Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2007

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005 and FY2006, the blood supply is safer today than at any time in history. Due to advances in donor screening, improved viral marker tests, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion continue to decrease. Overall, the number of transfusion related fatalities reported to the FDA remains small in comparison to the total number of transfusions. In 2006 there were approximately 30 million components transfused.[1] During the proximate period of FY2006, there were 73 reported transfusion related and potentially transfusion related fatalities, with a decrease to 63 in FY2007.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2007, to provide the combined data received over the last three fiscal years, and to compare the FY2007 reports to the fatality reports received in FY2006 and FY2005. We also include information on the infrequent reports of post-donation fatalities. Throughout this report we note changes over time, but the reader should interpret these changes cautiously, given the small numbers of reports and inherent variations in reporting accuracy. The significance of shifts in numbers derived from small populations may appear to be greater than they really are.

Refer to Sections 606.170(b) and 640.73 of Title 21, Code of Federal Regulations (21 CFR 606.170(b) and 21 CFR 640.73), for fatality reporting requirements. For information regarding the notification process, see our web page, Notification Process for Transfusion Related Fatalities and Donation Related Deaths, http://www.fda.gov/cber/transfusion.htm. For further information, see our *Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion*, September 2003.[2]

1 Whitaker BI, Green J, et al. The 2007 Nationwide Blood Collection and Utilization Survey Report. Washington (DC): Department of Health and Human Services; 2008.

2 Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/cber/gdlns/bldfatal.htm.

If you have questions concerning this summary, you may contact us using any of the three following options.

1. Email us at fatalities2@fda.hhs.gov,
2. Call us at 301-827-6220, or
3. Write us at:
   FDA/Center for Biologics Evaluation and Research
   Office of Compliance and Biologics Quality
   Division of Inspections and Surveillance (HFM-650)
   1401 Rockville Pike, Suite 200 North
   Rockville, Maryland 20852-1448

II. Results

During FY2007 (October 1, 2006, through September 30, 2007), we received a total of 93 fatality reports. Of these reports, 76 were transfusion recipient fatalities and 17 were post-donation fatalities.

Of the 76 transfusion recipient fatality reports, we concluded:
a) 52 of the fatalities were transfusion-related,
b) in 11 cases we were unable to rule out transfusion as the cause of the fatality,
c) 13 of the fatalities were unrelated to the transfusion.

We summarize the results of our review in the following sections. Sections A through D of this document present the transfusion-related fatalities. Sections E and F and Table 4 present the fatality reports which were unrelated to the transfusion, or in which we could not rule out the transfusion as the cause of death. Section G presents the post-donation fatality reports.

A. Overall Comparison of Transfusion-Related Fatalities Reported in FY2005, FY2006, and FY2007

In combined FY2005, FY2006, and FY2007, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (55%), followed by hemolytic transfusion reactions (22%) due to non-ABO (15%) and ABO (7%) incompatibilities. Complications of

microbial infection, Transfusion Associated Circulatory Overload (TACO), and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1and Figure 1).

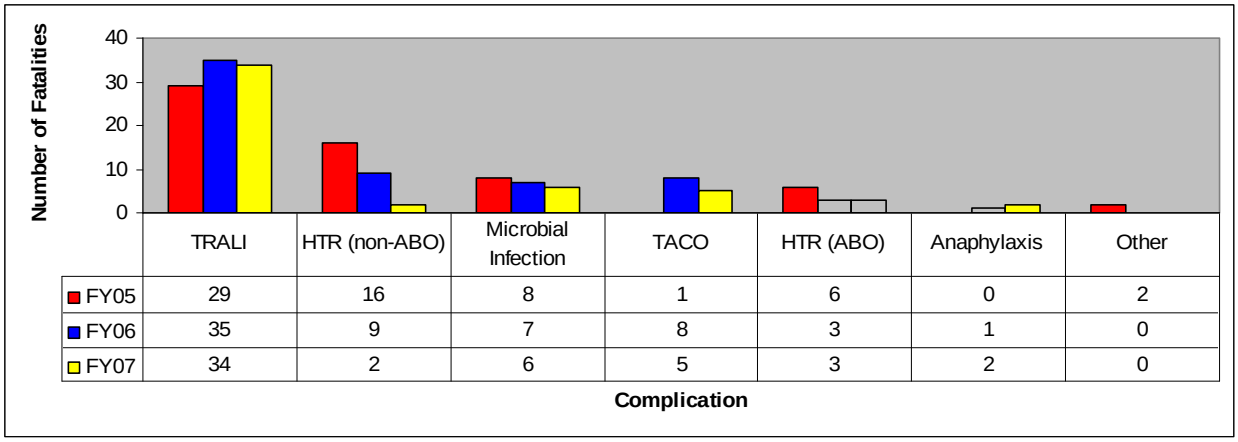
Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2007

Complication	FY05		FY06		FY07		Total (FY05+06+07)	
	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56%	34*	65%	98	55%
HTR (non-ABO)	16	26%	9	14%	2	4%	27	15%
Microbial Infection	8	13%	7	11%	6	12%	21	12%
TACO	1	2%	8	13%	5	10%	14	8%
HTR (ABO)	6	10%	3	5%	3	6%	12	7%
Anaphylaxis	0	0%	1	2%	2	4%	3	2%
Other	2**	3%	0	0%	0	0%	2	1%
Totals	62	100%	63	100%	52	100%	177	100%

*In FY2007, our review committee began using the Canadian Consensus Conference criteria[3,4] for evaluating TRALI cases – this number includes both "TRALI" and "possible TRALI" cases

**Other: Includes one case of Graft vs. Host Disease (GVHD) and one therapeutic plasma exchange (TPE) error (use of a treatment column contraindicated due to patient's medical history)

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2007



B. Transfusion Related Acute Lung Injury (TRALI)

In FY2007, as in the previous two fiscal years, TRALI continued to be the leading cause of transfusion related fatalities reported to CBER, representing 65% of confirmed transfusion related fatalities. Over the last three fiscal years, TRALI represented 55% of confirmed transfusion related fatalities. While the number of TRALI fatalities associated with receipt of Fresh Frozen Plasma (FFP) decreased from 22 (63% of TRALI cases) in FY2006 to 12 (35% of

[3] Goldman M, Webert KE, Arnold DM. et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 2005;19:2-31.

[4] Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44:1774-1789.

TRALI cases) in FY2007 (Figure 2), the number was comparable to that reported in FY2005 (13 cases). For the same three years there was an increase in reports of TRALI fatalities from Red Blood Cells (RBC) with 5 cases reported in each of FY2005 and FY2006 compared with 12 cases reported in FY2007.

When compared to the proportions of all transfused products, plasma products continue to be associated with a disproportionate share of TRALI cases. In Calendar Year 2006, for example, transfused plasma products accounted for approximately 13% of all transfused components, apheresis platelets (using platelet concentrate equivalent units) – approximately 30%, and red blood cell-containing products – approximately 49%.[5] In comparison, for the combined fiscal years 2005-2007, FFP and other plasma accounted for 52% (51/98) of reported TRALI fatalities, apheresis platelets accounted for 7% (7/98), and RBC's accounted for 22% (22/98).

In FY2007, there were 34 TRALI cases temporally associated with products from 162 donors. Of these donors, 104 (64%) were tested for white blood cell (WBC) antibodies (Table 2). Antibody tests were negative in 41% of those tested. Of those tested, Human Leukocyte Antibodies (HLA) were present in 43% of donors. Human Neutrophil Antibodies (HNA) were present in 22% of donors, but most of these reactions (12/17) were weak and non-specific. Many donors had multiple antibodies. Reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens in 7 of the 34 cases, implicating 11 donors (In 2 of these cases, there were recipient matches with 3 donors).

The gender of 25 (15%) of the donors was unknown or not provided by the reporting facilities. Of the remaining donors, reports identified 79 females (49%) and 58 males (36%).

Because TRALI continues to be the leading cause of transfusion-related fatalities, the transfusion community is taking voluntary measures to reduce this risk. Data show that the largest percentage of fatal TRALI cases are associated with female donors with white blood cell antibodies, and recent literature describes efforts to selectively use plasma from male donors for transfusion.[6,7,8] In November, 2006, the American Association of Blood Banks (AABB) issued an Association Bulletin, which included a recommendation that blood collection and transfusion facilities begin implementation of TRALI risk reduction measures for all high plasma-volume components. The measures include interventions to minimize the preparation of these components from donors known to have white blood cell antibodies or who are at increased risk for developing these antibodies.[9]

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[5] Whittaker BI, op.cit. Tables 4-1 and 4-2.

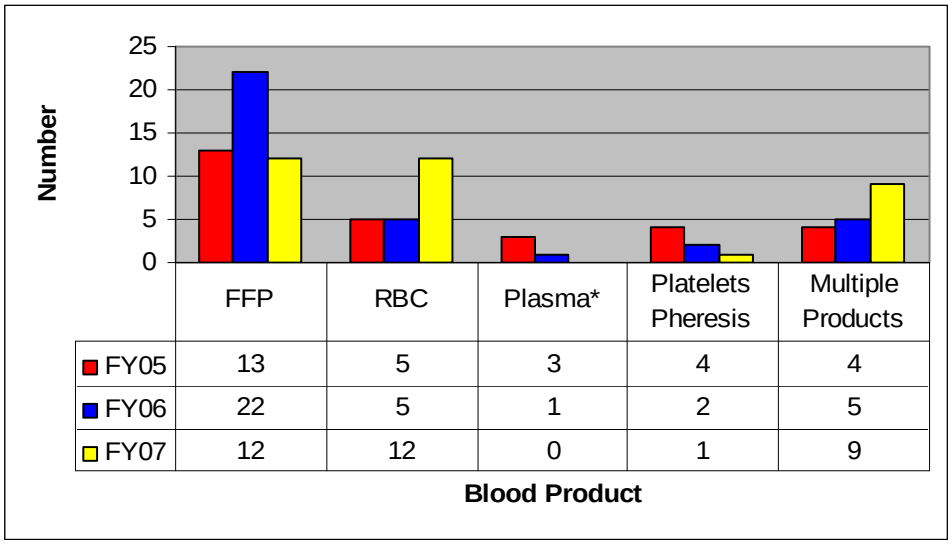
[6] Curtis, BR, Mcfarland JG. Mechanisms of transfusion-related acute lung injury (TRALI): anti-leukocyte antibodies. Crit Care Med 2006;34(5 Suppl):S118-S123.

[7] Eder AF, Herron R, Strupp A, et al. Transfusion-related lung injury surveillance (2003-2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. Transfusion 2007;47:599-607.

[8] Chapman CE, Williamson LM, Cohen H, et al. The impact of using male donor plasma on hemovigilance reports of transfusion-related acute lung injury (TRALI) in the UK (abstract). Vox Sang 2006;91(Suppl 3):227.

[9] Transfusion-related acute lung injury. AABB Association Bulletin. Bethesda: American Association of Blood Banks;2006 Nov 3.

Figure 2: Reports of TRALI by Implicated Blood Product, FY2005 through FY2007



*FY2005: Includes 2 FP24 (Plasma frozen within 24 hours after collection) and 1 Liquid Plasma
FY2006: Includes 1 FP24

Table 2: Donor Antibodies Identified in Association with TRALI, FY2007

FY07 Donor Leukocyte Antibodies	No.	%
HLA Class I	18	17%
HLA Class II	6	6%
HLA Class I and II	15	14%
HNA	17	16%
HLA and HNA	6	6%
Negative	42	41%
Total Donors Tested	104	100%

This table does not include the 59 donors that were not tested for WBC antibodies

C. Hemolytic Transfusion Reactions

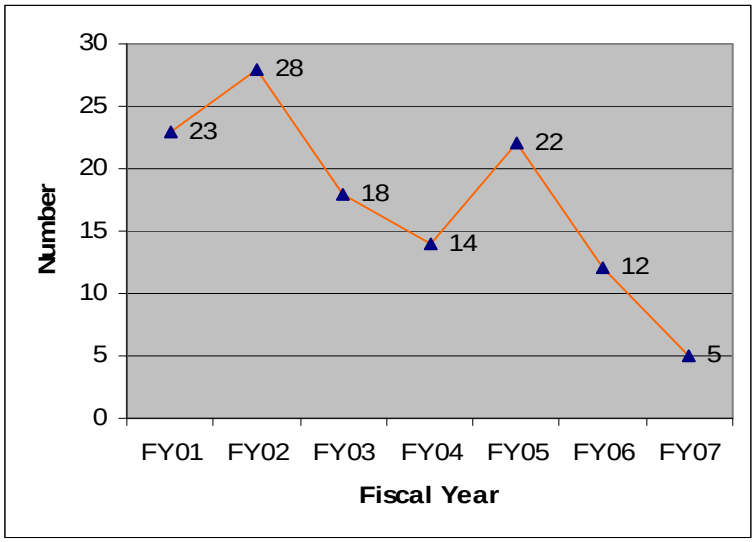
In FY2007, there was a continued decline in the number of reported fatal hemolytic transfusion reactions, with a total of five, as compared to 12 in FY2006, and 22 in FY2005. The recent decrease is due to a decline in reports of non-ABO hemolytic reactions, with reports of 16 fatalities in FY2005, 9 in FY2006 and 2 in FY2007 (Figure 1 and Table 3). We have seen an overall decrease in the number of reported fatal hemolytic transfusion reactions since FY2001 (Figure 3).

Table 3: Hemolytic Transfusion Reactions by Implicated Antibody, FY2005 through FY2007

Antibody	FY05		FY06		FY07		Total (FY05+06+07)	
	No.	%	No.	%	No.	%	No.	%
ABO	6	27%	3	25%	3	60%	12	31%
Multiple Antibodies*	6	27%	4	33%	1	20%	11	28%
Other**	3	14%	0	0%	0	0%	3	8%
Jk^b	3	14%	0	0%	0	0%	3	8%
Jk^a	1	5%	1	8%	1	20%	3	8%
K	1	5%	1	8%	0	0%	2	5%
Fy^a	0	0%	1	8%	0	0%	1	3%
Fy^b	0	0%	1	8%	0	0%	1	3%
E	1	5%	0	0%	0	0%	1	3%
I	1	5%	0	0%	0	0%	1	3%
Js^a	0	0%	1	8%	0	0%	1	3%
Totals	22	100%	12	100%	5	100%	39	100%

*FY2005 antibody combinations included E+c, Fy^a+K, Fy^a+Jk^b, E+I+A_1, possible C+E+K, Wr^a+warm autoantibody.
*FY2006 antibody combinations included E+c, S+K, Jk^b+cold agglutinin, unidentified auto- and alloantibodies.
*FY2007: anti-M+C
**Includes one report of non-immune hemolysis, one report of an unidentified antibody to a low incidence antigen, and one report of Cold Agglutinin Syndrome due to *Mycoplasma pneumonia* or Lymphoma.

Figure 3: Hemolytic Transfusion Reactions, FY2001 through FY2007



In FY2007, there were three reports of fatal hemolytic transfusion reactions due to ABO-incompatible blood transfusions:

- 1 case: recipient identification error at the time of transfusion
- 1 case: blood bank clerical error (incorrect sample used for testing)
- 1 case: initial recipient ABO/Rh typing results switched with another patient; ABO incompatible FFP issued prior to completion of required second typing

D. Microbial Infection

In FY2007, there were 6 reported fatalities attributed to microbial infection compared with 7 reported in FY2006 and 8 reported in FY2005. Three different bacteria were implicated in three fatalities, and three other fatalities resulted from Babesia transmission following Red Blood Cell transfusions from donors who subsequently tested positive for *Babesia microti*. The babesiosis cases accounted for 50% (3/6) of the microbial infections associated with transfusion fatalities in FY2007. Babesia accounted for 24% (5/21) of reported cases over the last three fiscal years, followed by Staphylococcus aureus, which accounted for 19% (4/21) (Table 4).

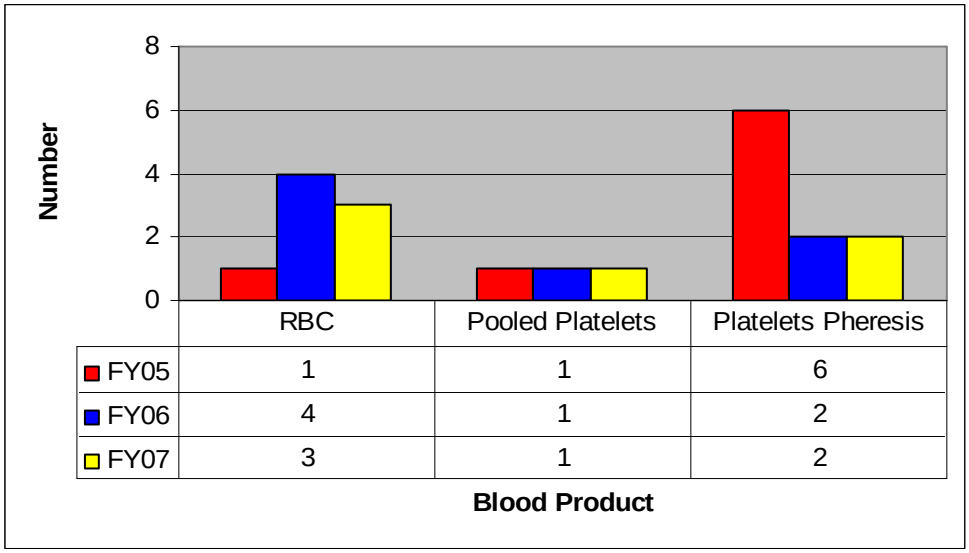
There was one strict anaerobe, *Eubacterium limosum,* implicated in a fatal bacterial infection during the 3-year reporting period; this fatality occurred in FY2005. The remaining bacteria are facultative anaerobes.

In FY2007, the decrease in reports of fatal microbial infections associated with apheresis platelets seen between FY2005 and FY2006 persisted (Figure 4). This finding is consistent with an overall decrease in the number of bacterial infections associated with apheresis platelets since FY2001 (Figure 5).

Table 4: Microbial Infection by Implicated Organism, FY2005 through FY2007

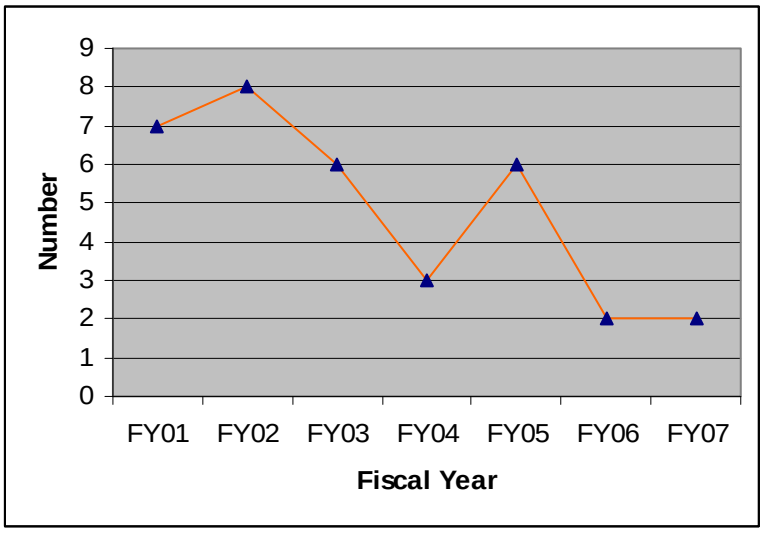
	FY05		FY06		FY07		Total (FY05+06+07)	
Organism	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Babesia microti	0	0%	2	29%	3	50%	5	24%
Staphylococcus aureus	3	37%	0	0%	1	17%	4	19%
Escherichia coli	0	0%	3	43%	0	0%	3	14%
Serratia marcescens	2	24%	0	0%	0	0%	2	10%
Staphylococcus lugdunensis	1	13%	0	0%	0	0%	1	5%
Staphylococcus epidermidis	1	13%	0	0%	0	0%	1	5%
Eubacterium limosum	1	13%	0	0%	0	0%	1	5%
Morganella morganii	0	0%	1	14%	0	0%	1	5%
Yersinia enterocolitica	0	0%	1	14%	0	0%	1	5%
Streptococcus dysgalactiae	0	0%	0	0%	1	17%	1	5%
Klebsiella oxytoca	0	0%	0	0%	1	17%	1	5%
Total	8	100%	7	100%	6	100%	21	100%

Figure 4: Microbial Infection by Implicated Blood Product, FY2005 through FY2007



Red Blood Cells microorganisms: *S. marcescens (1), E. coli (1), Y. enterocolitica (1), B. microti (5)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), Streptococcus dysgalactiae (1)*
Platelets Pheresis microorganisms: *S. aureus (3), S. marcescens (1), S. lugdunensis (1), S. epidermidis (1), E. limosum (1), E. coli (1), M. morganii (1), K. oxytoca (1)*

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2007



E. Transfusion Not Ruled Out as Cause of Fatality

In these reported fatalities, the reporting facilities were unable to identify a specific complication of transfusion as the cause of death. Often, these patients had multiple co-morbidities, and after review of the investigation documentation, our medical reviewers could neither confirm nor rule out the transfusion as the cause of the fatality (Table 5). We did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above.

Combining the transfusion related fatalities with those that our medical officers could not rule out, there was a decrease in total reported fatalities from 73 in FY2006 to 63 in FY2007.

F. Not Transfusion Related

After reviewing the initial fatality reports and the investigation documentation, we categorized a number of reported fatalities as "Not Transfusion Related." Our medical reviewers concluded that, while there was a temporal relationship between transfusion and subsequent death of the recipient, there was no evidence to support a causal relationship (Table 5). Thus, we did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above.

Table 5: Fatalities Not Related to Transfusion or Transfusion Not Ruled Out, FY2005 through FY2007

	FY05	FY06	FY07
Not Transfusion Related	21	8	13
Not Ruled Out	14	10	11
Totals	35	18	24

G. Post-Donation Fatalities

There was a small increase in the number of fatalities following Source Plasma donation, and two fatalities following donation of Apheresis Platelets (Table 6). In two cases (both Source Plasma donors), our medical reviewers determined that clear medical evidence supported a cause of death that was not donation related. For the remaining 13 of the 15 FY2007 fatalities following Source Plasma and Apheresis Platelet donations, our medical reviewers concluded that, while there was a temporal link between the donations and the fatalities, there was no evidence to support a causal relationship between the Source Plasma or Apheresis Platelet donations and subsequent death of the donors. This was also the case for the 12 fatalities following Source Plasma donation in FY2005 and FY2006.

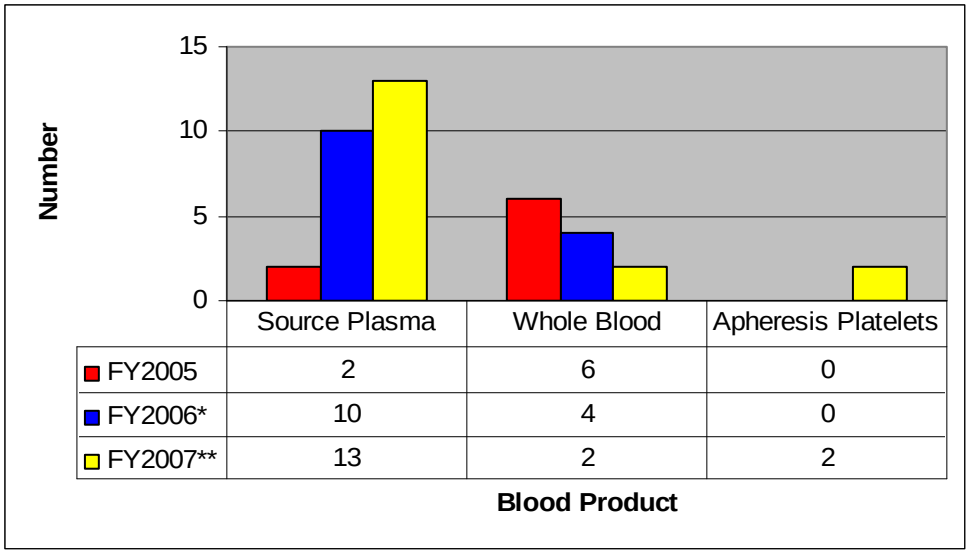
In FY2007, we received reports of two fatalities following Whole Blood donation, both autologous, collected by manual methods. In both cases, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor. For eight of the nine Whole Blood donations (includes two autologous donations) reported in FY2005 and FY2006, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor. In one FY2006 case, an autologous donation, our medical reviewers could neither confirm nor rule out the donation as contributing to the donor's death.

Table 6: Post-Donation Fatality Reports by Donated Product, FY2005 through FY2007

Donated Product	FY05	FY06	FY07
Source Plasma	2	10	13
Whole Blood	6	4*	2**
Apheresis Platelets	0	0	2
Total	8	14	17

*Includes 2 autologous donations
**Autologous donations

Figure 6: Post-Donation Fatality Reports, FY2005 through FY2007



*Includes 2 autologous Whole Blood donations
**Both Whole Blood donations in FY07 were autologous