, each company has put in place a robust Quality Program comprised of a number of complementary systems which are designed to provide control over all elements of the manufacturing process. This Quality Program is a key component of the multiple layers of safety that protect patients by providing a system of control for assurance of the quality of personnel, facilities, equipment, raw materials, manufacturing procedures and processes and final product. Surveillance also extends past the point of manufacture as quality systems also monitor product quality after distribution. The intense focus on quality and the cross checks that the Quality Program provides is a critical mechanism which works to mitigate the adverse impact of a potential lapse in GMP.

The summary table of these systems (Attachment 2) represents a sampling of some of the quality system check points that control each element of manufacturing. These quality systems of multiple tests and reviews provide a redundancy of systems to check and crosscheck that any released product meets its approved safety, purity, and potency.

In the end, we want to assure this committee that we continue to provide very safe products. Shifting regulatory emphasis from a scientific review of the process to a focus on cGMP compliance has resulted in increased 483 observations. However, the products we produce continue to be safe and effective. In the short term, this evolving regulatory environment has affected our members' ability to provide an adequate supply of several products. Consistent, stable and well-communicated requirements, with reasonable timetables for implementation, will help our industry to meet the expectations of this committee, the FDA, and the general public to further ensure adequate supplies of safe products. Our members have made and will continue to make the necessary investments in capital, personnel, and training to meet this obligation.

cGMP Element of Industry Safety Plan
As I stated earlier, our industry is committed to providing an adequate supply of safe products. Part of this commitment includes the assurance of quality conditions for product manufacturing by strict adherence to cGMP guidelines. To this end, IPPIA has initiated several activities under the overall heading of the cGMP compliance element of the IPPIA Strategic Safety Plan. I would like to outline these activities for the committee at this time:

Process Validation
Our members are working as members of a task force from the Parenteral Drug Association (PDA) to develop process validation guidelines for the plasma fractionation industry. The purpose is to evaluate the appropriate approaches to develop and implement process validation in an industry where many processes have been is use for many years. The task force plans to establish guidelines on what constitutes an acceptable level of documentation, and establish guidelines on how to obtain that level of documentation for our existing fractionation processes. Several meetings have already taken place on these issues.

cGMP Workshops
IPPIA, in cooperation with Pharma Conference Arrangements, is working to develop cGMP workshops for the fractionation industry. These workshops will provide an open forum where industry and our regulators can discuss strategies for enhancing compliance with cGMPs. The first workshop is tentatively scheduled for Spring 1999. We anticipate that the program will include issues on environmental monitoring and quality systems.

Industry Response to Product Shortages
I would like to focus my remaining testimony on the industry response to shortages of plasma products and their recombinant analogs. During a hearing of this committee on May 7, 1998 to discuss a shortage of Intravenous Immune Globulin (IVIG), IPPIA provided data from our members in an effort to quantify available supplies and determine the causes of the shortage. We also committed to providing updated data on a quarterly basis to better understand the supply situation as the shortage evolved. The data we supplied in May showed IVIG supply on a yearly basis, with a preliminary forecast for 1998. The data was also limited to IPPIA members only.

I am happy to announce here today that we have expanded this effort to include data initiatives that will provide this committee, FDA, patients, and other interested parties with more sensitive indicators of the U.S. supply situation. First, through Georgetown Economic Services we have expanded our data gathering effort. Now, we have included data from the American Red Cross and Novartis, the two major distributors of IVIG not accounted for in our last

discussion. We have also enhanced the usefulness of this information by collecting actual sales data on a monthly basis, and have data for the first six months of 1998. This monthly data is an accurate measure of actual U.S. consumption, and will provide a more timely indicator of changing supply situations. With the addition of the new participants, we will now allow be able to see the complete picture for the U.S. supply of IVIG, and changes to that supply on a more timely cycle. We have included a ratio of inventory to consumption that can be used as an indicator of trends in the balance of supply versus demand. The following table reflects the newest data:

1998 U.S. Supply of IVIG*

Kg	Jan	Feb	March	April	May	June
Inventory	626	844	585	478	501	812
Emergency Supply	75	87	101	121	102	121
U S Consumption	1162	1240	1343	1352	1326	1822
Ratio	.54	68	44	35	.38	45

* To date

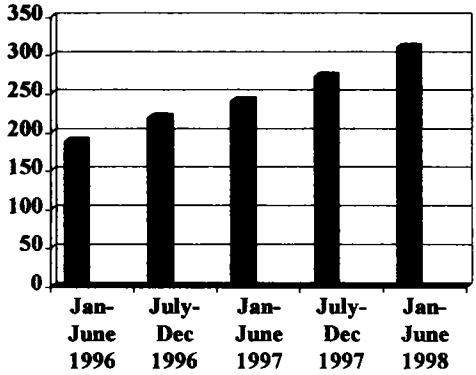
In ideal situations, manufacturers stock one and a half to two months sales as minimum inventory in an effort to manage product releases and provide an adequate supply for distribution. This would show up as 1.5 to 2 on the inventory to consumption ratio above. Any inventory below one months supply (1.0) indicates a critical supply situation. The ratios listed here very from .35 to .68, indicating that the inventory of IVIG is still less than one month's supply.

The good news from this table is that it shows that the supply levels have remained stable and actually show a slight increase over the six-month period. Now that we have established the data collection system, we will continue to monitor this situation and provide monthly updates of this information to this committee, FDA, consumer groups, and other interested parties.

In addition to the collected data on IVIG, we have also started an initiative to collect information on the supply of Factor VIII products in collaboration with Georgetown Economic Services. We will first focus on genetically manufactured (recombinant) Factor VIII products.

Our members have consistently made additional quantities of recombinant factor VIII available to the U.S. market as this therapeutic has gained in its use. The following graph illustrates the increasing U.S. supply for the years 1996-1998:

U.S. Consumption Recombinant Factor VIII
1996-1998*
(MIU)



* To date

In a further effort to monitor available supplies for these products, IPPIA initiated a data gathering effort similar to that for IVIG. The vast majority of hemophilia A patients use either recombinant or high purity plasma derived factor VIII for their treatment, consequently, we focused our data collection to these products.

1998 U.S. Supply of Recombinant FVIII*

Mio Units	Jan	Feb	March	April	May	June	Jul
Inventory	140.6	145.6	132.1	134.3	97.5	99.8	75.1
Emergency Supply						1.5	1.8
U S Consumption	48 1	45 1	48 8	52 8	50 8	65.4	48
Ratio	2.9	3.2	2.7	2.5	1.9	1.5	1.6

*To date

The trend from this data shows a decreasing inventory to consumption ratio. A factor to be taken into account is the fact that one of the manufacturers of recombinant factor VIII has announced that production problems have temporarily limited its ability produce this therapeutic. Given this, one could expect tight supply versus demand margins in the near future. The ratio calculated from the gathered data seems to be a good indicator for this. We will continue to closely monitor the supply situation. As you can see on this chart, an emergency supply of this therapeutic is beginning to be developed in response to this situation.

A tight supply to demand margin of recombinant factor VIII may have an impact on consumption of the plasma-derived factor VIII. As with the other products we have started to look at this ratio as well.

1998 U.S. Supply Ratio of Plasma Derived Factor FVIII*

Ratio	Jan	Feb	March	April	May	June
Ratio	3 3	3 8	2 5	3.0	3.7	1.4

*To date

The ratio indicates that changes occur throughout the year and went down in June. We will continue to monitor this situation very closely on a monthly basis.

Our industry is taking several actions to address any potential supply issues for factor VIII, similar to those taken to address the IVIG supply. Short term, our members are working with FDA to ensure quick lot releases for products as they become available. Additionally, an emergency supply of recombinant factor VIII is being developed for patients in critical need. More long-term, our companies are investing hundreds of millions of dollars to expand overall capacity to manufacture the needed therapies.

Conclusions

In conclusion, I would like to reiterate that our members are working in cooperation with the FDA to address issues associated with continued cGMP compliance. At the same time all of us are committed to continuing to provide access to adequate supplies of these life-saving therapies. At times, this can be a delicate balance. Our commitment here today is to make sure that by working with the FDA, this and other governmental bodies, and patient groups, this balance is reached. We will continue our constant efforts to provide a safe and adequate supply of these products.

The IPPIA members Alpha Therapeutic, Baxter Healthcare Corporation, Bayer Corporation, and Centeon, together with the American Red Cross and Novartis have already started to collect data on plasma products to better understand current and potential future shortages. The collection of actual consumption data gives an accurate picture of the current supply for our industry, and we believe that our newly developed model for collecting and sharing this data will be a good indicator of the current supply of our products. However, the use of this data for making accurate predictions is problematic due to unknowns, such as changes in clinical demand, the unexpected nature of technical manufacturing problems, and a changing regulatory environment including but not limited to the cGMP compliance issues discussed earlier. We will continue to collect and make

available supply data on a monthly basis, and we are willing to provide this information to assist interested parties including government agencies and consumer groups to understand supply related issues.

Thank you, and I would be happy to respond to any questions from the committee.

IPPIA International Plasma Products Industry Association
1100 New York Avenue • Suite 1080 • Washington, DC 20005 USA
Telephone: (202) 789-3100 • Telefax: (202) 789-4197
e-mail: 75424.1742@compuserve.com

Attachment 1

007842

IPPIA Voluntary Initiatives Presentation

Blood Products Advisory Committee

56th Meeting – 18-19 September 1997

Quality Suites Hotel – Rockville, MD 20850

Introduction: Douglas Bell, IPPIA

Good afternoon. My name is Douglas Bell . I am Director of Public Affairs for the International Plasma Products Industry Association or IPPIA. I will serve as moderator for our presentation regarding the ABRA Quality Plasma Program and IPPIA's Voluntary Initiatives. Immediately following me will be James P. Reilly, President of the American Blood Resources Association (ABRA) to discuss the background and history of QPP. Following him will be Dr. Tom Waytes for IPPIA who will outline the IPPIA Voluntary Initiatives and the scientific reasoning and data supporting their implementation. Finally I will return to summarize.

Before the technical presentations begin I would like to briefly outline for you the role of the IPPIA and its relationship with ABRA. It is also worth noting that IPPIA is affiliated with the European Association of the Plasma Products Industry which represents the vast majority of the commercial fractionation industry in Europe.

IPPIA is the international trade association representing the commercial producers of plasma-based therapies. IPPIA Members produce approximately 80% of the US market for plasma-based therapies. IPPIA Members include the four largest commercial fractionators: Alpha Therapeutic, Baxter Health Care, Bayer Corporation, and Centeon.

ABRA is the trade association representing the US source plasma collection Industry. Because many fractionators have plasma collection operations, there is overlap in the IPPIA/ABRA membership. Distinct from IPPIA, ABRA members also include both large and small independent source plasma collectors and other European/US plasma industry related affiliates.

With IPPIA representing the fractionation industry's interests and ABRA representing the source plasma collection industry's interests, we represent virtually the entire commercial plasma Industry.

Because of the unique way source plasma is collected and our membership being exclusive to the "commercial" sector, our Voluntary Initiatives and programs that exceed FDA regulatory requirements do not apply to those that exclusively collect or fractionate plasma recovered from whole blood collection.

Before I yield the floor to my colleague Jim Reilly, who will discuss the QPP program, I would like to provide you with a little background on the evolution of the IPPIA Voluntary Initiatives. About two years ago the industry of its own volition began formal discussions regarding innovative ways on an industry-wide basis we could improve upon the margin of safety in plasma based therapies. These discussions required a significant amount of time, personal commitment, compromise, and financial investment. The conclusion was that measures should be developed to reduce the potential that so called window-donations, a risk factor, could enter the manufacturing process.

As a result, industry drafted four voluntary initiatives that focus on minimizing the risk of "window units." We determined that there were three primary opportunities for window units to enter the manufacturing process:

- Units of plasma from previously untested one-time donors;
- Previously collected negative units of plasma from repeat donors who subsequently seroconvert; and
- Units of plasma collected from repeat donors who have tested negative but do not return after their last donation; and

We have developed an industry initiative to address each of these theoretical threats from window units and also developed a standard to institute new, more sensitive testing technology to further close the window period. More broadly, we believe that these initiatives address three fundamental risks: that of the known pathogens; that of the unknown or emerging pathogens; and that of limited access to plasma-based therapies. Dr. Tom Waytes will talk in more depth about each of the four voluntary initiatives.

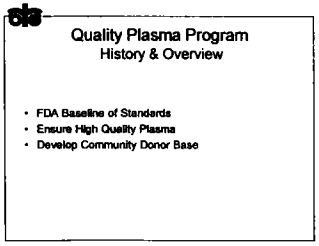
During 1997 IPPIA member companies, as well as the European members of the European Association of the Plasma Products Industry (EAPPI), in cooperation with ABRA, have been implementing these standards one by one as technology and regulatory approval will allow. We have started the collection of data to measure the progress and effectiveness of the program. Our objective is to continue to collect more data to validate the program and subsequently report publicly on the progress that we have made. These efforts will be a component part of an additional comprehensive initiative that we are in the process of developing.

I would ask that you hold any questions until the end of our presentation. Each of our speakers will remain at the front to answer any of your questions.

ABRA and QPP: James Reilly, ABRA

Good afternoon ladies and gentlemen. Before we move to some of the current and future initiatives of the plasma and plasma products industry, I would like to give you a brief overview of our Quality Plasma Program (QPP).

The QPP is a series of voluntary standards, that if adopted by an FDA licensed plasma collection center make them eligible for QPP.



The QPP requires, as a baseline, FDA licensure. From that point, as an industry we have developed consensus standards which take advantage of unique opportunities in our collection and testing procedures, and donor population to ensure high quality plasma. One of the most critical steps is the aggressive and targeted recruitment of a community-based donor population.

Quality Plasma Program
Facts & Figures

- Established 1991
- 380 of 410 Centers Certified
- 12 m of 13 m Donations Certified
- 1m to 2m Donors
- 11m Liters of Source Plasma
- NHF Support by Resolution & Letter
- Worldwide Recognition

Before I go into the standards themselves and some of the changes we have made to the program over the years, it would be useful to review a few basic facts about the industry and QPP.

QPP began in 1991 with the first center being certified. Today, 372 of the eligible 413 commercial plasma centers are QPP certified. To place this in a more meaningful context, roughly 1.5 million donors donate approximately 13 million times annually. About 12 million of those donations are at a QPP certified center. These donations produce about 11 million liters of plasma.

This program is supported by the National Hemophilia Foundation by Board Resolution and subsequently by a letter to all of the U.S. fractionators encouraging them to make it a requirement in their plasma collection specification.

Over the years, it has in fact become a requirement of all the U.S. plasma fractionators and most of the fractionators world-wide. To put the world market into perspective, the 11 million liters produced here in the U.S. is about 60% of the entire world supply of plasma for further manufacture.

Quality Plasma Program
Standards Upgrade History

- Employee Education & Training
  - Education added / Training updated
- National Donor Deferral Registry
  - Software Operating Improvements
  - FDA 510(k) Reviewed
  - Tests added (p24 & PCR)
- Viral Marker Rate Standards
  - HCV Added
  - HBV and HIV Lowered

I am going to work backwards a little and quickly review the changes to the QPP since 1991 and then discuss the current standards in total.

The employee training standards have been upgraded once and minimum educational requirement added.

The National Donor Deferral Registry (NDDR) has had several minor software upgrades since 1992, when it first entered pilot phase usage, and on March 20, 1997, it received FDA 510(k) determination of substantial equivalence allowing ABRA to market NDDR as a medical device.

We have also added additional positive test results as causes for listing a person on the NDDR. They are HIV p24 antigen and PCR test results.

The viral marker standard we currently have has been upgraded in two ways, by adding HCV and lowering the HBV and HIV rates in 1993.

Quality Plasma Program
Standards Overview

- Employee Education & Training
- Community Based Donor Population
- Facility Criteria
- Donor Screening Criteria
- National Donor Deferral Registry
- Viral Marker Rate Standards
- Bi-ennial Inspections

With the changes behind us, now let me describe in a little more detail all of the QPP standards. If you have any specific questions I would be happy to answer them at the conclusion of our overall presentation.

First, facilities must have a formal employee training program. The QPP provides guidance by dictating the components of the program such as initial, annual and interim training; documentation; retraining; and that all functions in the center are covered.

Some of the ways we create a community based donor population are through requirements for donor identification with a local address as an example. This criteria actually serves as a useful function on the rare occasions when we have positive viral marker test results, by improving our ability to contact the donor and appropriately counsel and refer those donors for further medical evaluation and treatment.

We have very rigid criteria intended to ensure that each location maintain their facility as a professional medical operation. These include criteria related to signage, cleaning, storage facilities, donor flow, lavatory facilities, etc.

Donor screening criteria include a variety of additional standards. Each is designed to focus on the retention of qualified donors and the exclusion or deferral of donors at increased risk of known and possibly unknown viral transmission. As you know, the unknown is very difficult, if not impossible, for us to quantify until it becomes the known. The additional screening criteria we require include increased emphasis on donor education of high risk activities, exclusion for incarceration, and drug testing.

We are particularly proud of the next requirement. It is participation in the National Donor Deferral Registry. We have successfully developed a national computer system capable of capturing the name and a donor identification number for any plasma donor who tests positive for any viral marker test. The donors are listed on the NDDR by industry testing laboratories utilizing a secure private computer network. Collection facilities can instantaneously check donors against the Registry utilizing an 800 telephone number and a series of location specific identification numbers and passwords. All of the QPP centers and associated laboratories are required to participate in the NDDR.

One of the more creative of the standards is the application of a viral marker rate standard to all locations. I will describe this standard in more detail in just a minute.

Finally, each facility is required to submit specific documents and data for review and they are subject to both bi-ennial scheduled and random unannounced inspections by third party inspectors.

Quality Plasma Program
Viral Marker Rate Standard

- Tests: HIV and HBV 1991
- Based on Applicant & Qualified Donor Rates
- Mean Plus Two Standard Deviations
- HCV Added 1993
- HIV and HBV Lowered 1993

I would like to describe the viral marker rate standard in a little more detail because we are developing a significant change to this standard this year. In 1991, we established a standard for HIV and HBV. At that time, and until very recently, plasma products were manufactured from plasma obtained from both applicant donors and qualified donors. With this in mind, we set the standard based on the mean industry average of all positive tests per center plus two standard deviations.

In 1993, we added a standard for HCV and lowered the acceptable standard for HIV and HBV by 19% and 32% respectively. The rates for HIV and HBV were lowered because we were seeing steady improvement in the industry mean as a result of the overall affect of the QPP.

In 1997, we are making an even more substantial change based on the imposition of an applicant donor exclusion standard which Dr. Waytes will describe in just a moment.

American Blood Resources Association

Future Initiatives

- Employee/Industry Training Workshops
- Expanding QPP Standards
  - NDDR
  - Viral Marker Rate
  - Donor Screening
  - cGMP & QA
- Expanded Patient & Regulatory Liaisons
- Location/Relocation Guidelines

Finally, before I turn the microphone over to my colleague Dr. Waytes, you should also be aware that we don't view the QPP, the current voluntary standards, or any of the industry's programs as stagnant. This slide is simply a list of a number of initiatives we currently have in various stages of discussion and implementation.

They are development of basic and train the trainers level workshops for plasma center personnel on QA and cGMP issues; further improvements to the QPP standards related to NDDR, viral marker rates, donor screening, and cGMP and QA criteria; expanding patient and regulatory liaisons and communication; and development of a plasma center location guideline.

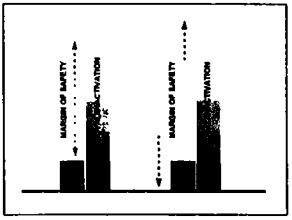
Quality Plasma Program
1997 Improvements

- Applicant Donor Standard
- Viral Marker Rate Standard

Next, Dr. Waytes will describe several new industry-wide voluntary standards. The two of these that are related to the plasma collection portion of plasma product manufacturing have and will become QPP standards. They are a Qualified Donor Standard or the exclusion of the use of plasma from non-returning applicant donors from further manufacture, which became effective in July of this year, and a new viral marker rate standard based on the confirmed positive viral marker tests in qualified donors.

Let me now introduce to you Dr. Thomas Waytes who will describe in more detail the new voluntary standards and provide you with some data in support of the standards and from our initial experience with these standards.

IPPIA and Voluntary Initiatives: Dr. Thomas Waytes, Immuno-US, Inc.



Good afternoon, my name is Tom Waytes, and today I am representing the IPPIA. The member plasma fractionators of the IPPIA have continuously sought to improve the quality of their therapies by increasing the theoretical "margin of safety," the difference between the maximum potential viral load of the manufacturing plasma pools and the sum of the virus removal/inactivation steps incorporated into the manufacturing processes.

My presentation will focus on industry initiatives to increase the safety of the plasma starting material.

To address further the issue of reducing the potential maximal viral load in manufacturing pools, the IPPIA took the historic step of implementing what are now known as the four "Voluntary Initiatives."

IPPIA Voluntary Standards

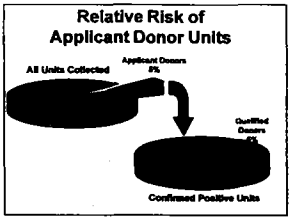
1. **Applicant Donor Standard**
2. **Viral Marker Rate Standard**
3. **Inventory Hold**
4. **PCR Testing**

These Initiatives include:

1. Applicant Donor Standard
2. Viral Marker Rate Standard
3. Inventory Hold
4. PCR Testing

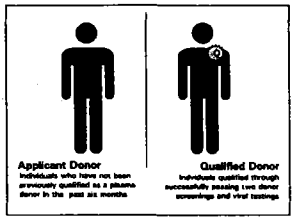
ABRA subsequently has endorsed these Initiatives and has committed to incorporating those standards applicable to plasma collection into its QPP. Over the next few minutes, I will discuss the Voluntary Initiatives in detail.

Applicant Donor Standard



A recent investigation has shown that, although only a small percentage of source plasma units are collected from first time donors, or "donor applicants," these units account for approximately 95 percent of all positive viral marker test results.

The first of the Voluntary Initiatives, implemented in July 1997 as an element of QPP, requires that no units of plasma be accepted for further processing unless the donor has successfully passed at least two health history interviews and two panels of all required screening tests. This standard takes advantage of the repeat donor population unique to the source plasma industry, to further reduce the risk of undetected infectious units of plasma being manufactured.



DEFINITIONS:

Applicant Donor - All individuals presenting themselves who have not been previously qualified as a donor in the past six (6) months.

Qualified Donors - All individuals who have been qualified for continued donations by successfully passing two donor screenings and viral testing.

STANDARD:

Individuals will be considered Applicant Donors until such time as they have successfully passed the following two-stage minimum donor screening process:

Persons presenting themselves for donation initially will be screened according to all applicable government and QPP screening and testing criteria. This applies whether a complete plasma unit or sample only is collected. At this stage the person will be considered an Applicant Donor.

Reclassification of a person from Applicant Donor to "Qualified Donor" is achieved by passage of a physical examination as required by government regulations and either:

a) Subsequent donation of a complete unit, and acceptable donor screening and testing based on all applicable government and QPP requirements, or
b) Subsequent donation of a sample only for the purposes of viral marker testing and successful passage of the complete medical history screening questionnaire.

The subsequent screening of Applicant Donors must occur no less than the minimum time interval allowed by applicable government requirements and no greater than six (6) months.

Testing and donor screening to classify a person as a Qualified Donor must be administered by collection centers operated by the same company.

No units of plasma from Applicant Donors will be acceptable for the manufacture of therapeutic plasma products until the person has become a Qualified Donor.

What this accomplishes, is that no plasma will be used for manufacture that has come from a donor who has not shown a commitment to repeat participation at the plasma centers. This markedly reduces the probability of using plasma from unacceptable populations such as persons who appear primarily for free viral testing, or those in immediate monetary need. This standard also ensures that at least two acceptable virus screening panels are performed on each prospective donor, which reduces the probability of testing error, and, to a lesser or greater degree (depending on the interval between samples), reduces the "window period" for each virus.

In summary, the use of plasma from one-time donors is completely eliminated through this initiative. Through this standard, Industry is also able to retrospectively assess the acceptability of initial donations with subsequent interviews and test results.

Viral Marker Rate Standard

The second Voluntary Initiative will redefine the existing standards to re-establish a maximum allowable viral marker rate for incidence of anti-HCV, anti-HIV, and HBsAg in qualified donor populations. It was agreed by the members of IPPIA and ABRA that the quality of plasma from a given center is best determined by measuring the confirmed reactive rates of all plasma units obtained from the Qualified Donors of each center. Because the donor population and testing requirements are precisely defined, this standard will provide an ability to monitor and assess the overall quality of the repeat donor population at each center.

All participating centers are committed to have begun to perform confirmatory testing of anti-HCV, anti-HIV, and HBsAg as of July 1997. From this date, the confirmed reactive rates of Qualified Donor units obtained at each center will be

collected for each of the three viral markers. The data collected over the first six months, will be analyzed statistically, so that a meaningful maximum cut-off level can be established. Each donor center will be required to maintain a viral marker rate below this limit as part of its QPP certification. Facilities exceeding the limit will be identified for corrective action or exclusion from the program. This standard will be implemented in January 1998.

ABRA Confirmed Viral Markers from Qualified Donors

HBsAg	0.005%
anti-HIV	0.0019%
anti-HCV	0.012%

In order to obtain an estimate of the expected viral marker reactive rates to be obtained in the above plan, ABRA has undertaken a viral marker data collection effort concerning confirmed positive rates of units from Qualified Donors at participating centers.

Retrospective data was collected prior to July of this year from varying time periods ranging from 6 weeks to 6 months from all industry laboratories. This data represents a total of 3.175 million donations collected from nearly all industry plasma centers, and is shown as follows:

ABRA Confirmed Viral Markers from Qualified Donors

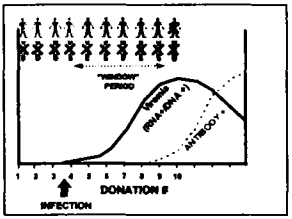
HBsAg	0.005%
anti-HIV	0.0019%

anti-HCV 0.0112%

This retrospective data was collected to obtain an immediate glimpse of where our prospectively determined rates are likely to be. ABRA will publish data collected during the July 1 - December 31 period, as well as that collected on an annual basis. Viral reactive data collected from all participating centers will be evaluated on a routine basis so that meaningful "cut-off" limits can be maintained.

Inventory Hold

The third Voluntary Initiative is the institution of an inventory hold for units of plasma prior to pooling for further processing. A minimum 60-day hold will be implemented on all units collected by January 1998.



The inventory hold program takes full advantage of the frequent and repeated participation of source plasma donors. As can be seen in this example, if a donor becomes infected with a given virus (e.g. HIV or HCV), a "window period" exists, during which time he/she is potentially infectious, but is not detected as such by current screening tests which measure antibody response to the viruses. By holding all seronegative units in an inventory hold, this standard provides manufacturers with the opportunity to retrieve units from previously qualified

donors who seroconvert on a subsequent donation, or are otherwise disqualified. Thus, "window period" units, as those shown in the cartoon, can often be prevented from entering the manufacturing pools.

Data have been obtained over a five-month period from an IPPIA member company incorporating an inventory hold program. During that time over 300,000 units of plasma were entered into the inventory hold. It is important to note that approximately 97% of these units were followed by a subsequent donation by the same donor. A total of 2555 units were removed from the inventory hold as the result of 331 donors being identified by subsequent seroconversions, other surrogate testing, or post-donation information. As a result, these units were prevented from entering the manufacturing pools.

The voluntary inventory hold identifies units obtained from seroconverters for HIV, HCV, and HBV. It also has the capacity of removing units that may contain any known or unknown virus of which transmission may be associated with the potential high-risk behavior identified by the current testing methods or post-donation information.

PCR Testing

The fourth Voluntary Initiative is the implementation of Genome Amplification Technology, commonly known as Polymerase Chain Reaction (PCR). This technology can further reduce the "window period" by identifying potentially infectious units which fall below the detection threshold of existing donor screening and testing technologies. Each of the manufacturers is working closely with FDA and other affected parties to obtain the required agency approvals necessary to implement PCR technology as rapidly as possible.

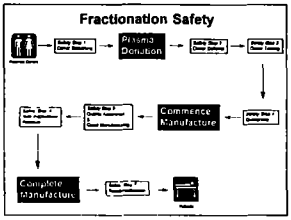
Not only can PCR testing limit the maximum potential viral load to the detection limit of this sensitive assay, it can also serve to validate the effectiveness of the previously described standards.

SUMMARY

The four Voluntary Initiatives, described above, represent a tremendous cooperative effort between plasma collectors and fractionators, and are expected to have a significant impact on increasing the margin of safety of all products derived from human plasma. It should be emphasized, however, that these standards represent not a final solution, but a dynamic process which will be continuously evaluated and improved. These Voluntary Initiatives discussed **above are part of a comprehensive package of initiatives put fourth by Industry to take advantage of new information systems and technology used to continuously improve the margin of safety in plasma-based therapies.

It is hoped that the significance of these efforts will be recognized by the appropriate regulatory agencies, as well as the consumers of our life-saving products.

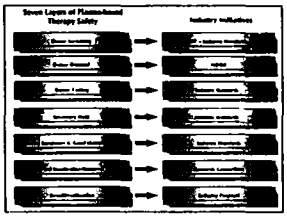
Summary: Douglas Bell, IPPIA



Our commitment to safety is clearly illustrated by the QPP and the voluntary initiatives. More importantly, what can be seen is that we have responded to the challenge and the pursuit of making plasma-based therapies ever safer not with rhetoric, but with action.

You have heard a detailed discussion of the ABRA Quality Plasma Program and the IPPIA voluntary initiatives. As you can see, these initiatives are dynamic and continually evolving in our search for safer therapies. Some of these initiatives have been in place for years, others are being implemented and we are proud to announce yet another addition to our safety initiatives.

In our testimony this summer before Congressman Shays Human Resources subcommittee we outlined seven layers of safety in the manufacture of plasma-based therapies. The uniqueness of fractionation allows for these additional layers of safety. We believe that these layers of safety are fundamental to achieving the level of safety our patients expect and need.



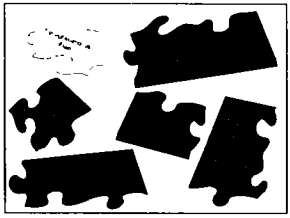
- **Donor Screening**
- **Donor Deferral**
- **Donor Testing**
- **Inventory Hold**
- **Quality Assurance & Good Manufacturing**
- **Viral Inactivation/Removal**
- **Recall/Notification**

As you have just heard, industry has for years actively and methodically undertaken a series of voluntary initiatives to address these opportunities for defense. These industry initiatives serve to compliment the individual efforts made by each manufacturer to safeguard against impurities. Together, these efforts form a protective safety barrier that is far stronger than each of the

component parts. Yet, all of these parts must be strong in order to provide the best assurance of safety.

What we are pursuing -- and what we committed to at Chairman Shays oversight hearing -- is a comprehensive plan that builds upon the seven layers of safety. A comprehensive plan that will review the existing initiatives to measure their progress, assess the need for new initiatives, and communicate to key individuals our objectives and the progress we have made. In a staged-process, we are assessing our existing voluntary initiatives, our commitment to reduce pool size, and the need for new programs. In the context of this examination we will determine accurate forms of measurement to quantify our progress.

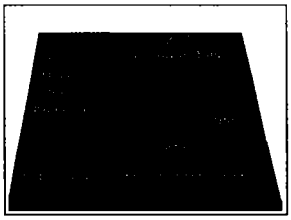
As IPPIA Executive Director Robert Reilly stated "That is our goal, our challenge, and our commitment -- and we will verify the success of our efforts through accurate measurements."



If you examine the QPP certification standards and the four voluntary initiatives at the macro-level, each is an important piece of the safety puzzle. Each has its

critical role in maximizing safety. Each has its critical time in the process. Finally, each has its critical place in the system.

What is evolving -- and what industry has committed to develop -- is a keystone to these programs that will be the glue bringing all of the pieces of the puzzle together.



IPPIA over the next several months will be examining the key elements of this plan. We will share those key elements with Congress, the FDA and Consumer groups for feedback and comment. After receiving comment from interested parties, the industry will then finalize the details.

The seven layers of safety are the foundation upon which we are building in our on-going commitment to making plasma-based therapies safer still. The basis of our strategic plan should then be no surprise. The industry has a long history of multi-faceted voluntary initiatives that address the seven layers of safety. We are looking toward expanding those voluntary initiatives to include a keystone or comprehensive plan that will help interlock the existing voluntary initiatives together with the seven layers of safety into one unified program.

As providers of plasma-based therapies we are, and must continue to be, leaders in the commitment to safety. It is a responsibility that we take very seriously. The message we are sending through these voluntary initiatives and our commitment to this comprehensive plan should be clear: industry is dedicated to continuous improvement, so that the people who depend upon plasma-based therapies for their health and their very lives will know that those therapies are safe, available, and effective.

Finally, we invite you to watch us grow as we reach out to the Internet to communicate our message. Our address is IPPIA.ORG. The web page is a work under progress right now but will be a critical component in our comprehensive plan.

Attachment 2
Quality Systems in the Fractionation Facilities Provide a System of Redundant Quality Crosschecks

Quality Systems	Personnel	Facilities	Equipment	Raw Materials	Process	Final Product
Documentation	Job descriptions Training files Facility access Job certifications	Validation studies Maintenance logs Cleaning Procedures FDA approval/license Personnel access	Use logs Cleaning logs Maintenance logs Preventative Maintenance Procedures	Specifications Contracts Acceptance tests Material identifications FDA approval	Procedures Operating parameters Change control Deviations FDA approval Investigations	Release specifications Adverse events Batch records FDA approval/license FDA batch release in some cases
Validations	Specific job functions Sterile fill qualifications Job certifications	Water Air Steam Compressed gasses	Installation, operation and process qualifications	Changes require qualification or validation	Developmental reports Initial process validation Specific step validations, e.g., media fills Revised processes	Stability studies Post market surveillance Annual production review
Change Control	New job responsibilities Facility access New or revised procedure training	Design Air System FDA approval Validations	Operational parameters Functional changes FDA approval	Specifications Vendor qualifications Process validation	Individual steps Operating parameters Validations FDA approval	Specifications Labeling Documentation FDA approval
Investigations	Perform functions correctly Training effectiveness	Operating as designed Adequate corrective actions	Operating as designed Adequate corrective actions	Vendor qualifications Specifications Process impact Additional testing	Per procedures Anomalies Training of personnel Trending	Meets specifications Anomalies Trending Complaints/Adverse events
Corrective Actions	Retraining Termination	Redesign improvements Revised or increased testing FDA approval	Redesign improvements Replacement Reestablish parameters FDA approval	New materials New vendors New process Additional testing Revision of acceptance tests	Per procedures Redesign of process or equipment Change control FDA approval	Discard/Quarantine Change process Withdraw/Recall FDA approval

Quality Systems	Personnel	Facilities	Equipment	Raw Materials	Process	Final Product
Testing	Dry runs Supervisory review Proficiency testing Job certifications	Environmental monitoring of air, water, steam, compressed gases	Special studies Validations/revalidations In-process testing	Validation In-process testing Acceptance tests Validations/revalidations	Validation In-process testing Documentation Validations/revalidations	Specifications CBER lot release QA review Stability Validations/revalidations
QA Review and Audit	Training records Job functions Certifications Training effectiveness	Audits Trending environmental monitoring Corrective action implementation and effectiveness	Trending Audits Adequacy of corrective actions	Trending Audits Investigation results Adequacy of corrective actions	Trending Audits Record review Change control Investigations	Trending Audits Record reviews Change control Investigations
TQM	On-going training	Technology improvements Increasing regulatory and industry expectations	Technology improvements	Material improvements Revised or additional testing	Technology improvements for safety, purity and potency Revised or additional tests	Technology improvements Revised or additional testing

Mr. SHAYS. Mr. McDonough.

Mr. MCDONOUGH. Chairman Shays, thank you and members of the House Human Resources Subcommittee. I'm Brian McDonough, the chief operating officer and responsible head of the American Red Cross Blood Services, and I thank you for the opportunity to respond to the report by the General Accounting Office on the safety of plasma derivatives.

By way of background, the American Red Cross Blood Services is the Nation's largest supplier of transfusable blood components, serving more than 3,000 hospitals across the country. We collect almost 6 million units of whole blood through the generous donations of nearly 4½ million volunteer donors. The Red Cross provides both transfusable blood components and plasma derivatives. Consistent with the needs of transfusion medicine, units of whole blood are separated into specific components following donation, those being red blood cells, platelets and plasma. Due to the relatively limited need for plasma for transfusion, most of the plasma Red Cross recovers from whole blood donations is fractionated into the various plasma derivatives.

The Red Cross plasma derivatives account for approximately 15 to 20 percent of the Nation's supply; however, the Red Cross does not fractionate its own plasma products. Rather, we contract with Baxter Healthcare's Hyland Division and the Swiss Red Cross to manufacture AHF, IGIV, and albumin products under FDA licenses.

Mr. SHAYS. That's done in Europe.

Mr. MCDONOUGH. In Switzerland at the Baxter plant, Hyland in L.A.

Approximately 80 percent of the plasma the Red Cross recovers is fractionated by Baxter. As a distributor of plasma derivatives fractionated under the FDA licenses of other companies, the Red Cross is not directly responsible to the FDA for the compliance of these firms. We do, however, exercise great diligence to ensure the products distributed under our label are manufactured in compliance with cGMP's and FDA regulations. We have worked with Baxter and the Swiss Red Cross to support them in their compliance efforts and continue to monitor and evaluate these compliance actions undertaken by both fractionators. Further the Red Cross is responsible for maintaining its own good manufacturing procedures during the processing of blood donations from the time of collection through distribution to hospitals or the fractionators.

We were pleased to work with the GAO staff on the study, and commend them for their diligence in assuring that the study accurately compared differing data sets presented by the Red Cross and the American Blood Resources Association. We believe that the GAO report offers an accurate assessment of the comparative viral marker rates between volunteer blood donors and paid plasma donors and the possibility of incorporating a unit of plasma within the infectious window period into plasma pools.

The GAO faced several challenges in attempting to compare the safety of plasma derivatives from these two donor populations and insuring that the study accurately compared apples with apples. First, the length of time between donations as regulated by the FDA is significantly different between the two groups. Volunteer

blood donors are allowed to donate every 56 days with an average time between donations of approximately 154 days. Paid plasma donors may return every 48 hours, not to exceed two donations per week, and have an average time interval between donations of 5.3 days.

Second, the GAO was asked to look at the effect of plasma pool size on safety. A unit of recovered plasma is significantly smaller than that of source plasma, an average of 250 milliliters compared with 825 milliliters. The result is that an initial pool of recovered plasma incorporates plasma from more than three times the number of donations as the same size pool made exclusively from source plasma. Both of these factors, time between donations and the number of donors included in the plasma pool, have a distinct impact on the chance of incorporating a window period unit into the pool from which the plasma product is derived.

The remainder of my comments today will focus on efforts undertaken by the Red Cross to continuously improve the safety of transfusable blood components and plasma products distributed under our label. These efforts include improved viral inactivation methods, continuous surveillance of blood donors to identify potential emerging infections, improved testing methods, and our role in developing a system to notify patients in the event of a withdrawal or recall.

Researchers at the Red Cross Holland Laboratory are investigating methods to inactivate all viruses in plasma derivatives. The current virus inactivation procedures work most effectively on lipid-enveloped viruses, that is those which incorporate the fatty coats of cells in their structure, such as HIV and HCV, and they do not work as well on nonenveloped viruses.

One method of pathogen inactivation under study involves the use of iodine to inactive viruses and bacteria in plasma products. In this method iodine is chemically linked to a resin called Sephadex.® The resulting product is used in a filtration system which inactivates the pathogenic organisms. So far the use of this process is focused on IGIV, but we are also investigating the use of iodine with Sephadex® in the purification of other plasma products.

Promising efforts are also underway at our Holland Laboratory to identify methods of inactivating viruses in traditional transfusable blood components. To date it has been impossible to virally inactivate red cells or platelets without destroying their efficacy. Red Cross is investigating the use of a light-activated dye, dimethyl methylene blue, called 491. With this process a light-activated molecule, 491, binds to the nucleic acids of viruses and, when activated by light, causes the viral nucleic acids to break thereby destroying the infectivity of the virus. This type of system is feasible for use in red blood cells, because they contain no nucleic acids of their own. Preliminary studies show that the process successfully inactivated viruses without damaging the quality of the cells.

As Red Cross has previously shared with this subcommittee, we are actively engaged in several surveillance initiatives and remain vigilant in monitoring for emerging infectious diseases. There are three efforts which I would like to highlight for you.

First, the Red Cross research and surveillance program, known as ARCNET, researchers at the Holland Lab and in Red Cross regions throughout the country monitor the epidemiology of transfusion-transmitted diseases. ARCNET investigators work with our current and deferred volunteer blood donors to gather information critical to disease surveillance. Through an Internet-based communication system, ARCNET allows speedy exchange of the latest scientific information about existing and emerging infectious diseases. The system maintains a central repository for epidemiologic data used to support research studies undertaken at Hyland and at a number of our regions. At present the Red Cross is studying the possible impact of Chagas' disease and a number of tick-borne infections on the safety of the blood supply through this mechanism.

Next, Red Cross is a key participant in the National Heart Lung and Blood Institute retrovirus epidemiology study known as REDS. The REDS program supports a wide range of clinical, laboratory and epidemiology investigations of infectious disease agents in blood donors.

Mr. SHAYS. Mr. McDonough, I'm trying to follow you. I admit I should have had more sleep. I should have had some sleep. But I want to know the relevancy of what you're testifying now to the issue at hand. What's the bottom line point that you want me to know?

Mr. MCDONOUGH. The bottom line point is that we are working in several different avenues to identify risk associated with blood transfusion, emerging risks such as Chagas' or other tick-borne diseases which could or certainly may impact the safety of both whole blood and components and plasma derivatives, and a point that I would conclude on is that we're also implementing new testing technology for the same purpose.

Mr. SHAYS. I had a sense that this is all happening, and what I would love you to address, and then we'll get to Dr. Boyle, is the issue of the standard that exists now throughout the industry, the good manufacturing practices that take place and the issue of compliance versus noncompliance. Those would be the issues that I think that this committee has a sense that there has been tremendous progress and the desire to improve systems, but that's——

Mr. MCDONOUGH. Mr. Chairman, with that comment I'd be glad to conclude my remarks and defer comments about compliance on GMP——

Mr. SHAYS. If there's anything else that you want to cover in that statement, I'm happy to give you a second just to look at it.

Mr. MCDONOUGH. No, I think I've covered it adequately, Chairman.

[The prepared statement of Mr. McDonough follows:]

Chairman Shays, Representative Towns, and Members of the House Human Resources Subcommittee, I am Brian McDonough, Chief Operating Officer and Responsible Head of the American Red Cross Blood Services. Thank you for this opportunity to respond to the report by the General Accounting Office (GAO) on the safety of plasma derivatives.

As the Subcommittee is aware, the principal role of American Red Cross Blood Services is that of the nation's largest supplier of transfusable blood components, serving more than 3,000 hospitals across the country. The American Red Cross collects almost 6 million units of whole blood through the generous donations of 4.5 million volunteer donors annually. The Red Cross is both a provider of transfusable blood components and plasma derivatives. Consistent with the needs of transfusion medicine, units of whole blood are separated into specific components following donation -- red blood cells, platelets and plasma. Due to the relatively limited need for plasma for transfusion, most of the plasma recovered from whole blood donations is fractionated into various plasma derivatives.

Red Cross plasma derivatives account for 15 to 20 percent of the nation's supply. Unlike the commercial providers of plasma derivatives, the Red Cross does not fractionate its own plasma products. We contract with Baxter Healthcare's Hyland Division and the Swiss Red Cross to manufacture antihemophilic factor, intravenous immune globulin (IGIV) and albumin products under the FDA licenses of those companies. Approximately 80 percent of the plasma Red Cross recovers from six million volunteer donations of whole blood is fractionated by Baxter.

The American Red Cross is a distributor of plasma derivatives fractionated under the FDA licenses of other companies. As such, while not directly responsible to the FDA for the compliance of these firms, we must exercise due diligence to ensure that products distributed under our label are manufactured in compliance with FDA regulations. We have worked with Baxter and the Swiss Red Cross to assist them in their compliance efforts, and continue to monitor and evaluate corrective actions undertaken by both fractionators. Further, the American Red Cross is responsible for maintaining its own Good Manufacturing Practices (GMPs) during the processing of blood donations, from the time of collection through distribution.

GAO Report on Plasma Derivative Safety

We were pleased to work the GAO staff on this study, and commend them for their diligence in assuring that the study accurately compared differing data sets presented by Red Cross and the American Blood Resources Association (ABRA). We believe that the GAO estimates pertaining to volunteer blood donors are generally accurate. Susan Stramer, Ph.D., Director of the Red Cross National Confirmatory Testing Laboratory and Roger Dodd, Ph.D., Director of the Transmissible Diseases Department of the Red Cross Holland Laboratory, worked closely with the GAO staff. As you know, the American Red Cross Jerome Holland Laboratory, located in Rockville, Maryland, is the world's premier blood research facility. Drs. Stramer and Dodd provided data to the GAO and discussed the various issues involved in identifying and quantifying the viral marker rates among first time and repeat volunteer blood donors.

The GAO, and others, faced several challenges in attempting to compare the safety of plasma derivatives from volunteer recovered plasma with those using source plasma from paid donors. Several distinctions between recovered plasma and source plasma needed to be taken into account to assure that the study accurately compared apples with apples. First, the length of time between donations as regulated by the FDA, is significantly different between the two groups. Volunteer blood donors are allowed to donate every 56 days, with an average time between donations of 154 days. Paid plasma donors may return every 48 hours, not to exceed two donations per week, and have an average time between donations of 5.3 days.

Second, the GAO was also asked to look at the effect of plasma pool size on safety. Therefore it was necessary to take into account the fact that a unit of recovered plasma is significantly smaller than that of source plasma -- an average 250 ml compared with 825 ml. The result is that an initial pool of recovered plasma incorporates plasma from more than three times the number of donations as the same size pool made exclusively from source plasma. Both of these factors -- time between donations, and the number of donors included in a plasma pool -- have a distinct impact upon the chance of incorporating a window period unit into the pool from which the plasma product is derived.

We believe that the GAO report offers an accurate assessment of the comparative viral marker rates between the two donor populations, and the possibility of incorporating a unit of plasma within the infectious window period into plasma pools. Further, GAO cites viral inactivation as a "more significant step in reducing the risk of infection." Indeed, the efficacy of viral inactivation techniques is such that there has been no reported transmission of infectious disease through plasma derivatives since the introduction of viral inactivation techniques.

Red Cross Efforts to Improve Safety

The American Red Cross remains committed to ensuring that an ample supply of transfusable components and plasma derivatives derived from voluntary donations of whole blood by healthy individuals is available for patients in need. The remainder of my comments today will focus on efforts undertaken by the American Red Cross to continuously improve the safety of transfusable blood components and plasma products distributed under our label. These efforts include:

- improved viral inactivation methods;
- continuous surveillance of blood donors to identify potential emerging infections;
- improved testing methods; and
- the role of the Red Cross in developing an system to notify patients in the event of a withdrawal or recall.

Viral Inactivation Methods

Plasma Derivatives

Researchers at Holland Laboratory are investigating methods to inactivate all viruses in plasma derivatives. Current virus inactivation procedures work most effectively on lipid-enveloped

viruses—those viruses that incorporate the fatty coats of cells in their structure, such as HIV and HCV—and do not work as well on non-enveloped viruses such as hepatitis A virus (HAV) and Parvovirus. (HAV and Parvovirus are substantially reduced by partitioning during the fractionation process.) One method of pathogen inactivation being developed involves the use of iodine to inactivate viruses and bacteria in plasma products. In this method, iodine is chemically linked to resin called Sephadex®; the resulting product is used in a filtration system in which the plasma product is passed through two tubes, one containing iodine-Sephadex® and the second Sephadex® alone. Pathogenic organisms are inactivated by the iodine bound to the Sephadex® in the first tube, and excess iodine is trapped in the Sephadex in the second tube, resulting in a product that contains no active pathogens and no iodine. So far, the use of the iodine/ Sephadex® virus inactivation procedure has focused on IGIV. Holland Laboratory scientists are now investigating the use of iodine/ Sephadex® in the purification of other plasma products.

Cellular Blood Products

Holland Laboratory researchers are also researching the inactivation of viruses in cellular blood products, such as Red Blood Cells (RBCs). Virus inactivation procedures like iodine/Sephadex® are only applicable to noncellular blood products, such as plasma. Current efforts underway at Holland Laboratory to inactivate viruses in cellular products are focused on the use of a light-activated dye, dimethyl methylene blue, called 491. A light-activated molecule 491 binds to the nucleic acids of viruses, and when activated by light, causes the viral nucleic acids to break, thereby destroying the infectivity of the virus. This type of system is feasible for use in RBC products because RBCs contain no nucleic acids of their own and therefore cannot be damaged by 491 action. The results of the preliminary studies using 491 showed that the product successfully inactivated viruses in RBCs without damaging quality of the cells after storage. 491 can also inactivate white cells present in RBCs because, unlike red cells, white cells do contain their own DNA. White cells, or leukocytes, are associated with some adverse transfusion reactions and filtration to remove leukocytes from RBCs is recommended in some instances.

Surveillance for Emerging Infectious Diseases

ARCNET

The American Red Cross research and surveillance program, known as ARCNET, is a cooperative program between the Holland Laboratory and researchers in Red Cross Blood Services Regions throughout the country to monitor the epidemiology of transfusion-transmitted diseases. ARCNET investigators work with our current and deferred volunteer blood donors, to gather information critical to disease surveillance. Through an Internet-based communications system, ARCNET allows speedy exchange of the latest scientific information about existing and emerging infectious diseases. ARCNET maintains a central repository for epidemiologic data, used to support research studies undertaken at the Holland Laboratory and at a number of Blood Services Regions. In addition, Red Cross is studying the possible impact of Chagas' disease and a number of tick-borne infections on the safety of the blood supply.

NHLBI Retrovirus Epidemiology Study
Three Red Cross Blood Services Regions participate in the National Heart Lung and Blood Institute (NHLBI) Retrovirus Epidemiology Donor Study, known as REDS. The REDS program supports a wide range of clinical, laboratory, and epidemiology investigations of infectious disease agents in blood donors. The regions provide complete donation data and selected blood samples for repository collection and further testing. REDS continues to provide valuable information on behavioral risk factors of donors, and the effectiveness of donor screening measures.

Research Efforts Related to CJD:
To date, the American Red Cross has committed over $1 million to research studying possible links between CJD and transfusion-- more than any other private organization. We have several research studies underway at Holland Laboratory, and in collaboration with Dr. Paul Brown at the National Institutes of Health and Dr. Robert Rohwer at the Veterans Administration. The Red Cross is also continuing to work with Marian Sullivan, of the American Association of Blood Banks (AABB), who is directing a CJD "lookback" study, involving recipients of blood transfusions from donors subsequently diagnosed with CJD. These recipients have been followed for up to 25 years following transfusion, and none of them has died of CJD or shown any sign of the illness.

Improvements in Testing
As the Subcommittee heard at its hearing in May, the Red Cross has successfully implemented Transformation, a seven-year, $287 million program to re-engineer literally every aspect of Red Cross collection, processing, testing and distribution systems. Transformation has placed the Red Cross in a leadership position to further enhance the safety of the blood supply by adding genome amplification technology (GAT) testing to our donor testing processes. GAT employs a new technology that directly detects the genetic material of viruses that have infected human cells. This is a distinct improvement over current tests which detect antibodies formed by the body in response to infection. The result is a significant reduction in the "window period" (the time between infection and our ability to detect infectivity) for HCV (from the current 82 days to a projected 23 days), and a further reduction in the already small window period for HIV (from 14 days to a projected 9 days).

We are working with the FDA to secure approval of an Investigational New Drug (IND) application in order to implement GAT testing for HCV and HIV of plasma to be manufactured into derivatives later this year. This work is being done in collaboration with GenProbe Inc., the test kit manufacturer. At present, GAT testing of individual units of transfusable components is not operationally feasible. We remain committed however, to pursuing this technology for all of our products.

Patient Notification of Recalls
In response to concerns expressed by patient groups and this Subcommittee, the Red Cross moved aggressively to establish a system whereby patients using our plasma derivatives could be

notified as soon as possible in the event of a withdrawal or recall. Working with the National Notification Center, the Red Cross established an 800# and registry in which patients could voluntarily enroll to be notified in a confidential manner of any actions related to products in their possession. This system was developed with input from patient groups, including the National Hemophilia Foundation, Immune Deficiency Foundation, Committee on Ten Thousand and the Alpha One Foundation. Red Cross has made this system available to the International Plasma Products Industry Association for implementation of an industry-wide system.

Conclusion

State-of-the-art safety and consistent availability of plasma derivatives and transfusable components for patients in need remains the highest priority of the American Red Cross Biomedical Services. We commend you Mr. Chairman, Representative Towns, and Members of the Subcommittee for continuing your review of issues related to plasma safety, and thank you for the opportunity to take part in today's hearing.

Mr. SHAYS. Dr. Boyle.

Mr. BOYLE. Can you hear me?

Mr. SHAYS. I can hear you.

Mr. BOYLE. Mr. Chairman, members of the subcommittee, I'm John Boyle. I'm here on behalf of the Plasma Users Coalition. The coalition includes the Alpha One Foundation, the Alpha One National Association, the Committee of Ten Thousand, the Hemophilia Federation, the Immune Deficiency Foundation and the National Hemophilia Foundation. The coalition represents patients who depend upon the long-term use of plasma products for their health and very lives.

As you know, more than 500,000 Americans use plasma products each year; however, persons with alpha one antitrypsin deficiency, bleeding disorders and primary immune deficiency diseases must use plasma products many times each year for their entire lives. Collectively we represent about 50,000 Americans.

I'm here today speaking on behalf of these individuals who consume plasma-based products repeatedly and in large quantities to avoid painful, debilitating and life-threatening diseases. My infant son was diagnosed with one of those disorders nearly 20 years ago.

Four factors influence the Plasma Users Coalition on the issues before this committee. First, plasma products are essential to the health and well-being of persons with these chronic disorders. Second, there is no medically equivalent product available for alpha one or primary immune deficiency diseases. Third, the safety of these products is of utmost concern to chronic users. And fourth, we are experiencing serious shortages in these products.

Just last week the Surgeon General endorsed the use of recombinant AHF as the preferred treatment for hemophilia and recommended accelerated implementation for all individuals currently using plasma-based derivatives to recombinant usage. However, there is a continuing shortage of recombinant AHF, which, along with prohibitive costs, will keep persons with bleeding disorders members of the plasma products user community for some time to come.

The alpha one community is served by a sole manufacturer who has been at 50 percent production for the major portion of 1998. Moreover, even at 100 percent production by that manufacturer is not producing an adequate supply of protease inhibitor for augmentation therapy for eligible patients.

For nearly 20 years IVIG has been recognized as a safe and effective treatment for primary immune deficiency diseases. However, beginning in the fall of 1997, widespread shortages of IVIG developed. We are here today to report that the product availability has not improved significantly since the meetings in April or May, and we are very concerned the situation will get worse in the near future.

Now to document where we are with IVIG, we have just completed a survey of 100 doctors treating more than 2,000 immune-deficient patients. Over 90 percent of those doctors reported difficulty in obtaining IVIG for their patients since our previous survey in April. Half of the doctors who have had difficulty in obtaining IVIG report that that shortage since April has had negative effects on the health of their patients. Specifically patients are suf-

fering from increased infections that normally would have been checked by the recommended IVIG therapy.

Mr. SHAYS. Given that there's just one member here right at the moment, would you say that we need to take a look at this a few weeks from now or months from now after—with the ban lifted by Dr.——

Mr. BOYLE. Personally I don't think that lifting of that ban is going to have that much effect on the shortage. It certainly would be useful. We intend to continue monitoring the situation on a quarterly basis. But there are a number of factors that contribute to the shortage. I'm not aware of all of them.

Mr. SHAYS. OK. We'll come to that then.

Mr. BOYLE. This brings us to the substance of the GAO report. The GAO reports numerous deficiencies in adherence to good manufacturing practices in recent inspections of the four major fractionating companies. These deviations led to two consent decrees, including one which required a company to cease distribution of its products. This shutdown was one of several factors in the IVIG shortage.

The GAO report suggests a manufacturing industry that has significant problems with the production of plasma derivatives, with over 50 percent of the manufacturers under consent decree. I can tell you as a parent of a plasma user that the 429 deviations from good manufacturing practices cited in that report scares me, and I have to wonder is my son getting bathtub gamma globulin. At the same time, a few months ago my wife and I were pulled off a plane and told that my son had a medical emergency. It turned out that he and his medical center could not get gamma globulin through any mechanism at the moment, and that was quite scary.

So are plasma product users truly faced with a choice between safety and availability, or is neither of them possible? The GAO report unfortunately does not evaluate the state of manufacturing and specifically the safety of manufacturing at these plants. The 429 deviations could represent a broken industry which is the result of old plants, low investment and the company's indifference to the product and consumer, and it's inability to manufacture safe product. Or the same number could represent too much of a metermaid mentality on the part of the regulatory agency. A better understanding of the true situation is critical because it tells us about the future availability of safe plasma products for persons whose lives depend upon them. If the industry is currently unable to produce enough products according to reasonable manufacturing guidelines, we need to decide how to address the long-term production issues while trying to redirect the distribution system to get the available product to those patients for whom it is lifesaving.

Mr. Chairman, the consumers thank you and your subcommittee for its vigilance in oversight of this area. We thank you for the opportunity to comment on these issues. However, we hope that you will hold both industry and government to their responsibilities and commitments in this area. In the aftermath of the plasma product shortages earlier this year, we thought we had a promise from the industry for increased production. Based upon what we're hearing, we are likely to see further reductions in production in the

coming months rather than increases. If this is true, there will be high human costs.

We also thought we heard a promise from the FDA to try to address the distribution problems by a more extensive program of educating providers to the appropriate allocation of scarce resources, particularly in the area of IVIG. We don't think that promise has come to pass.

Please remember we are discussing life-sustaining therapies. Twenty years ago my wife and I were told that our 6-month-old son might not live through that night in the hospital. Today he is a college student, he has no health impairments, he has no activity limitations, he has not suffered a hospitalization in nearly 20 years. That's the difference that a safe product can make. We want to make sure that tens of thousands of other patients will continue to have access to safe plasma product.

Six months ago consumer organizations were asking for more information about the reasons for the shortages. Now in light of what we think is a worsening situation, we want to see more. We would like to see action. At the May 7 hearing Mr. Bacich of Baxter invited you to point at industry and challenge them to fix the problem. Did they fail to hear the challenge, or are they unable to meet it? We will wait to see action—while we wait to see action, better information is still necessary. The consumer organizations need to be made aware of FDA and industry actions taking place and how these actions will affect their product supply.

In conclusion, we offer the patient notification system as a model for cooperation and communication. While trying to fix the production problems, the plasma product distribution system should be approached in the same cooperative manner by the industry, government and consumers, assuring that delivery is made to those for whom it is life-sustaining.

Finally, the consumers wish to commend you, Mr. Chairman, for the recent recall amendment you offered to the appropriations bill. This type of legislation serves to further patient awareness, education and most importantly safety. The Plasma Users Coalition have a series of recommendations which are presented in my written testimony, but with the time limit, I haven't presented it here.

Thank you.

[The prepared statement of Mr. Boyle follows:]

Mr. Chairman and members of the Subcommittee, I am John Boyle and I am here today on behalf of the **Plasma Users Coalition**. The Coalition includes the Alpha One Foundation; the Alpha One National Association; the Committee of Ten Thousand; the Hemophilia Federation; the Immune Deficiency Foundation; and the National Hemophilia Foundation.

The Coalition **represents patients who depend on the long-term use of plasma products for their health** and very lives. As you know, more than 500,000 Americans use plasma products each year. However, persons with alpha one antitrypsin deficiency, bleeding disorders and primary immune deficiency diseases must use plasma products many times each year for their entire lives. There are approximately 4,000 alpha one plasma users, 15,000-18,000 bleeding disorder users, and 20,000-30,000 immune deficient plasma users. Collectively, we represent about 50,000 Americans. The Coalition exists so that we may exchange information and support the needs of individuals dependent on frequent and life long usage of plasma based products. Hence, Mr. Chairman, I am here today speaking on behalf of the 50,000 to 60,000 individuals who consume plasma-based products repeatedly and in large quantities to escape suffering from painful, debilitating and life threatening diseases. Personally, I am here today because my infant son was diagnosed with one of these disorders nearly twenty years ago.

First, it is very important to note that **plasma products are essential to the health and well being** of persons with these chronic disorders. For example, before the introduction of gamma-globulin for the treatment of immune deficient patients nearly fifty years ago, persons with these disorders could expect to suffer repeated infections until one finally killed them. Today, many immune deficient patients can be expected to live long and relatively asymptotic lives, thanks to intravenous gamma globulin. Second, there is currently **no medically equivalent product available** for alpha one or primary immune deficiency diseases. The bleeding disorders community does have a recombinant option, however, recombinant products are in short supply, and more expensive than some patients can afford.

Mr. Chairman, you requested that the Coalition address the following issues; the GAO report comparing viral marker rates of paid versus volunteer donors, the regulatory compliance of plasma manufacturers; current and chronic shortages of plasma products and finally the Department of Health and Human Services efforts to address product availability. Given our limited time and urgency of the latter issues I will focus my remarks on GMPs, product availability and efforts to address those issues.

As we noted earlier, the development of plasma products for alpha one, bleeding disorders, and immune deficiency diseases have dramatically extended the lives and improved the quality of life for tens of thousands of Americans. However, **a current and ongoing shortage of these products has** caused serious adverse health consequences. For example, in Alpha One Antitrypsin Deficiency, a congenital emphysema, diagnosis is usually made after 70% of lung function is gone, the lung deterioration is arrested but not reversed by treatment with plasma derivatives. Effective augmentation therapy is dependent on regular dosage and infusion. One study indicates a sixty-percent difference in mortality with treatment. Unfortunately, the Alpha One community is served by a sole manufacturer who has been at 50% production for the major portion of 1998. Moreover, even at 100% production there is not an adequate supply of Protease inhibitor for augmentation therapy of eligible patients.

Approximately seventy percent of immune deficient patients are treated with intravenous gamma globulin. For nearly twenty years, IVIG, has been recognized as a safe and effective treatment for primary immune deficiency diseases. However, beginning in the fall of 1997, widespread shortages of IVIG developed. Within this past week, we completed a survey of 100 doctors treating more than 2,000 immune deficient patients to document the current situation. Over ninety percent of these doctors reported difficulty in obtaining IVIG for their patients since April. As a result, they report postponing infusions, increasing the intervals between infusions, and reducing prescribed dosages of IVIG to their patients. How serious is this for these patients? Well, half of the doctors who have had difficulty in obtaining IVIG report that the shortage since April has had a **negative effect on the health of their patients**. Specifically, patients are suffering from increased infections that normally would have been checked by recommended IVIG therapy.

It should be clearly remembered that persons with bleeding disorders have been victims as well as beneficiaries of plasma products. With the introduction of recombinant alternatives to plasma based clotting factors the treatment of hemophilia leapt into the 21st century. No longer did individuals with bleeding disorders have to stand in the corridor of fear and pain, deciding to endure painful bleeds or risk exposure to possible viral contaminants like HIV which devastated their community. Last week the Surgeon General endorsed the use of recombinant AHF as the preferred treatment for hemophilia, and recommended accelerated implementation for all individuals currently using plasma based derivatives to recombinant usage.

However, there is a continuing shortage of recombinant AHF, which along with prohibitive costs will keep persons with bleeding disorders members of the plasma products users community for some time to come.

The Department of Health and Human Services Advisory Committee on Blood Safety and Availability reviewed the chronic product availability problems at its April meeting followed by the attention of this subcommittee in May. At both of these meetings short and long term recommendations were made. We are here today to report that the product availability has not improved significantly since those meetings and we believe that the situation will get worse in the near future. May I repeat, we believe that a very bad situation is getting worse, not better, despite the recognition of the seriousness of the problem by both government and industry.

This brings us to the substance of the GAO report. The GAO reports numerous deficiencies in adherence to good manufacturing practices in recent inspections of four major fractionation companies. These deviations led to two consent decrees, including one requiring a company to cease distribution of its products. This shut down was one of several factors in the IVIG shortage.

At first glance, the GAO report suggests a manufacturing industry that has significant problems with the production of plasma derivatives, with over 50% of the manufacturers under consent decree. I can tell you as a parent of a plasma user that the 429 deviations from good manufacturing practices cited in the report scares me. A few months ago my wife and I were pulled off a plane because my son could not get his gamma globulin, which is equally scary. At the same time, none of us want bathtub plasma products carrying infectious agents that kill rather than cure.

The GAO report, however, does not evaluate the state of manufacturing and specifically, the safety of manufacturing at these plants. The 429 deviations could represent a broken industry, which as a result of old plants, low investment, and company indifference to the product and customer, is unable to manufacture a safe product. Or, the same numbers could represent too much of a meter-maid mentality on the part of the regulatory agency. A better understanding of the true situation is critical because it tells us about the future availability of safe plasma products for persons whose lives depend upon them. If the industry is currently unable to produce enough products according to reasonable manufacturing guidelines, we need to decide how to address the long term production issues while trying to redirect the distribution system to get the available product to the patients for whom it is live saving. For example, less than half of all IVIG produced in the United States goes to immune deficient patients or other on label uses.

With not nearly enough plasma products available for the dependent users we offer the following recommendations:

- Industry needs to identify and prioritize customers with essential medical needs, for whom these products are life sustaining, (previously untreated patients (PUPs) with bleeding disorders, immunocompromised hemophiliacs, primary immunodeficient, and Alphas currently on product).
- Industry and government need to work cooperatively with hospital pharmacies and buying coalitions to encourage rationing protocols.
- Industry and government need to work with medical societies to promote responsible usage of products during shortages.
- Homecare pharmacies, wholesalers, and specialty distributors should report on product distribution and purchasing should be restricted so that they are not able to amass a surplus.
- Industry and government should support safety net programs established by consumer organizations which use small portions of the available supply, but allow access to physicians treating large numbers of patients.
- Industry should accelerate its compliance performance and take responsibility to fulfill its commitment to consumers for whom their products are life sustaining.
- The FDA should coordinate GMP activities and communicate within the agency new programs or protocol that could affect supply.
- We are also concerned that regulators and the industry need to change their collective dynamic from adversarial to cooperative. Increased communication and cooperation is essential, including technical assistance from the regulators.
- In the case of Alpha One augmentation therapy there is not, and will not be an adequate supply of product until another manufacturer introduces an additional product to the market place. We therefore recommend an allocation system that prioritizes patients currently on product and guarantees delivery of product to these patients regardless of the healthcare delivery system they choose.
- The above recommendations must be met or we will have to reconsider export policy. If we are not able to meet US demands under the guidance of conscientious product use, American consumers of plasma derivatives are going to ask for export controls. In the case of recombinant AHF products we feel it is unacceptable to export over 50% of the market supply.

Mr. Chairman, the consumers thank you and your subcommittee for its vigilance in the oversight of this area. We thank you for the opportunity to comment on these issues. However, we hope that you will hold both industry and government to their responsibilities and commitments in this area. In the aftermath of the plasma product shortages earlier this year, the industry promised increased production. Based on what we are hearing, we are likely to see further reductions in production in the coming months. There will be high human costs if this comes to pass. The FDA promised to try to address the distribution problems by a more extensive program of educating providers to the appropriate allocation of these scarce products. This promise has not been fulfilled.

Please remember we are discussing life-sustaining therapeutics! Twenty years ago, my wife and I were told that my six-month-old son might not live through the night. Today, he is a college student with no health impairments or activity limitations. He has not suffered a hospitalization in nearly twenty years. That is the difference that a safe, effective and available plasma product can make. We want to make sure that tens of thousands of other patients will continue to have that chance in the future.

Six months ago consumer organizations were asking for more information about the reasons for the shortages. Now, in light of a worsening situation, we want action. At the May 7th hearing Mr. Bacich of Baxter invited you to point at industry and challenge them to fix the problem. Did they fail to hear the challenge or are they unable to meet it? While we wait to see this action, better information is still necessary. The consumer organizations need to be made aware FDA and industry actions taking place and how these actions will affect the product supply.

In conclusion, we offer the patient notification system as a model for cooperation and communication. The industry has a consumer advisory panel, all companies have agreed to participate, and the patient information will be registered with a neutral third party that ensures patient confidentiality. The distribution system should be approached in the same cooperative manner, by the industry, government and consumers, assuring that delivery is made to those for whom it is life sustaining.

The consumers wish to commend you, Mr. Chairman for the recent recall amendment you offered to the appropriations bill. This type of legislation serves to further patient awareness and education and most importantly safety.

Immune Deficiency Foundation

IGIV Shortage - Physician Surveys

August, 1998

SAMPLING FRAME: DOCTORS, PATIENTS BY DIAGNOSIS

DIAGNOSIS	NUMBER OF DOCTORS REPORTING	NUMBER OF PATIENTS REPORTED
ATAXIATELANGIECTASIA	134	558
C1 INH DEFICIENCY	11	41
CD4 LYMPHOPENIA	6	10
CGD	234	841
CHEDIAK HIGASHI SYNDROME	2	3
CHRONIC MUCOCUTANEOUS CANDIDIASIS	160	1,070
COMPLEMENT DEFICIENCY	273	757
COMMON VARIABLE IMMUNODEFICIENCY	1,039	5,557
DIGEORGE ANOMALY	202	734
HYPER IGD SYNDROME	4	7
HYPER IGE SYNDROME	50	116
HYPER IGM SYNDROME	192	402
IgG SUBCLASS DEFICIENCY	799	5,307
LAD	17	30
SCID ADA	76	170
SCID OTHER	120	400
SCID X-LINKED	74	359
SELECTIVE IGA DEFICIENCY	936	5,502
WISKOTT-ALDRICH SYNDROME	142	388
X-LINKED AGAMMAGLOBULINEMIA	277	894
X-LINKED LYMPHOPROLIFERATIVE	7	16
OTHER	61	179
TOTAL	**1,567**	**23,341**

April 1998

Sampling Frame: Physicians by number of patients with primary immunodeficiencies

# of patients	# of physicians	total patients
25 +	221	15,044
< 25	1,346	8,297
Total	1,567	23,341

Physician Survey Methodology: 25 + Patients

Physician Type	April	August
Drawn Sample	221	221
Completed Sample	147	98
Use IVIG	121	95

During the past six months, have you had any difficulty in obtaining intravenous gamma-globulin for your patients with primary immune deficiency diseases?

	April Physicians 25+ Patients (N=121)	August Physicians 25 + Patients (N=95)
YES	93.4%	90.5%
NO	5.0%	8.5%
Blank	1.7%	0%

NOTE: Yes includes 2 cases which left the question blank but reported problems subsequent questions and 4 cases which indicated no in Q3 but reported problem in subsequent questions.

As a result of shortages in IGIV supply during the past six months, which of the following (if any) has happened to your patients? CIRCLE ALL THAT APPLY)

	APRIL Physicians 25 + Patients (N=121)	AUGUST Physicians 25 + Patients (N=95)
a) Postponed scheduled infusions	74.4%	64.2%
b) Switched to different IVIG brand	81.8%	76.8%
c) Switched to less preferred IVIG brand	65.3%	50.5%
d) Interval between infusions increased	65.3%	55.8%
e) Dosage at infusion reduced	50.4%	40.0%
f) Unable to obtain product for indigent patients	22.3%	2.1%
g) Substituted alternative therapies for IVIG	27.3%	14.7%
h) None of these	1.7%	1.0%
i) Blank	9.1%	0%

To date (since April), has the shortage of IGIV supply had a negative effect on the health of any of your patients?

	APRIL Physicians 25+Patients (N=121)	AUGUST Physicians 25+ Patients (N=95)
YES	51.2%	45.3%
NO	40.5%	47.3%
Blank	8.3%	7.4%

How much difficulty are you experiencing now in obtaining normal supplies of IGIV products?

	APRIL Physicians 25+ Patients (N=121)	AUGUST Physicians 25+ Patients (N=95)
A lot of difficulty	47.1%	16.8%
Some difficulty	38.0%	63.2%
No real difficulty	5.8%	13.7%
Blank	9.1%	6.3%

NATIONAL INSTITUE OF HEALTH

REGISTRY OF U.S. RESIDENTS AFFECTED

BY

SEVERE COMBINED IMMUNODEFICIENCY DISEASE

COMMON VARIABLE IMMUNODEFICIENCY DISEASE

CHRONIC GRANULOMATOUS DISEASE

X-LINKED AGAMMAGLOBULINEMIA

WISKOTT-ALDRICH SYNDROME

LEUKOCYTE ADHESION DEFICIENCY

HYPER IGM SYNDROME

DIGEORGE ANOMALY

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Mr. SHAYS. Thank you very much. Let me just say, Dr. Boyle, we sometimes have the consumers speak first when we have our hearings because it gives a little reality to what we are doing.

How as an individual patient in the consumer groups, how would you learn of a regulatory or production problem affecting the supply of product? How do you find out about it?

Mr. BOYLE. As an average consumer with a primary immunodeficiency disease, you wouldn't. If you were aggressive and were on the mailing list of a consumer organization, you would look for some description in newsletters, but they do not come out all that often. You might call the consumer organization, you might get on the Web and try to get it. But the bottom line is that most consumers have little or no access to information about the types of things that you are talking about.

For many years, even when we started the IDF 20 years ago before we actually became involved in the regulatory arena, we had no idea that there were any problems. We had no idea of any issues because we had no information about that. And we were informed consumers.

Mr. SHAYS. Do you get sent some of the information—do you have access to the information that would be provided to the FDA? Is that on the Internet?

Mr. BOYLE. Can I ask our staff representative to speak to that?

Mr. SHAYS. I think you were sworn in?

Ms. O'DAY. Yes, I was.

Mr. SHAYS. Do you have a card?

Ms. O'DAY. Yes. My name is Miriam O'Day, vice president of the Immune Deficiency Foundation.

The question is how easy is it for us to access information from the FDA?

Mr. SHAYS. Right. Is that on the Internet?

Ms. O'DAY. Some materials are on the Internet and they are available under Freedom of Information. But again, you have to be savvy enough to know what you are looking for and how to access it.

Mr. SHAYS. If the FDA does not have the resources or the focus to take some of this information and maximize its use, the consumer groups sometimes can provide a significant amount of response to it. Maybe I can ask the industry the same question. There would be nothing inconsistent with making this information available, or would some of this be proprietary information?

Mr. BULT. I think you are touching on a very important issue. Some information is proprietary.

In an initiative that we took, we invited IDF to come to one of our board meetings, and we did that as an initiative for them to have a better understanding what is going on.

Mr. BOYLE. Could we use perhaps recall notices of something that would obviously be of great interest to consumers, and Miriam can you tell how the recall notices come to us?

Ms. O'DAY. Oftentimes individual companies will contact the national organization and we will do distribution. But in the case of the CBER recall notices listed on their Web site, the individual consumer has to be the one to seek the information. They do not contact you and outreach that information.

Mr. SHAYS. Mr. McDonough, I want to make sure since I did interrupt you, if there was anything in your statement that you feel that you need to bring up, I will welcome you to jump in.

Mr. MCDONOUGH. There is one thing relative to this and that is through the National Notification Center we have established an 800 number and a registry that patients can sign up for and learn the status of any recall identified Red Cross lot numbers, and we keep that posted on a daily basis. We are just beginning to roll that out, but referenced in his comments that we are working with them to extend this to modify it industry-wide. As we sit here today, I am aware only that the Red Cross system has this number.

Mr. SHAYS. What is the best way—Mr. Bult, you addressed this—to predict shortfalls. Is there a model that the industry is working on?

Mr. BULT. Yes, this is a difficult question because if you want to have a reliable model, some of the issues raised this morning in the questions to FDA, it is very difficult to predict clinical demand. Further——

Mr. SHAYS. Predict what?

Mr. BULT. Clinical demand. You don't know exactly what the use is going to be.

Mr. SHAYS. Why is that, because there are new uses? I don't know why that would be difficult.

Mr. BULT. You can look at historical data and see that there is a trend of immune globulin use, an increase of 9 percent per year, but it is not worthwhile for all indications and it depends from plasma product to plasma product.

The second is if you have technical problems, nobody knows when these will occur.

The third is if you live in the current regulatory environment, we see the impact of current compliance issues. There may be others that do occur. So there is not a reliability to work on the model.

What we can do, and I think that is important, is to collect actual data, and that is what we have provided to you in our testimony, and provide that data to consumers, FDA and GAO and work on the model.

Mr. SHAYS. I am going to have staff jump in here in a second, but one of the things that we learned from the previous hearing was that there were contracts out. The industry has long-term contracts so that gives us a sense of demand on the individual companies; isn't that true?

Mr. BULT. I remember from the previous hearing one company stated they were the sole supplier of immune globulin in Canada, for example, but that is not true for the whole capacity that is available nowadays. In addition to the data that we provided to you in May, we have data now available for six companies, and that does not take into account all of these parameters. So we are focusing on domestic supply and what we can do to increase that supply.

Mr. SHAYS. Before we go to staff, I tried to have a sense—I happen to think that competition in most cases allocates resources well, not in every instance, obviously, but logically it should make for a more efficient operation. I get the sense that this isn't true in this industry, and I am trying to figure out why.

In other words, I don't get the sense that there is this kind of competition. I get the sense that old practice has stayed on too long. Maybe somebody can tell me if I am way off on that. If I am not, why?

Mr. BULT. If I may respond first, Mr. Chairman, I don't know where this feeling is coming from. What we have to realize, and we really want to work and cooperate with all agencies to work on a model if that is a possibility and provide the data.

Mr. SHAYS. Let me say that I think there has been some significant progress made in the last few years. I ask myself why didn't that happen sooner? What was wrong with the system that didn't make that happen earlier?

Mr. REILLY. I think competition has driven a number of improvements over the years. The drive within the group Mr. Bult represents toward monoclonals and ultimately recombinants for AHF is clearly competitive.

On the source materials side, issues like RQPP have been driven in large measure by competition. When we first initiated it, the NHF took a look at the program and endorsed it, and that was a major factor in a drive toward it being what I reference as a de facto requirement for source material. So there is substantial competitive pressure to improve products and maintain a safety and compliance record.

Mr. SHAYS. It seems to me that the competition might make you want to come to the marketplace and have larger lots and so on. There is not as much—it seems to me that the safety area, you don't have as much of an incentive unless the FDA does shut you down. And I get the sense that sometimes the FDA is not going to shut you down because they simply need your supply.

Mr. REILLY. The improvements that I just discussed were all largely around safety initiatives.

Mr. SHAYS. That is in the last 2 years.

Mr. REILLY. No, those things that I described were over the past 15 years. The speed at which we are adopting them, I think the committee deserves a great deal of credit for. These hearings have brought a lot of focus on the aggressiveness of compliance and the speed we are at looking at new initiatives, and they have focused in the past several years much more specifically than in the past.

Mr. SHAYS. Let me invite the minority staff to ask a few questions.

Ms. BRANSON. There has been quite a bit of discussion about 40 percent of the industry being under consent degree. I am wondering what percentage of the product that represents?

Mr. BULT. It is difficult to make an accurate number. I have not made a calculation. We have two companies who are working on the consent decree. I don't know exactly what the total percentage of product is that is affected.

Ms. BRANSON. There was a discussion earlier about lipid enveloped viruses versus nonlipid enveloped viruses and the effectiveness of viral inactivation. First of all, what does the FDA require you to test for, and are those particular infections, viruses, whatever you choose to call them are lipid enveloped or nonlipid enveloped? Anybody on the panel can answer that.

Mr. BULT. Maybe we can divide the question to the collection side first and then continue with manufacturing.

Mr. REILLY. Maybe you can repeat the question.

Ms. BRANSON. What does the FDA require you to test for as far as viral markers are concerned? The second part of the question is, are those particular viruses lipid enveloped or non-lipid enveloped?

The concluding part of the question is whether inactivation techniques are effective against those particular viruses that you are required to test for?

Mr. SHAYS. Sir, if you would identify yourself and also give a card to the transcriber.

Mr. DODD. I am Roger Dodd, head of the American Red Cross Transmissible Diseases Department, Holland Laboratory.

Currently all blood donations are required or recommended to be tested for antibodies to HIV 1 and 2, for the P 24 antigen of HIV, for antibodies to hepatitis C virus, for hepatitis B surface antigen. And additionally, all donations are tested for syphilis.

For the voluntary sector, there is also testing for HTLV–I and II. That is the human T-cell lymphotropic retroviruses I and II, and also antibodies for hepatitis B core. And some locations also test for alanine amino transferase, which is an additional indicator of potential liver damage.

Hepatitis B, hepatitis C, HIV, and HTLV are all lipid enveloped viruses.

Ms. BRANSON. Thank you, Mr. Chairman.

Mr. SHAYS. Thank you.

I invite the majority staff, Anne Marie Finley, to ask a question or two.

Ms. FINLEY. Mr. Reilly, how can your members be certain that the qualified donor program reduces viral marker rates in collected plasma if your organization does not collect and maintain records of viral marker rates for applicant donors?

Mr. REILLY. I think through the data that has been provided to GAO and I believe even your office as well. In the past we made pools of plasma, if you will, out of all of the donations. So the comparable viral marker rate was the viral marker rate of the entire population or the prevalence rates as compared to the qualified donor only rates. So that is the way that we are able to establish that.

So when you look at the overall rate, all donors, applicant and qualified, that was the pool of product before and that would be the risk assessment, and then you take that against the comparative qualified only rate.

Ms. FINLEY. I am not sure that I understood you. Let me ask again and perhaps you can explain it.

The GAO requested applicant donor information, specifically the viral marker rates for individuals walking into a plasma collection center who had not donated before, in comparison to the individuals who have gone through the qualified donor program. Is it true that ABRA and your members do not collect viral marker data for individuals who come in for the first time to donate?

Mr. REILLY. Late in the preparation of the report GAO did come back and ask for applicant only donor data. Let me go back and address your initial question, how to compare the past situation

and an assessment of its risk versus with the qualified donor process in place.

The pool that you would manufacture from included all donors, applicant and qualified. So the rate—the way to assess that risk is by looking at the combined rate of all of those positive donations, and that was the prevalence rate, which we did provide to GAO.

If you want to compare that against the new pool, the new pool would be created from qualified donors only. And so you would look at it and compare it against the overall rate, and that assessment was made and we did provide GAO prevalence rates for the overall group as well as the rate for the qualified only.

The request that came late in the process for applicant only data, we have attempted to comply with. Our problem is simply around timing. Many of the companies did collect it, but they all had a different mechanism to collect it and the data sets were not compatible. We have gone back to the companies and we are right in the middle of beginning to collect that data in a standardized format so it is usable and validated data. The problem was meeting the timeframe.

Ms. FINLEY. As you assess the efficacy of the qualified donor program, isn't it necessary to compare the data collected from applicant donors to that data collected from donors who successfully complete the qualified donor program?

Mr. REILLY. No.

Ms. FINLEY. Can you explain that?

Mr. REILLY. Let me try this again.

When you look at the plasma that is used—that was used before we put the qualified donor standard in place, the plasma that was used was from all donors, applicants and qualified. You would look at the rate for all of those donors because that was what we made the product out of.

Subsequent to the qualified donor standard being in place, we now use the plasma only from qualified donors. So we now look at that rate, and we would compare it against what we used to do.

Ms. FINLEY. I see the point that you are making, but wouldn't it be necessary as you evaluate the viral load for individual collection centers to evaluate the people that come through the door versus those that you actually want as continuous donors?

Mr. REILLY. The load in the pool is only related to those that we retain as continuous donors.

Ms. FINLEY. I think the question that I am trying to get at is not necessarily the load in the pool but rather the confidence that you would have in the qualified donor program. Isn't that in fact a reflection of the improvement in the viral marker rate in qualified donors versus the applicant donors who have not been qualified?

Mr. REILLY. We are looking at or we are in the middle of establishing a viral marker rate of qualified donors that each facility would be measured against so that the facility can see how they measure against an industry-wide viral marker rate standard. And the objective is continuous improvement over that baseline.

Rather than look at the applicant donor data and say that is what we screened out and then look at the qualified donor that is what we retained, we focused on what do we retain and how do we continuously improve what we retain, and have not put a lot of fo-

cused effort or limited resources into figuring out what we have already screened out because we have already screened it out.

Ms. FINLEY. What percentage of ABRA members are QPP, qualified plasma program, certified?

Mr. REILLY. Nearly 100 percent.

Ms. FINLEY. And all plasma collected that goes into further fractionation of IVIG, AHF and some of those other products would come only from QPP certified donors?

Mr. REILLY. I believe the four major fractionators in this country have all committed that they would only distribute AHF, and I don't know if the commitment has extended to immune globulins, although you would assume that it would, from QPP certified facilities.

Mr. BULT. I can confirm that statement.

Ms. FINLEY. OK, thank you.

Mr. SHAYS. I want to make sure I put in the record and ask unanimous consent that a copy of the National Institutes of Health document Report of the Expert Panel on Donor Pool Size Immune Globulin Products be inserted into the record of this hearing. I probably should have done that a little earlier, but we will do that without objection.

[The information referred to follows:]

REPORT OF THE EXPERT PANEL ON DONOR POOL SIZE OF IMMUNOGLOBULIN PRODUCTS

National Institute of Allergy and Infectious Diseases

National Institutes of Health

September, 1998

TABLE OF CONTENTS

Executive Summary
- Introduction
- Findings and Recommendations

Appendix A: Meeting Agenda
Appendix B: Panel Members
Appendix C: Panel Member Biographical Sketches
Appendix D: Professional Societies and Patient Advocacy Groups Invited to Submit Written Comments
Appendix E: Summary and Individual Responses from Interested Groups
Appendix F: Presentation of Rebecca H. Buckley
Appendix G: Presentation of Thomas J. Lynch
Appendix H: Presentation of Mary Ann Lamb
Appendix I: Presentation of Fred Feldman
Appendix J: Presentation of Donald Baker
Appendix K: Presentation of Sue Preston
Appendix L: Presentation of Jean-Jacques Morgenthaler
Appendix M: Presentation of Chris Lamb
Appendix N: Presentation of Paul R. McCurdy
Appendix O: Donor Pool Size for IGIV: Safety and Efficacy Considerations, Donald L. Tankersley

EXECUTIVE SUMMARY

INTRODUCTION

Antibodies have been used to confer passive humoral immunity since the early 1900s. Intravenous immunoglobulin (IVIG) to prevent serious bacterial infections in antibody-deficient individuals became available in the U.S. in 1981. It soon became apparent that IVIG possessed immunomodulatory, as well as immunoprotective properties, leading to clinical trials in a wide range of non-infectious, immune-mediated diseases. In the late 1980s and throughout the 1990s, utilization of IVIG grew rapidly, fueled largely by increasing off-label use.

In the face of rapidly increasing demand, manufacturers of IVIG "scaled up" production, increasing the numbers of plasma units pooled during the manufacture of IVIG. With some donor pool sizes[1] reported to be in excess of several hundred thousand, public attention focused on the potential effects of large donor pools on the risks of transmitting infectious agents. In 1997, growing shortages of a number of plasma products raised concerns that steps to limit the size of plasma pools might further reduce availability of IVIG.

In 1997 and 1998, the shortage of IVIG and the topic of donor pool size were discussed at meetings of the Public Health Service Advisory Committee on Blood Safety and Availability, the Blood Products Advisory Committee of the U.S. Food and Drug Administration, and the Subcommittee on Human Resources of the House Committee on Government Reform and Oversight.

In the fall of 1997, the Subcommittee requested assistance from the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), to determine the minimum donor pool size needed for safety and efficacy of immunoglobulin products.

In April 1998, the NIAID convened an Expert Panel of federal and non-federal physicians and scientists to review published data and other information pertinent to the issue of donor pool sizes for immunoglobulin products. The panel included experts in science and public health policy, adult and pediatric medicine, infectious diseases, rheumatology, immunology, transfusion medicine, epidemiology and statistics, and medical ethics. The Expert Panel reviewed information presented by medical experts, professional societies, patient advocacy organizations, and representatives of the U.S. Food and Drug Administration and the plasma products industry.

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[1] "Donor pool size" refers to the total number of individual donors contributing source or recovered plasma to a product lot. Because multiple plasma units from a given individual may be pooled during manufacture of plasma products, the donor pool size may be smaller than the number of plasma or blood donations/units comprising each product lot.

The Expert Panel was asked to address these issues in the context of current medical indications for immunoglobulin products, including intravenous and intramuscular immunoglobulins and hyper-immune globulins[2]. In the absence of data to form evidence-based recommendations, the Expert Panel was asked to address the feasibility, design, and advisability of additional studies that could form the basis for such recommendations. The findings and recommendations of the Expert Panel are summarized in this report.

FINDINGS and RECOMMENDATIONS

1. **Based on the available data, it is not possible to establish minimum donor pool sizes needed for optimal efficacy of immunoglobulin products.** This is particularly true of IVIG, the product with the broadest range of medical uses. Recent recommendations concerning donor pool size deserve comment. In 1997, the source plasma industry[3] proposed that IVIG donor pool size be limited to 60,000. The FDA is now considering lower limits, i.e., ~15,000 donors per lot[4]. Both recommendations appear to be based less on published evidence concerning the effects of donor pool size on efficacy of immunoglobulin products than on estimates of "tolerable" risks of transmitting infectious agents. In the absence of scientific data to establish minimum donor pool sizes, the Expert Panel recommended that the FDA ensure that donor pool sizes do not exceed current manufacturing levels. In considering this topic, the Panel's deliberations touched on many of the issues considered earlier by the Institute of Medicine:

   "The management of a public health risk requires an evolving process of decisionmaking under uncertainty. It includes interpretive judgement in the presence of scientific uncertainty and disagreement about values. Public health officials must characterize and estimate the magnitude of the risk...They must also develop and test public health and clinical care strategies, and communicate with the public about the risk and strategies for reducing it. .... Lack of scientific consensus becomes a kind of amplifier for the usual discord and conflict that can be expected whenever an important science-based public policy decision – one profoundly affecting lives and economic interests – must be made. First, uncertainty creates opportunities for advocates of self-interested and ideological viewpoints to advance plausible arguments that favor their desired outcome. Second, uncertainty intensifies bureaucratic cautiousness."[5]

2. **Evidence is accruing that antibody dimerization may contribute to the biological activity of IVIG in immune-mediated diseases.** Modeling studies and laboratory

[2] Immunoglobulin products considered by the panel included intravenous and intramuscular immunoglobulins, and hyperimmune globulins (anti-Rh immune globulin, anti-RSV immune globulin, anti-CMV immune globulin, Hepatitis B immune globulin, Varicella-Zoster immune globulin, rabies immune globulin, and tetanus immune globulin).

[3] Immunoglobulin products are currently manufactured from plasma recovered from whole blood (designated "recovered plasma") or obtained by plasmapheresis (designated "source plasma").

[4] Transcripts of FDA Blood Products Advisory Committee, December 12, 1996.

[5] HIV and the Blood Supply: An Analysis of Crisis Decisionmaking, L.B. Leveton, H.C. Sox, Jr., and M.A. Stoto, eds. National Academy Press, Washington, D.C. (1995); p209-211

observations suggest that donor pools ≥10,000 may be needed to support a high level of dimerization. However, the published studies are not sufficient to form the basis for regulatory decisions. Therefore, the Expert Panel recommended that agencies of the Department of Health and Human Services (DHHS) including the FDA, Centers for Disease Control and Prevention (CDC), and NIH support: **a)** additional independent, peer-reviewed modeling studies; and **b)** laboratory research to test hypotheses generated from such studies.

3. **The Expert Panel did not recommend clinical trials to explore the effects of donor pool size on safety and efficacy of IVIG.** Instead, the Panel recommended careful clinical monitoring and continued vigilance with any further reductions in donor pool size. In drawing this conclusion, the Expert Panel considered the multiplicity of off-label uses and the paucity and speculative nature of the available information on the mechanisms of action of IVIG in autoimmune and immune-mediated disorders. In the absence of more precise information on mechanisms of IVIG action, it is neither possible to establish minimum donor pool requirements, nor to design clinical trials, the results of which could be broadly applied.

   In particular, the Expert Panel felt strongly that the conclusions of individual trials would not necessarily apply to the use of IVIG in other diseases or in different clinical settings Furthermore, because there are manufacturing and end-product differences among commercially manufactured IVIGs, panel members voiced concerns that conclusions drawn from individual clinical trials might not necessarily apply to the clinical uses of different commercial preparations of IVIG.

   A stronger argument could be made for trials to assess minimum donor pool needs for the hyperimmune globulins, due to their more narrowly focused clinical indications. However, the Expert Panel noted that these products are currently manufactured using relatively small donor pools. In addition, at least one product, Rho (D) immune globulin, is licensed not only to prevent hemolytic disease of the newborn, but also for idiopathic thrombocytopenic purpura. Because it is likely that different immunological mechanisms account for the activity of Rho (D) immune globulin in these two disorders, panel members expressed concerns about the interpretation and broader applicability of disease-specific trials of this agent.

4. **Among all blood derivatives, immunoglobulin products stand out for their extensive record of safety.** Advances in donor screening, viral detection, and viral inactivation have resulted in plasma derivatives that appear safer than ever, relative to known viruses. Current screening and manufacturing procedures incorporate multiple "layers of protection," which were not in place in the 1980s and early 1990s, when the transmission of hepatitis and AIDS was linked to blood products. Of note, the transmission of Hepatitis C virus (HCV) by intravenous immunoglobulin (IVIG), occurred prior to the industry-wide use of solvent-detergent treatment, a viral inactivation procedure effective against all lipid-envelope viruses (e.g., Human Immunodeficiency Virus [HIV], Hepatitis B virus [HBV], and HCV).

Reducing the number of donors contributing to plasma pools is one important measure to decrease the risk of exposure to infectious agents, especially for infrequent users of plasma products. However, for patients requiring repeated or continuous treatments, the risks of exposure would be reduced to a lesser extent, even by large reductions in donor pool size. Therefore, in addition to efforts to reduce pool size, the Expert Panel stressed the need for continued vigilance and further improvements in donor screening and in procedures for viral inactivation and elimination.

5. **The federal government should evaluate claims that reductions in donor pool size will decrease product availability.** The government should provide a mechanism (e.g., a General Accounting Office review) to guarantee that the analysis is comprehensive, credible, fair, and in the public domain. Expert Panel members emphasized that neither they nor the FDA staff had sufficient information or the capacity to evaluate claims that reductions in donor pool size would have such an effect.

6. **The panel strongly supported the development of recombinant therapies to replace plasma-derived products.** The purification of non-immunoglobulin derivatives (e.g., clotting factors, α-1 antitrypsin) consumes source plasma and may necessitate donor pool sizes that exceed those most appropriate for IVIG. Therefore, the panel supported the development of recombinant products in order to: **a)** minimize overall dependence on plasma derivatives; **b)** diminish "competition" among different products for source plasma; and **c)** assure that all plasma derivatives are manufactured, to the extent possible, from donor pools of optimal size.

   DHHS agencies and industry should support research to develop a variety of recombinant plasma proteins and monoclonal antibodies for clinical use. Furthermore, federal agencies and third party payers should make such agents available to all patients who need them.

7. **Industry should collect, and make available to DHHS agencies, information on donor immunization status and the potential value and costs of measures to improve donor immunization.** Efforts to improve donor immunization could potentially contribute to a reduction in the risks of viral transmission (e.g., hepatitis A and B) and to improved antibody profiles of IVIG (i.e., IVIGs that would provide broader humoral immunity to common pathogens, including influenza viruses, Hemophilus influenza type B, and pneumococci).

8. **Federal agencies should assist in the development of patient databases for comprehensive surveillance and longitudinal monitoring of recipients of IVIG.** Such databases would allow IVIG treatment records to be correlated systematically with information on immune function, seroconversion, and prevalence of chronic infection. Certain patient advocacy groups (e.g., the Immune Deficiency Foundation) currently support databases that could facilitate the collection and analysis of such information.

9. **DHHS agencies and industry should expand support for research to develop innovative methods for donor screening and elimination and inactivation of transmissible agents.** The Expert Panel believed that the potential rewards from such investments could greatly exceed the incremental gains that may be achievable with further reductions in donor pool size.

In summary, the Expert Panel: **a)** emphasized the safety of immunoglobulin products; **b)** recommended that regulatory decisions that would cap donor pool sizes below current manufacturing levels await assurances that such reductions would not result in products with substantially altered biological activities; and **c)** recommended various additional measures to improve immunoglobulin safety.

Mr. SHAYS. Is there any comment that any of you want to make, starting with you, Dr. Boyle? Let me just say I would like you to state again for the record what your impression of the last hearing was, and I would like the others to respond to it just to see how far we are away from living up to that. One, do others agree that was the understanding of the hearing? And two, are we following up on it?

Mr. BOYLE. Our understanding from the previous hearing was that on the industry side there was a commitment to increased production, recognizing that one of the things that we still don't understand is if industry understood demand was going up by 10 percent per year over a period of time, why production was never increased.

Mr. SHAYS. From your standpoint, I do have a sense that production was going to increase. We did have one plant obviously not producing, and we also had some of the product taken out of the market, but that has now come back in.

Why can't manufacturers respond to increased demand? You would think intuitively profits would increase. Why doesn't that happen?

Mr. BULT. First of all, manufacturers have participated in increased demands. First, you should realize that the critical shortage occurred in November 1997, and after that we had a couple of events that could not be corrected until now. And you may recall at the May hearing there were three major reasons that contributed to these shortfalls. One was the increase in clinical use. Second was the recall because of Creutzfeldt-Jakob disease-related issues, and the third was compliance issues.

Since then we have not been able to recover from the shortfalls. We are working hard to do so.

Mr. SHAYS. Has the production increased?

Mr. BULT. Where possible, production has increased. However, one company under the consent decree was able to maintain operating at a 100-percent level. You have heard of the situation with another member. We have a third member who just got the FDA approval to increase their capacity at one of the plants, which will certainly contribute to an increase in supply. And the other company had a long term commitment to increase production capacity and they are on track. Increases cannot be done overnight. It takes about 200 days to manufacture product between collection and finished product. It is a time-consuming process.

Mr. SHAYS. I don't want to labor on this too long, but I do want to have a better appreciation. I am just struck by the fact that if one company can get more market share, you jump at the opportunity. With paper mills, if you have a shortage, a whole host will increase their production and then you have too much because they each did it thinking they were the only one going to increase production. I am still having a difficult time understanding why one company wouldn't want to seize that market share.

Mr. MCDONOUGH. By way of example, in July and August we worked pretty hard to try to increase our throughput, and that means increasing the number of donations that ultimately can go through. Unfortunately, we had a laboratory GMP problem that held up for 2 months a number of products. We also had two CJD

cases that held up a significant amount of material, which is still being held up.

In addition to that, our primary fractionator, Baxter Hyland goes through an annual shutdown to retool the plant, and that happened in the month of August. Notwithstanding that retooling, our experience with Baxter is that the compliance issues loom very significant here because their total throughput is significantly diminished while they wrestle with these problems and while they try to bring the plant back up into full compliance, and that doesn't happen very soon, as Mr. Bult said. So despite trying to increase throughput, it is our impression that these compliance issues, which are appropriate and significant, are being managed by reducing the amount of output.

Mr. SHAYS. Was it your understanding from the hearing that we would see an increase in production?

Mr. MCDONOUGH. It was. And I think everybody anticipated with Centeon coming back online that more product would be available. But now with their reclosure, there is some question what the impact will be.

Mr. SHAYS. How might Centeon's current compliance problems affect the availability of medically necessary products?

Mr. BULT. I would like one of my colleagues to stand up and give that answer.

Mr. SHAYS. Sure. You have been sworn in, and if you have a card we will pass it down.

Mr. DELONGCHAMP. I am Alain Delongchamp, and I am the general manager for Centeon North America, and the question dealt with the near term supply availability of IVIG.

At this point in time, as stated earlier this morning, we are still discussing the action plan with the FDA to release the existing inventory of our IVIG product we have which is pending release. As we don't have a final conclusion on that discussion, I am afraid I am unable to give you a firm answer regarding the time table regarding the release of this product, and I would say that it is probably premature to speculate about this. We would expect to see some supply in the near term, although I cannot quantify the amount at this point.

Mr. SHAYS. I have no sense what your market share is. What would that be?

Mr. DELONGCHAMP. Roughly in the order of 12 to 15 percent.

Mr. SHAYS. Your second part?

Mr. BOYLE. Since we heard the production difficulties last time and we knew there were going to be shortfalls, although we hoped that production was going to be increased, we recognized that not all patients were going to be able to receive these products, and we were under the impression from the FDA that there was going to be an attempt to deal with the distribution problem by identifying to doctors and hospitals the proper allocation of IVIG in terms of what was medically indicated. Only 40 percent probably of all IVIG is used for primary immune deficiency diseases, and it is probably not a lot more for the other indicated uses. And so our understanding was that there was going to be a Dear Doctor letter that was going to outline——

Mr. SHAYS. FDA is not here, but could someone from this panel respond to that? OK, that is something we will followup on. There was a sense that we did want to make sure where there were high priorities that the high priorities received the product.

Is there anyone else who was raising their right arm who could jump in?

Mr. BULT. Mr. Chairman, I think one of the initiatives that the industry has taken to buildup an emergency supply, we have made a prediction that for year 1998 we will have 400 kilograms available for emergency supply. Up to now the first half year we made available already about 500 kilograms which means that companies have made an attempt to have higher numbers of emergency supply available for critical patients such as pediatric AIDS patients, HIV patients and other patients in critical need.

Mr. SHAYS. We need to get the word out though, don't we.

Mr. BOYLE. Of the doctors that we have spoken to, 90 percent said that they have been having difficulty in getting IVIG, and of those who say that they have had difficulty, 50 percent say their patients have had health problems as a result.

Mr. SHAYS. You are using percentages in a congressional hearing. Are you comfortable with those percentages?

Mr. BOYLE. Yes. There are only approximately 200 physicians who see 25 or more immune deficient patients. Of those 200 and some, we have received responses from approximately 100. There is not much sampling error about that type of response. It would probably be improper to take the 40 percent and try to project it onto all patients.

Mr. SHAYS. The danger is that the people who contact you are the ones who are not getting the supply.

Mr. BOYLE. For doctors who respond, there may be some likelihood if you are having a problem, you are more likely to respond. So 50 percent.

Mr. SHAYS. So I will take the numbers based on that.

Mr. BOYLE. The issue is that there is a health problem out there that is affecting patients right now.

Mr. SHAYS. I am going to conclude this hearing. Are there any additional questions?

Mr. HALLORAN. I just wanted to touch on CJD with Red Cross first. Why do you think that CJD has such a far greater impact on the volunteer sector than the paid? As a tracer for some future uncharacterized agent, it kind of worked against expectations or type there.

Mr. MCDONOUGH. I am not sure that we know or understand; and, frankly, there is probably some disagreement. There is some argument that the demographics of volunteer donors lend themselves more to people who either have had dura mater transplants or have taken pituitary growth hormone. There are arguments that say voluntary donors know how to answer the question.

I don't think that we can honestly say with accuracy why the impact. The majority of our donors identified to us their risk status almost on all occasions by being asked the question, have you ever had a dura mater transplant or growth hormone. They would go home and interact with a family member and then call us back and

say, I didn't know it, but yes, I did in fact have growth hormone after some thought and deliberation about it.

That anecdote of information probably is not very helpful, but all I can tell you is the source of information from our donors which clearly had an adverse impact on volunteer donors.

Mr. REILLY. We took a look at this issue and had some professionals, statisticians and so on, try to look at the demographic issues and figure out why was there such a difference. There really were two driving factors. One is that it related to age. Age has an effect related to this, and when you look at the demographics of the two donor populations, the volunteer sector was a more elderly group. So that sort of drove the conclusion that you might see the increases seen here.

The other was simply the size of the donor pool where in the whole blood sector they deal with the longer duration period, so consequently they have a larger number of donors contributing to the pool, if you will. And in the plasma sector we have a smaller number of donors making more frequent donations.

When you look at those two factors combined, what you found was that the expected number of recalls or donors that sparked a recall out of the volunteer sector, and then when you factored in those two demographic issues, what you would expect out of the plasma industry was pretty much exactly what we got. So that is why it looks like it is disjointed.

Mr. HALLORAN. Thank you.

Mr. SHAYS. Any last comment before we close this hearing?

Sir, if you would just identify yourself. We did swear you in.

Mr. COLLINS. My name is Patrick Collins and I am with the National Hemophilia Foundation with Dr. Boyle.

I would just like to bring to the committee's attention the fact that in addition to the immune globulin shortage, which is dire, that there is currently a recombinant factor A shortage, which Dr. Boyle alluded to. And quite frankly it is rather startling that all of the manufacturers are rationing their recombinant A product. For example, Bayer sent out a notice to all of their consumers that they are rationing at 62 percent of allocation, that Baxter is currently having problems meeting their supply of recombinant factor A product, and Centeon, which distributes product made by Baxter and Bayer, has also resorted to rationing because of a lack of product.

This is compiled with the fact that Dr. Satcher, in making his CJD recommendation, also endorsed the switch to recombinant product which is in short supply for the population that currently uses it, let alone the population that will switch as a result of Dr. Satcher's recommendation. I just felt that the committee should be made aware of that, in addition to the alpha I antitrypsin shortage and the fact that they are relying specifically on one manufacturer of product and they are having great difficulty in getting that product as well.

Mr. SHAYS. Thank you very much, sir.

Any comments?

Mr. BULT. It might be useful to comment on recombinant factor 8. I want to underline the importance of factor 8 products for hemophilia patients, and if we focus on recombinant factor 8 as part of

the testimony, we are able to show that over the last 2½ years, there has been a constant increase in supply of recombinant factor 8 for the American hemophilia patients. At the same time, we are starting an initiative to look closely on a monthly basis with a recombinant factor 8. What we see at this moment is a decrease in ratio, which tell us that inventories are going down. We developed a ratio which is inventory divided by consumption. If you have a ratio of 1 equal to a 1 month supply, what we see is that the ratio is going down so we feel there is a reason to closely monitor recombinant factor 8, and that is what we are doing at this moment.

Mr. SHAYS. Well, with that, I thank you, all of our participants, and thank you for coming forward.

This hearing is closed.

[Whereupon, at 12:38 p.m., the subcommittee was adjourned.]

[Additional information submitted for the hearing record follows:]

Alpha One Foundation

09.07 98

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† Executive Committee

* Denotes diagnosed alpha$_1$ – antitrypsin deficient

+ Denotes mz with diagnosed family member

Anne Marie Finley
Subcommittee on Human Resources
Committee on Government Relations and Oversight
U.S. House of Representatives
Washington, DC

Dear Anne Marie:

Pursuant to our discussion at the CBSA meeting on August 27th, I wish to reiterate my appreciation for inviting the PUC testimony at your upcoming hearing on the GAO Report on Blood Plasma Safety. The members of PUC have given their input on Dr. John Boyle's testimony and I think his testimony will make a significant contribution to the Subcommittee's deliberations.

As you are aware, the critical shortages of plasma derived products for IGIV and AAT deficiency and recombinant factor product is our primary concern at this time. Pleased find my written testimony for submission to the Subcommittee at this hearing attached hereto. I would appreciate it if you could include this testimony with the PUC written testimony for distribution to Chairman Shays and the members of the Subcommittee.

I have noted some of our concerns regarding the vulnerability of additional product approval and IND trial design issues at FDA. Per my facsimile of last week, we're still having difficulty with Dr. Ross Pierce. I expect to see either Dr. David Feigel or Dr. Jay Epstein at your hearing and hope that they will have an update for us at that time. I will keep you advised accordingly. Thank you for your interest in this issue.

Please advise if you need additional detail regarding my testimony. I look forward to seeing you on Wednesday and appreciate your continued vigilance on behalf of consumers of blood products. With best regards, I am

Sincerely,

John W. Walsh
President and CEO

2937 S.W. 27th Avenue, Suite 302, Miami, Florida 33133
Telephone: (305) 567-9888 · (888) 825-7421 · Fax: (305) 567-1317 · e-mail: aof@bellsouth.net

Mr. Chairman and members of the Subcommittee, the Alpha One Foundation and Alpha$_1$ National Association would like to formally endorse the testimony presented by Dr. John M. Boyle, on behalf of the Plasma Users Coalition (PUC). As Dr.Boyle has testified, the Coalition represents over 50,000 chronic consumers of plasma derivatives. The critical shortages of plasma derived products is of the utmost importance to us at this time. We appreciate Chairman Shays' and the Subcommittee on Human Resources' continued interest in addressing these critical shortages and including this issue in your deliberations on the GAO report on Blood Plasma Safety.

As stated in our testiomony before this Subcommittee on May 7, 1998, the Alpha One community embraces those families that are affected by the IVIG shortage. Similar to those afflicted by primary immune deficiency, individuals with alpha 1-antitrypsin deficiency depend on alpha-1-protease inhibitor (α1PI) to prevent lung damage from infection that causes the loss of lung function, disability and ultimately death. In addition we embrace the Hemophilia Community challenged by the current shortage of recombinant factor products for clotting disorders.

The Alpha One community has experienced a severe shortage of Prolastin® (h-α1PI) and has been on an allocation of only 50% most of this year. Our product shortage was the result of having a single manufacturer decreasing production to respond to the recommendations of the FDA warning letter regarding GMP improvements. Although Bayer has made every effort to increase supply and production levels at both their Clayton, NC and Berkeley, CA facilities; they will not be able to meet current demand when they reach 100% of their production capability. The shortage of product will continue until another manufacturer's product and manufacturing facility is approved.

Throughout this shortage numerous inequities in the distribution process were identified. The Alpha One community has presented testimony at this Subcommittee's hearing last May, at the DHHS Advisory Committee on Blood Safety and Availability (ACBSA) meeting, and the FDA Blood Products Advisory Committee (BPAC) meetings calling for the immediate development of a direct consumer allocation program and evaluation of the current distribution process. The precedent established by the development of the national notification program may well serve as a blueprint for a consumer allocation program. The collaboration of the PUC, FDA, IPPIA, Novartis and the ARC made it possible to work through the issues of notification of withdrawals and recalls and collectively contract with a third party to maintain consumer confidentiality. This collaboration provides for input from all stakeholders and gives the industry the ability to share the cost of operating this system, while providing a central platform for all consumers.

As referenced in the GAO Draft Report on Blood Plasma Safety, 50% of the plasma derivative manufacturers were shut down last year because of consent decrees. Additionally, our community was severely impacted by a warning letter to the sole producer of our h-α1PI for augmentation therapy. Our community remains vulnerable to the potential of delays in the approval of the BLA for a second manufacturer of an h-α1PI product and the immediate possibility that a third manufacturer may be delayed in producing product to complete phase II/III trials.

We, by no means, want to sacrifice safety or compliance of GMP; however, we ask that every consideration be given to manufacturers to make corrections without affecting production and product releases. It is imperative that the FDA and industry work in concert to resolve GMP issues without impacting the production of these life saving plasma derived therapies.

We are extremely concerned about the continued delays in the approval of final trial design for phase II/III for the third manufacturer. This IND and trial has been delayed for more than a year. The current delay appears to be the result of a proposed requirement to divert an excessive amount of product, already in short supply, to conduct a randomized, prospective comparison trial. This is contrary to the BPAC's recommendation not to change clinical trial design and the ACBSA's recommendation, through Secretary Shelala, to expedite the availability of additional α1PI products.

It is significant that Secretary Shalala and the Surgeon General have both called for the increasing efforts to transition plasma derivative consumers to recombinant products. We encourage the Subcommittee to support these recommendations. I have been assured by the Director of the Office of Technology Transfer that there will be no delays in responding to the multiple applications for licensure of the patent for the *aerosilization of protein therapeutic agent (patent no.5,618,786)*. The Alpha One Foundation has also requested that Chiron, the co-owner of this patent, cooperate with industry to license this patent without further delay. The technology to transition people afflicted with alpha1-antitrypsin deficiency from plasma based augmentation therapy to recombinant has existed for over 10 years and we must support manufacturers' interest in developing these products. There are ongoing trials for aerosolized delivery of a transgenic recombinant form of α1PI (tg-hAAT) as a therapy for treating cystic fibrosis patients and this same company is designing a trial for alpha 1-antitrypsin deficiency. This effort will be delayed if patent licensure and/or trial design is delayed. We also ask this Subcommittee to support current initiatives to accelerate the development of gene-based products and gene-directed therapies for alpha 1-antitrypsin deficiency and other rare disorders.

We ask that the Subcommittee review the progress in the issues that we addressed in our testimony at the IGIV shortage hearings in May. We are still concerned about dependence of plasma derivatives as the sole option for life saving therapy and the importance of constant vigilance by government, industry and the consumer communities. We still recognize that the timely application of new therapies can only occur in an environment that promotes the close collaborative effort of the NIH, FDA and the pharmaceutical industry. The leadership and vigilance of this Subcommittee has brought attention to the impact of shortages, initiated some response by industry and supported more collaboration between the FDA and industry. We encourage the Subcommittee to take the next step and support the recommendations of the PUC, address the delicate balance of GMP compliance and product availability and move to correct the inequities in the distribution process.

As a member of the DHHS Advisory Committee on Blood Safety and Availability and a plasma derivative consumer, I ask that the Subcommittee support Secretary Shalala's policy initiatives to transition to recombinant technologies and respond to the critical shortage of IGIV, α1PI and recombinant factor products.

I would also encourage the committee to support more collaboration between industry and the FDA and provide the resources necessary for the FDA to assume more regulatory responsibilities in the distribution of products in short supply.

On behalf of the Alpha One community, I wish to reiterate our appreciation for your continued vigilance on these issues and commend the Subcommittee for your efforts in ensuring a safe and available supply of life saving plasma derivative products.

Thank you for your consideration.

Alpha One Foundation

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† Executive Committee

* Denotes diagnosed alpha$_1$ – antitrypsin deficient

◊ Denotes *az* with diagnosed family member

DECLARATION OF GOVERNMENT FUNDING

THE ALPHA ONE FOUNDATION

HAS NOT RECEIVED ANY GOVERNMENTAL FUNDING

AND HAS NO PENDING FUNDING REQUESTS,

AS OF SEPTEMBER 9TH, 1998.

John W. Walsh, President, CEO

2937 S.W. 27th Avenue, Suite 302, Miami, Florida 33133
Telephone: (305) 567 9888 · (888) 825 7421 · Fax: (305) 567-1317 · e-mail: aof@bellsouth.net

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725 15th Street, NW ♦ Suite 700 ♦ Washington, DC 20005 ♦ 202-393-5725 ♦ 1-888-USBLOOD ♦ FAX 202-393-1282
Web Site: http://www.americasblood.org ♦ e-mail: abc@americasblood.org

Testimony of America's Blood Centers
House Government Reform and Oversight
Subcommittee on Human Resources
September 9, 1998

Mr. Chairman and members of the Subcommittee:

America's Blood Centers (ABC) appreciates this opportunity to submit a statement to the Subcommittee on Human Resources Committee on Government Reform and Oversight regarding the US General Accounting Office (GAO) study on Blood Plasma Safety. From our knowledge of the plasma industry the GAO report is accurate as well as compelling. We applaud GAO for another good and useful analysis and thank Congressman Shays for requesting the study.

One important aspect of the study compares safety of volunteer donor plasma with that from compensated individuals. The members of America's Blood Centers provide nearly half of the nation's volunteer donor blood supply. This includes over 10 million blood components for transfusion and over 900,000 liters of recovered plasma for further manufacturing into plasma pharmaceuticals. In its 36 year history, ABC has supported an all volunteer blood and plasma system. ABC endorsed, and continues to support, the National Blood Policy promulgated by the Federal government in 1974 calling for an all volunteer blood supply. We also have supported an all volunteer donor plasma supply. Yet we recognize today that this latter goal may be unachievable and potentially unnecessary.

Less than 25 years after the virtual elimination of compensation to donors who provide blood for transfusion and the rise of the commercial paid-plasma donor sector, both the US blood and plasma supplies are remarkably safe.

For example, in spite of residual risks in the volunteer and paid donor sectors, there have been no reports of HIV transmission from plasma pharmaceuticals since 1987. This is due primarily to viral inactivation procedures. Despite the continued lack of such procedures to apply to blood components, likely less than a handful of HIV transmissions occur annually from the voluntary sector. Early next year, implementation of a powerful test (Gene Amplification Technology or GAT) in the voluntary sector will virtually eliminate the transmission of HIV, hepatitis C (HCV), and eventually (we hope) hepatitis B (HBV).

Indeed, the US blood and plasma supplies are very safe. Few people are harmed each year by their appropriate use, while many millions of American lives are saved by their therapeutic value.

Yet history has some important lessons:

- No other step has improved blood safety more than the elimination of paid individuals as donors of blood for transfusion.
- The rates of HIV in persons with hemophilia, who were treated in the early 1980s with multiple single-donor products from volunteer donors (i.e., cryoprecipitate), were far lower than those of patients treated with pooled pharmaceuticals.
- The GAO report confirms that paid donations still represent significant risks over volunteer programs. For example, despite all the safety measures in place (many that cannot be applied practically to blood for transfusion), paid plasma donations that are used to make pharmaceuticals still have a two-fold residual risk for HBV when compared with volunteer donors. (The risk for HIV and HCV are roughly equivalent.)
- In spite of proven and overlapping safety measures, breakthrough infections can still occur when mistakes are made.
- Emerging infectious agents, such as nvCJD, may be resistant to the viral inactivation processes already in place.

In the 1970s and 80s, the US voluntary sector tried but failed to establish volunteer donor plasma programs that would meet the needs for plasma pharmaceuticals. Other countries have recently had similar experiences. This has given rise to the worldwide dominance of the commercial paid donor sector in providing plasma pharmaceuticals.

Although volunteer donor plasma is potentially a superior starting material, it remains doubtful that the voluntary sector could ever supply all the plasma required to meet patient needs for plasma pharmaceuticals. It is equally doubtful that the voluntary sector will be able to supply the large numbers of red cells soon to be required by pharmaceutical companies for manufacturing hemoglobin solutions.

With the emergence of more and better synthetic substitutes (i.e., genetically engineered products), it is likely that within 20 years most simple human plasma products will be replaced by biotechnology. Cells, tissues and organs will remain the final frontier, but eventually the synthetic biotech products will dominate there as well. Good estimates do not exist for when the need for volunteer donors of blood, tissue, marrow and organs will eventually dissipate. Despite rapid advances in biotech, the tasks to find effective and safe substitutes for human products are very complex.

Thus, both the private and the public sectors need to take all practical steps to assure the continuing improvement of blood and plasma safety. Calls that steps may be too difficult, too expensive, or not worth the benefit should be carefully evaluated. It was only 4 years ago that FDA Commissioner David Kessler called for the implementation of

GAT testing for improving blood and plasma safety by closing "the HIV window shut." Most experts at the time saw Kessler's 5-year time frame as impractical and that the costs would be in the hundreds of millions. Less than 5-years later, the plasma sector already uses that test and the voluntary sector will do so shortly. Costs are about one-tenth of those estimated just a few years ago. Such visionaries are required to assure that Americans have the safest blood supply available.

In America's pursuit of an absolute safe blood supply, ABC has the following four recommendations:

1. **Continue Strong FDA Compliance Actions.** There is no doubt that FDA action in the early 1990s to raise the bar on GMP compliance has resulted in a safer blood and plasma supply. No doubt too, there have been excesses by overzealous inspectors. Overall, however, these strong actions have been appropriate.

2. **Use Negotiated Rulemaking to Promulgate New Standards.** In the past 10 years the number of new blood and safety requirements promulgated by FDA have been astounding. Most have been appropriate. To attain uniform good outcomes FDA often feels compelled not only to state what must be done, but how it should be done. While this is not always inappropriate, FDA has no operational expertise in most of the areas it regulates. Thus, and sometimes despite numerous hearings on a subject, FDA often does not identify the most effective or efficient way to achieve its public health goals, or necessarily in the most timely or inclusive manner. Other federal agencies effectively use the consensus process of negotiated rulemaking to achieve public health goals on controversial and or complex matters. Negotiated Rulemaking has proven to be an effective way to get consumers and industry to work together for promulgating effective and efficient regulations in a timely manner. For reasons we do not understand, FDA resists using this inclusive process. Congress should compel such use for blood safety issues.

3. **Justify Not Following More Stringent World Solutions.** Blood safety is a global concern. Thus, countries around the world implement blood safety standards to address the same problems faced in the US, often with different solutions. Sometimes those measures are more stringent than those in the US, sometimes less so, and sometimes just different. Global pharmaceutical companies must meet the highest standards of all countries. For blood components that are not usually exported (e.g., red cells and platelets), FDA should publicly examine new

requirements implemented by other countries to determine whether and how those measures should apply in the US. For example:

- Britain and Canada now filter all red cell products. Should the US? If not, why not?
- Why does FDA allow up to 2,500 donations to be pooled for solvent/detergent treated plasma, but France has a standard of 200 donations?
- Germany and Switzerland have just approved the use of methylene blue treated plasma, yet no clinical trials for this product are underway in the US. Why not? Should FDA facilitate the introduction of this viral inactivation method?
- Next year the FDA will approve the first fully automated blood testing technology. Yet this technology, which was invented in the US, has already been in use in Europe for over two years. Why?

4. **Implement a no-fault compensation system for blood injuries.** Two years ago the Institute of Medicine made many sweeping recommendations to assure no repeat of the AIDS tragedy. Nearly all of IOM's highest priorities have been addressed, except for the implementation of a no-fault compensation system for blood injuries. There needs to be a program that would respond to blood-related injuries, in a manner such that the National Childhood Vaccine Injury Act has responded to vaccine injuries. Congress should commission an HHS or GAO study now for recommendations on this issue with a report back next year in time for the possible passage of enabling legislation.

ABC thanks the Chairman and members of the Subcommittee for this opportunity to present our views.

Baxter

FOR IMMEDIATE RELEASE

Media contact: Mary Thomas, (847) 948-2815

FDA APPROVAL OF BAXTER'S ROCHESTER FACILITY TO INCREASE PRODUCTION OF MUCH-NEEDED MEDICAL THERAPY

*****

Company Makes Progress with FDA on Licensing a Second Brand of IVIG

DEERFIELD, Ill., September 9, 1998 -- Baxter Healthcare Corporation announced today that it has received approval from the U.S. Food and Drug Administration (FDA) to process an intermediate form of intravenous gamma globulin (IVIG) at its facility in Rochester, Michigan. The approval will enable Baxter to increase by 15 to 20 percent its production of IVIG, which will help to alleviate an industrywide shortage of the therapy.

IVIG, which is derived from human plasma, is prescribed for patients suffering from deficiencies in their immune systems, cancer, and other often life-threatening conditions. For many years, there have been periodic shortages of IVIG throughout the world. Most recently, the shortage has been the result of a several factors including: better diagnosis and treatment of patients; product withdrawals due

to the theoretical risk of Creutzfeld-Jakob disease transmission; and temporary reductions in production due to industry efforts to enhance production facilities.

The FDA's approval will allow Baxter to process an "intermediate" called fraction 2, which is the main ingredient in IVIG. Baxter will then ship the fraction 2 to its facility in Lessines, Belgium, where the process is completed. IVIG produced in Lessines is imported back to the United States for patients' use. Baxter will also continue to process fraction 2 at its facility in Glendale, California. This facility has been operating at full capacity.

Additionally, Baxter continues to work with the FDA to license a second brand of IVIG to import to the United States. This will supplement the current Baxter brand, which is produced in Lessines. The second brand is processed in the company's Vienna, Austria facility. When Baxter receives licensure for its second brand in the United States, it will increase the company's supply of IVIG by an additional 15 to 20 percent.

# # #

Bayer

Fax Cover Sheet

Date:	September 8, 1998	**No. of Pages (including this page):**	**2**
To:	**Anne Marie Finley**	**From:**	**Greg Lane**
Company:	Office of Christopher Shays	**Div/Dept.:**	Pharmaceutical Division
Fax:	202/225/2382	**Fax:**	1-203-812-6478
Phone:	202-225-2548	**Phone:**	1-203-812-3283

Dear Anne Marie:

Further to our earlier conversation, we have undertaken an assessment of the anticipated shortfall of Bayer-produced IGIV in 1998 versus 1997. The following summarizes the situation as we see it today:

1. The 1998 estimated releases of IGIV now appear to be 22% less than 1997 total releases. Mr. Jan Turek estimated this figure at 50% of 1997 performance at the May hearing based on the latest information available at that time.
2. CJD has had no impact on 1998 IGIV releases to date.
3. HVAC: Unanticipated problems with the heating, ventilation and air conditioning system (HVAC) in our liquid fill area, required replacement and validation of the unit. The submission of this change, affecting Line 1 and 2, resulted in a delay in production until June.
4. FDA Compliance: As a result of the FDA review, it was necessary to review production processes to assure the quality and safety of all plasma-derived products, including IGIV. It is difficult to separate out the effects of the FDA review from the impact of the HVAC problems, as the latter required equipment replacement, validation and FDA approval of the system.

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5. Capacity: As Bayer worked through completion and validation of these improvements, capacity was adjusted to reflect the status of these changes. We are now operating at our current optimum capacity with plans to increase fractionation capacity utilization in the 1999 fractionation year by up to 22% over 1998 production.

I regret that I have not been able to provide a more detailed breakdown of the impact of the various issues on total production, however the overlap of factors (i.e. HVAC and compliance) makes it difficult to precisely segment their individual effects.

I hope that this addresses your questions regarding Bayer's production of IGIV.

Sincerely,

Greg Lane/ep

Greg Lane

cc: Jan Turek

FAX IN BRIEF

TO: ANNE-MARIE FINLEY, SHAYS SUB-COMM.
FAX: 1 202 225 2382
FROM: COMMITTEE OF 10,000

PAGES (INCLUDING COVER): 8

Wednesday, September 9, 1998

ANN-MARIE-HERE IS OUR WRITTEN ADDITION FOR RECORD-ALOT ON ECONOMICS-HAVE A LOOK-ANY COMMENT ARE WELCOMED-ALL THE BEST AND THANKS FOR THE HARD WORK-COREY

1.

On August 27, 1998 the US Surgeon General, Dr. David Satcher, stated that for persons with clotting disorders Recombinant Factor Concentrates shall become the standard of care. He also stated that for other plasma derivative dependent communities, the usage of recombinant products, when and where available, should be the product of choice. Dr. Satcher also cited the need or developing and bringing to market recombinant products for diseases such as Alpha-1 Deficiency and others.

Two years ago the Committee Of Ten Thousand called for the establishment of a new standard of care for the treatment of hemophilia and other bleeding disorders. We asserted then and now that recombinant factor concentrates provided bleeding disorder clients with the highest degree of safety possible. This call came subsequent to our earlier push In 1994 for the usage of recombinant factor in all persons with hemophilia whose immune systems were compromised by HIV and HCV. This was based on our reading of the 1993 Swedish study which demonstrated a higher degree of CD4 count stability in HIV immune-compromised hemophilia clients who only treated with recombinant factor concentrates.

During that historical period we found a serious lack of understanding by American hemophilia doctors regarding the relationship of product purity and immune system stability. The issue still has not been given the attention it deserves, however, a greater clarity on the part of clients themselves has led to much more widespread usage of recombinant factors in immune compromised hemophilia clients.

While we all agree that moving all persons with clotting disorders to recombinant factor usage is a desirable goal and does represent a safety margin increase, the current discussion and proposal is occurring in a vacuum as there currently not a sufficient supply of recombinant factor to reach the desired goal.

In fact, we are facing a degree of shortage that will not only prevent the expansion of recombinant usage, but will require some current users to return to the infusion of human derived factor concentrates. It is important to understand at this juncture, that for a person with

hemophilia, the usage of recombinant factor has resulted in a higher degree of individual security regarding the margin of safety and the dangers associated with the usage of clotting factor in general. This becomes even more critical for an individual who has already been subjected to the nightmare of the AIDS and hepatitis C epidemics that have ravaged the hemophilia community. For these individuals, a return to human product can have intense psychological and emotional repercussions.

This situation is exacerbated by the industry's lack of candidness regarding why this shortage is occurring. Individual companies continue to be secretive and vague about the specific causes of a given shortage. Our inability to ascertain the reason for this current recombinant shortage leaves us, at times, suspicious and distrustful regarding our overall relationship with the manufacturers of the products we depend on.

An adequate supply of plasma derivative and recombinant products is obviously a shared goal of the consumers, manufacturers and the federal government. However, we certainly are tired of the sometimes overt and sometimes more subtle connection made by industry between safety margin and adequate supply. We continue to reject the bipolar graph that places supply at one pole and safety at the opposite pole. A safe and adequate supply should be the attainable goal that the industry and the government work together to reach.

Simultaneously, the federal government must ensure that good manufacturing practices and standard operating procedures are strictly and vigilantly enforced in order to guarantee that current safety margin technologies are, in fact, effective.

The recent Government Accounting Office, GAO, report, *"Plasma Product Risks Are Low If Good Manufacturing Practices Are Followed"*, painted a distressing picture of the current GMP landscape. It chronicled a fairly lengthy list of violations by certain companies involved in the manufacture of plasma derivative products. Violations that could potentially result in end user harm if not substantively addressed in a timely fashion.

It is clear that the violative lipid envelope viruses that we know about such as HIV, HBV, and HCV can be addressed in an efficacious manner if viral inactivation technology is applied within a context of vigilant quality control and regulatory oversight. The GAO report raises serious questions regarding whether or not this is, in fact, what is currently occurring. Products considered the safest such as albumin, in one instance failed existing standards as they were being prepared to be shipped. The degree of GMP problems currently identified by the GAO report paints a troublesome landscape, especially when you consider that half of the current manufacturers, 50 percent, are currently under consent degrees due to GMP failures.

While it appears that the FDA has intensified the regulatory climate in some areas, that intensification has yet to result in what we would view as an acceptable GMP landscape. Either the agency is not aggressive enough in its follow through or the manufacturers are not complying at an acceptable level. Whatever the basis it is clear that GMP failure is a significant contributing factor in the current shortages of plasma derivative products. The FDA must use the regulatory authority it possesses to whatever degree necessary to gain manufacturer compliance in a timely fashion.

We continue to be appalled by the fact that the FDA Blood Products Advisory Committee continues to make critical recommendations regarding safety margin issues without the data necessary to ensure that the recommendations being formulated are the best possible. Why is the BPAC not receiving regular updates on the status of the consent decrees currently in force with Centeon, Alpha Therapeutics and the American Red Cross? Why are full voting members of the BPAC told that the only way they can view the consent decrees is through a Freedom Of Information Act petition? Why do senior FDA regulators shrug their shoulders when queried about why the necessary data is being withheld by the industry? Why has it taken ten years to begin to get aggregate monthly production data from the industry?

From our perspective a critical question not being discussed is how do we view the plasma derivative products marketplace? Is it a

traditional products market which is basically moderated by market forces and the decisions of given manufacturers? Or, is this a unique situation due to the nature of the products produced and the life or death dependence of certain communities on these products?

COTT contends that the medical and social need for plasma derivative products should impact the way we view and regulate this marketplace. It is also important to note that the profits incurred by these particular manufacturers are, in large part, paid for by the society as a whole. The extreme costs of plasma derivative products are, to a high degree borne by the states and the federal government, in essence the taxpayers. From our perspective the social necessity of these products and the willingness of the public sector to underwrite industry profits in order to ensure sufficient supply, has resulted in a marketplace that is essentially sheltered. Normal market forces are not a moderating force on price in this instance as the four manufacturers have for thirty years worked in concert to ensure a stable and artificially high price structure. The federal government has tolerated a situation that raises serious anti-trust questions and leaves four manufacturers in total control over the safety and supply of products that represent life or death for the majority of individuals who depend on plasma derivatives to remain healthy.

Blood products are a social utility, a medical product that the society requires in order to ensure the health of those with clotting disorder and other diseases such as Alpha-1 and primary immune-deficiency. The regulation of this industry should reflect the social nature of the products being produced as well as the public sector's underwriting of the costs. Society, the public sector has also borne the human and financial costs of the industry's failure during the 1980s regarding HIV and the blood supply. The medical costs of treating nearly over twenty thousand Americans who contracted HIV/AIDS through blood/blood products has been in the hundreds of millions of dollars at a minimum. Now the society will pay for the industry and regulatory failure regarding the transmission of Hepatitis C to potentially one million Americans. These "clean-up" costs never appear to be factored into the costs/benefit equation when assessing the blood/blood products industry and its regulation. Society has underwritten the costs of the treatment, blood

products, and then also had to shoulder the costs when the system failed and the treatment became the transmitter of a deadly virus. Taken as a whole, we can only conclude that this is a unique marketplace where the relationship between government regulation and industry cannot be left to the traditional accepted norms. It is a marketplace where government regulation must be rooted in an understanding of the unique situation and the role of the public sector in underwriting the costs and profits of the four major corporations involved in the manufacture of plasma derivative products.

Yet the federal government continues to regulate through so-called consensus building and recommendations rather than wielding the power it possesses in order to ensure a safe and sufficient supply of plasma derivative products. Why does the regulatory system for blood/blood products not reflect the social value placed on these products? Why does the federal government continue to allow these four manufacturers to collectively control critical data and information? Information that is crucial to the development and implementation of sound regulatory and safety standards. Why does the FDA continue to operate as if these four manufacturers have the right to withhold critical safety and supply data?

Have we not yet concluded that the self-regulation that has prevailed since the introduction of factor concentrates has failed? Why has the hemophilia holocaust and the transfusion associated HIV infection of thousands of Americans not resulted in substantive changes in the way we approach regulating this essential industry? It is past due the time when the federal government reassesses the regulation of the blood products industry and begins to regulate these manufacturers within the context of the social utility of these products. Consensus building has obviously failed and must be abandoned. The regulatory "culture of decision making" is not only flawed in terms of the financial costs to the public sector it is also flawed in terms of protecting the health and well being of the end users, consumers, of blood products. Was it not a vivid and disturbing lesson when we learned from the earlier hearing before the Subcommittee on Human Relations the truth regarding the pool sizes the manufacturers had been employing over the last 25 years. Persons with hemophilia had believed that their risk factor was based on 20 thousand

donors per plasma pool. We were shocked at a minimum to learn that, in fact, our risk factor had consistently been five times that number and that the industry had been outright lying to us, their customers, for twenty-five years.

Since 1993 the Committee Of Ten Thousand has been calling for a new paradigm in blood/blood products. We have worked to develop relationships with industry and government, in part, to ensure that this nightmare we have been subjected to does not occur again and, in part, to attempt to develop relationships of trust between industry, government and consumers. However without significant change in the regulatory decision making process and a new willingness on the part of the industry to not continue with "business as usual" this new paradigm will never evolve and we will certainly continue to place the users of blood products in harms way.

International Plasma Products Industry Association

1350 I Street, NW • Suite 1020 • Washington, DC 20005 USA
Telephone: (202) 789-3100 • Telefax: (202) 789-4197

September 9, 1998
Reference: FINL98009

Ms Anne Marie Finley
Professional Staff Member
Subcommittee on Human Resources
U.S. House of Representatives
Washington, DC 20515

Dear Anne Marie:

You requested an update on the commitments that IPPIA member companies made at the May 7, 1998 hearing before the subcommittee. The companies have supplied us the following information:

Alpha	
$75 million to expand manufacturing capacity	funding approved
40-50% increase in IVIG production by 2003	on track
Operating at 100% capacity in 1998	unchanged
Alpha-1 submission	in progress
Bayer	
Double IVIG emergency supply	accomplished
Boost IVIG production over next few years	in process, on track
Centeon	
Achieve full production in 1998	affected by recent inspection
Baxter	
Increase IVIG production at Rochester, MI	FDA approved additional capacity 8/10/98
Import new form of IVIG (*ENDOBULIN*)	Submission completed. FDA priority attention. Possible action by end of yr.

All companies checked their distributors for anomalies as committed.

Please let me know if you have any further questions.

Thank you.

Dennis Jackman
Vice President, North America

DJJ/mmp