United States General Accounting Office

GAO

Testimony

Before the Subcommittee on Human Resources, Committee on Government Reform and Oversight, House of Representatives

For Release on Delivery
Expected at 10:00 a.m.
Wednesday, September 9, 1998

BLOOD PLASMA SAFETY

Plasma Product Risks and Manufacturers' Compliance

Statement of Bernice Steinhardt, Director
Health Services Quality and Public Health Issues
Health, Education, and Human Services Division

GAO/T-HEHS-98-242

Blood Plasma Safety: Plasma Product Risks and Manufacturers' Compliance

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

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

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 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 takes 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]

[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.

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 for 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.

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

[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.

[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).

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 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

[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.

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.

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.

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

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 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

[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.

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]
- 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,

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

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.

Ordering Information

The first copy of each GAO report and testimony is free. Additional copies are $2 each. Orders should be sent to the following address, accompanied by a check or money order made out to the Superintendent of Documents, when necessary. VISA and MasterCard credit cards are accepted, also. Orders for 100 or more copies to be mailed to a single address are discounted 25 percent.

Orders by mail:

U.S. General Accounting Office
P.O. Box 37050
Washington, DC 20013

or visit:

Room 1100
700 4th St. NW (corner of 4th and G Sts. NW)
U.S. General Accounting Office
Washington, DC

Orders may also be placed by calling (202) 512-6000
or by using fax number (202) 512-6061, or TDD (202) 512-2537.

Each day, GAO issues a list of newly available reports and testimony. To receive facsimile copies of the daily list or any list from the past 30 days, please call (202) 512-6000 using a touchtone phone. A recorded menu will provide information on how to obtain these lists.

For information on how to access GAO reports on the INTERNET, send an e-mail message with "info" in the body to:

info@www.gao.gov

or visit GAO's World Wide Web Home Page at:

http://www.gao.gov

PRINTED ON RECYCLED PAPER

United States
General Accounting Office
Washington, D.C. 20548-0001

Bulk Rate
Postage & Fees Paid
GAO
Permit No. G100

Official Business
Penalty for Private Use $300

Address Correction Requested