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BLOOD SAFETY

Recalls and Withdrawals of Plasma Products

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Blood Safety: Recalls and Withdrawals of Plasma Products

Mr. Chairman and Members of the Subcommittee:

We appreciate the opportunity to be here this morning to discuss our examination of plasma product recalls and withdrawals. Plasma is the liquid portion of blood, containing nutrients, electrolytes (dissolved salts), gases, albumin, clotting factors, hormones, and wastes. Many different components of plasma are used for medical treatment, from treating the trauma of burns and surgery to replacing blood elements that are lacking as a result of disease, such as hemophilia. It is estimated that each year some half million people receive products manufactured from human plasma, including over 20,000 who receive intravenous immune globulin (IVIG).

In the past 6 months, there have been reported shortages in certain plasma products, particularly the immune globulins. Many different factors have been cited as possible causes of the current shortage, including recalls and withdrawals of plasma products, delays in production due to problems in compliance with the Food and Drug Administration's (FDA) current good manufacturing practices, and increased demand due partly to new uses of the products.

You asked that we review the first of these possible causes—recalls and withdrawals—to determine the amount of plasma products, and in particular, the amount of IVIG, that was being lost due to removal of products from the market. Recalls are used to remove products from the market that violate the laws or are defective, while withdrawals are used to remove products that present only minor or unknown risks or are removed completely at the manufacturer's discretion. Specifically, you asked us to report on the number of recent product recalls and withdrawals, the reasons for these actions, the different types of plasma products affected, and the amount of product that has been returned as a result of these actions. You also asked that we examine the impact on the current shortage of IVIG of reducing the number of donors for each plasma product.

To answer these questions, we obtained information from FDA and the major plasma product manufacturers.[1] Specifically, we obtained data on

[1]The major manufacturers of plasma products distributed in the United States include Alpha Therapeutic, Baxter Healthcare, Bayer Corporation, Centeon, and the Swiss Red Cross. The American Red Cross collects and distributes plasma products, but its products are manufactured under contract by Baxter Healthcare and the Swiss Red Cross. For convenience, we discuss all of these entities as manufacturers. Together, these manufacturers account for over 95 percent of the production of plasma products.

recalls from FDA, and because companies are not requested to provide FDA with data on market withdrawals, we obtained these data from the manufacturers.[2] We sought information on all plasma product recalls and withdrawals from December 1996 through mid-April 1998.

In summary, the data showed that only a small proportion of distributed IVIG—about 1.1 percent—has been removed from the market as a result of recalls or withdrawals. However, only 5 percent of the vials of plasma products that were recalled or withdrawn has been retrieved to date. While additional quantities might still be retrieved, some portion of these products has already been transfused or is otherwise unretrievable. Further, changes to reduce the number of donors in each product appear unrelated to the current shortages.

During the period we reviewed, 11 manufacturers reported to FDA that they undertook a total of 12 recalls (affecting 33 lots of 7 types of plasma products) and 38 withdrawals (affecting 1,001 lots of 10 types of products). The reasons for the product recalls varied, but generally they related to specific manufacturing errors resulting in problems in product potency, sterility assurance, or incorrect labeling. The product withdrawals were all related to donors who were diagnosed with Creutzfeldt-Jakob disease (CJD) or were considered to be at increased risk for CJD.[3]

As reported to FDA, the proportion of IVIG vials retrieved following a recall was 15 percent, which amounted to less than 1 percent of the total IVIG distributed in 1997. In total, about one-third, or 38 percent, of the number of vials of all plasma products recalled has actually been retrieved from distribution or known to be destroyed. The proportion of distributed products retrieved following a withdrawal has been much lower. Data from the plasma product manufacturers showed 6 percent of the vials of IVIG that were withdrawn to actually have been recovered, representing 1 percent of the total product distributed in 1997. For other plasma products, the proportion of distributed vials retrieved following a withdrawal was 2 percent. Manufacturers also claim that their production of IVIG was reduced by 5 to 10 percent in 1997 because they had to quarantine or destroy plasma because of CJD risk, but these amounts cannot be verified.

[2]Manufacturers are requested to notify FDA when they are recalling or withdrawing products from the market; they are requested to report to the agency on the amount of product returned under a recall, but not under a withdrawal.

[3]Creutzfeldt-Jakob disease is a degenerative neurologic disease that leads to progressive dementia and death.

Background

Plasma products are manufactured through a process known as fractionation. This process separates the various active components of plasma, which are further manufactured into clotting factor products for hemophiliacs, albumin for burn and shock victims, and immunoglobulin preparations for immune-deficient persons and to treat and prevent a variety of diseases. (See appendix.)

Most manufacturing facilities use large plasma pools to manufacture sufficient quantities of products. These plasma pools are derived by combining units from individual donations. The number of units combined into a common mixture for processing is known as "pool size." In the past, these plasma pools included as many as 400,000 donors, but recent steps to reduce the number of donors to which a patient may be exposed have led to reductions in the size of the plasma pools to the general range of 60,000 donors. Plasma used for plasma-derived products manufactured and distributed in the United States is donated only by U.S. donors in collection facilities licensed and registered with the FDA.[4]

Manufacturers must be licensed and registered with the FDA and must comply with regulations governing current good manufacturing practices. Each product must be separately licensed, and the manufacturing facilities are subject to FDA inspection. FDA regulations govern the recall or withdrawal of marketed plasma products.

Recalls are a manufacturer's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action—for example, seizures—if the product was not recalled. A recall is generally a voluntary action on the part of the manufacturer to protect the public from products that present a risk of injury or are otherwise defective, although FDA can order a recall if the manufacturer does not act. In any case, FDA monitors recalls and assesses the adequacy of a manufacturer's efforts in a recall. Among other checks, the recalling manufacturer is requested to submit periodic recall status reports to the appropriate FDA district office so that the agency can assess the progress of the recall.

Withdrawals are defined as a manufacturer's removal or correction of a distributed product that involves a violation not subject to legal action by the FDA or that involves no violation, such as normal stock rotation practices, routine equipment adjustments, and repairs. Companies are not

[4]Plasma products manufactured by the Swiss Red Cross for distribution in the United States use plasma obtained from the American Red Cross, the New York Blood Center, and other blood establishments in the United States.

requested to submit information on products retrieved under voluntary market withdrawals. FDA has stated that it does not routinely request such information because it focuses its limited resources in areas in which the risk to the public health is viewed to be the most significant.

FDA classifies actions to remove products from the market due to CJD risks as voluntary market withdrawals because the products are not considered to be in violation of the regulations and laws administered by FDA. Because there are no known cases of CJD transmission resulting from blood transfusion, FDA concluded that the risk of transmission of CJD by blood components and plasma derivatives is theoretical. The agency has nevertheless been developing a policy that recommends the exclusion of donors at risk for CJD and the withdrawal of blood components and plasma products prepared from such donors.

Since FDA issued a memorandum to blood establishments in December 1996 stating this policy, many withdrawals of plasma products related to CJD risks have occurred. This memorandum noted that CJD may be acquired by exposure to infectious material[5] or may arise spontaneously at high frequency in persons with certain genetic mutations or at low frequency on an unknown basis. Those considered to be at increased risk include donors who have had blood relatives with CJD or have been told that their family is at an increased risk for CJD, those who have received pituitary-derived human growth hormone, and those who have received a dura mater graft.

The memorandum recommended that when blood establishments identify donors who were either subsequently diagnosed with CJD or at risk for CJD, plasma manufacturers should (1) immediately retrieve and quarantine products under the control of the blood establishment that were previously collected from the donor, (2) direct their consignees to immediately retrieve and quarantine any implicated products, and (3) quarantine and destroy any plasma derivatives.

[5]Transmission of CJD has been documented to have occurred in transplants of infected dura mater or from treatments with pituitary-derived human growth hormone from an infected source. Dura mater is the fibrous membrane forming the outer sheathing of the brain.

Recalls and Withdrawals Have Not Removed Significant Portions of Marketed Products

The removal of marketed products through voluntary recalls and withdrawals has been widely cited as a major contributor to the current shortage. Our review determined that only a small portion of product has thus far been returned or destroyed in response to either of these types of actions.

Recalls Have Not Resulted in Significant Losses of IVIG

Manufacturers reported to FDA that they voluntarily initiated a total of 12 recalls of plasma products within the United States during the 16-month period we reviewed. Recalls were related to such issues as breaches in sterility, lots tested at less than full potency, and patients reporting hives after injection of a product. We obtained data for each of the recalls from FDA, including the number of vials distributed and the number of vials returned or destroyed. Details for each recall are provided in table 1.

Table 1: Plasma Product Recalls, December 23, 1996, to April 9, 1998

				Vials returned or destroyed	
Product	**Manufacturer**	**Date of recall**	**Number of vials recalled**	**Number[a]**	**Percent**
Rho (D) immune globulin	Ortho Diagnostic	Mar. 9, 1998	Unknown	Unknown	Unknown
Albumin	Bayer Corporation	Jan. 9, 1998	15,777	19	0.1%
Rho (D) immune globulin	Ortho Diagnostic	Oct. 16, 1997	60,975[b]	47,982	79
Antihemophilic factor	Baxter Healthcare	July 12, 1997	5,324	4,820	91
Rho (D) immune globulin	Bayer Corporation	June 26, 1997	41,190	284	0.7
Antihemophilic factor	Baxter Healthcare	May 24, 1997	18,116	7079	39
Cytomegalovirus immune globulin	Massachusetts Public Health Biologic Labs	May 6, 1997	3,677	28	0.8
Immune globulin (IV)	Baxter Healthcare	Apr. 23, 1997	10,173	480	5
Immune globulin (IV)	Alpha Therapeutic	Mar. 7, 1997	2,189	1,363	62
Coagulation factor IX	Centeon	Feb. 28, 1997	883	546	62
Thrombin	Parke-Davis	Feb. 27, 1997	5,915	1,062	18
Antihemophilic factor	Centeon	Feb. 21, 1997	1,908	28	1
Total[c]			**166,127**	**63,691**	**38%**

[a]As of April 1998.

[b]Recall of this Rho (D) immune globulin is based on number of syringes (not vials).

[c]Totals do not include the most recent recall, for which the amount of product returned or destroyed is not yet available.

The proportion of product recovered or destroyed as of April 1998 varied widely across the separate recalls, ranging from a high of 91 percent to a low of 0.1 percent, with an average recovery rate per recall of 33 percent. However, the recovery rate was high enough on one large recall so that, of the total 166,127 vials recalled, some 38 percent had been returned or destroyed.

Two of the recalls involved IVIG: one because of a labeling problem, and the other because of a higher than expected rate of hives in the recipients. As a result of the two recalls, 15 percent of the vials have been returned or destroyed. This represented 0.07 percent of the total volume of 15.7 million grams of IVIG the manufacturers told us they distributed in the United States in 1997. Both IVIG recalls occurred in the spring of 1997, prior to reports of severe shortages in these products.

Only a Small Proportion of Product Listed for Withdrawal Has Been Recovered

From December 23, 1996, to April 9, 1998, manufacturers initiated 38 withdrawals of plasma products in the United States.[6] Among the major plasma manufacturers, the Swiss Red Cross had the most withdrawals announced during this period (16), while Alpha Therapeutic had only 1, and Centeon had none. Each withdrawal was related to donors who were at increased risk of CJD. Overall, only 3 percent of the vials withdrawn has been returned to manufacturers.

Twenty-six of the 38 withdrawals by four manufacturers involved at least some lots of IVIG. Of the 381,442 total vials withdrawn, only 23,404, or 6 percent, were recovered as of April 1998. The proportion withdrawn that was actually recovered varied from a low of 0.3 percent to a high of 18 percent across the different manufacturers. The portion retrieved amounts to 161,212 grams, which represented 1 percent of the 15.7 million grams of IVIG distributed in the United States in 1997. Information for each of the involved manufacturers is provided in table 2.

[6]Because companies are not required to provide FDA data on market withdrawals, we obtained data on the proportion of product withdrawn and, of that, the proportion recovered as of April 1998 from the manufacturers involved in these actions. We did not verify these figures.

Table 2: Withdrawals of IVIG, December 23, 1996, to April 9, 1998

Manufacturer	Number of withdrawals	Number of vials withdrawn	Number of vials returned[a]	Percent of vials returned
American Red Cross[b,c]	6	110,702	2,703	2%
Alpha Therapeutic	1	8,048	1,472	18
Baxter Healthcare[c]	5	109,942	312	0.3
Swiss Red Cross[d]	14	152,750	18,917	12
Total	**26**	**381,442**	**23,404**	**6%**

[a]As of April 1998.

[b]Data received from the American Red Cross represent 80 percent of the product they supplied (the other 20 percent is captured in the Swiss Red Cross data).

[c]In addition, the American Red Cross and Baxter Healthcare had withdrawals of fraction IV-1 paste and fraction IV-4 paste, which can be further processed into IVIG. It is unknown how much this would represent in terms of number of vials.

[d]These data include plasma obtained from and processed under contract for distribution by the American Red Cross.

Of the 38 withdrawals, 30 included plasma products other than IVIG. Some withdrawals were of a single product, while others involved multiple products. The withdrawn products included albumin, alpha-1 proteinase inhibitor, antihemophilic factor, coagulation factor IX, and plasma protein fraction. In addition, pastes that are distributed for further manufacture into plasma derivatives were also involved in some of the withdrawals.[7] Data related to the recovery of these other withdrawn plasma products are provided in table 3.

[7]Specific lots of fraction I+II+II paste, fraction IV-1 paste, and fraction IV-4 were variously involved in 12 of the withdrawals.

Table 3: Withdrawals of Other Plasma Products, December 23, 1996, to April 9, 1998

Manufacturer	Number of withdrawals	Number of vials withdrawn	Number of vials returned[a]	Percent of vials returned
American Red Cross	9	742,377	17,523	2%
Alpha Therapeutic	1	57,032	14,951	26
Baxter Healthcare	7	623,988	1,486	0.2
Bayer Corporation	7	131,011	3,800	3
Swiss Red Cross[b]	9	193,411	222[c]	0.1
Total	**30[d]**	**1,747,819**	**37,982**	**2%**

Note: Products include albumin, alpha-1 proteinase inhibitor, antihemophilic factor, coagulation factor IX, and plasma protein fraction.

[a]As of April 1998.

[b]These data include plasma obtained from and processed under contract for distribution by the American Red Cross.

[c]Information provided to us by the Swiss Red Cross noted that they did not know how many vials were returned for the vast majority of withdrawals of albumin.

[d]Some withdrawals involved multiple manufacturers.

Of the 1,747,819 vials of other plasma products that were listed for withdrawal, only 37,982 have been returned to the manufacturer. This represents a rate of 2 percent. When all the withdrawals are combined across the full set of products, including IVIG, only 3 percent of the total number of vials of distributed products that were sought have been returned.

Overall, of the 393,804 vials of IVIG the manufacturers attempted to remove from the market through either recalls or withdrawals, only 25,247 vials, or 6 percent of this amount, has been recovered, representing 1.1 percent of the total volume of IVIG distributed in 1997. Across all the plasma products that the manufacturers attempted to remove from the market through either recalls or withdrawals, of the 2,295,388 total vials sought, only 125,077 vials, or 5 percent of this amount, has been recovered.

The recalls and withdrawals represented attempts to recover products that had already been distributed. In addition to these distributed products, the FDA memorandum on CJD also calls for quarantine and destruction of plasma derivatives that are in production. The manufacturers have stated that their in-process losses due to CJD notifications have been significant. Three manufacturers provided data to us showing that they lost

approximately 5 to 10 percent of their 1997 production of IVIG due to CJD risks. However, we did not verify these data.

Changes to Reduce the Number of Donors in Each Plasma Product Appear Unrelated to Current Shortages

We also examined the impact of reducing the number of donors in each plasma product, which some plasma product suppliers have cited as contributing to the current shortage of IVIG. In testimony before this Subcommittee last July, the major plasma product manufacturers pledged to reduce the risk of transmission from infected donors by adopting voluntary restrictions on pool size and limiting to 60,000 the number of different donors whose plasma could be used in a single production run.[8] However, the manufacturers stated that it would take some time to implement the changes necessary to achieve such a reduction, and implementation of the policy was set for January 1998. Because the manufacture of plasma products takes approximately 6 months, products manufactured under the reduced plasma pool size restrictions are still in production and have not reached the market. In fact, the manufacturers told us that they expect it will be January 1999 before they finish distributing all plasma products manufactured prior to the pool size reductions. At the time that the severe shortage of IVIG was first noted in November 1997, plasma products being released for distribution were those that had begun production approximately 6 months earlier, around April to May 1997. Thus, the current shortages predate changes to reduce the number of donor exposures.

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.

[8]"Food and Drug Administration Oversight: Blood Safety and the Implications of Pool Sizes in the Manufacture of Plasma Derivatives," hearing before the Subcommittee on Human Resources of the Committee on Government Reform and Oversight, House of Representatives, 105th Congress, First Session, July 31, 1997.

Plasma Products Manufactured and Distributed in the United States

Table I.1 lists the plasma products manufactured and distributed in the United States and the primary uses of each.

Table I.1: Plasma Components and Their Primary Uses

Component	Primary uses
Albumin	To restore plasma volume in treatment of shock, trauma, surgery, and burns
Alpha-1 proteinase inhibitor	To treat emphysema caused by genetic deficiency
Antihemophilic factor concentrate (factor VIII)	For prophylaxis and treatment of hemophilia A bleeding episodes
Anti-inhibitor coagulant complex	To treat bleeding episodes in the presence of factor VIII inhibitor
Antithrombin III	To prevent clotting and thromboembolism associated with liver disease, antithrombin III deficiency, and thromboembolism
Coagulation factor IX (human)	For prophylaxis and treatment of hemophilia B bleeding episodes and other bleeding disorders
Cytomegalovirus immune globulin	For passive immunization subsequent to exposure to cytomegalovirus
Factor IX complex	For prophylaxis and treatment of hemophilia B bleeding episodes and other bleeding disorders and for warfarin (anticoagulant) reversal
Hepatitis B immune globulin	For passive immunization subsequent to exposure to hepatitis B
Immune globulin: intravenous and intramuscular	To treat agamma- and hypogamma-globulinemia; for passive immunization for hepatitis A and measles
Plasma protein fraction	To restore plasma volume subsequent to shock, trauma, surgery, and burns
Rabies immune globulin	For passive immunization subsequent to exposure to rabies
Rho(D) immune globulin	To treat and prevent hemolytic disease of fetus and newborn infant stemming from Rh incompatibility and incompatible blood transfusions
Tetanus immune globulin	For passive immunization subsequent to exposure to tetanus
Vaccinia immune globulin	For passive immunization subsequent to exposure to smallpox
Varicella-zoster immune globulin	For passive immunization subsequent to exposure to chicken pox

Source: Adapted from the American Blood Resources Association, “Basic Facts About the Commercial Plasma Industry.”

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