

Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2008

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005, FY2006, and FY2007, 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 subsequent decreases to 63 in FY2007 and 54 in FY2008.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2008, to provide the combined data received over the last four fiscal years, and to compare the FY2008 reports to the fatality reports received in FY2007, 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

A team of CBER medical officers reviews the documentation submitted by the reporting facilities and obtained by the FDA investigators, to assess the relationship, if any, between the blood donation or transfusion and the reported fatality.

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 FY2008 (October 1, 2007, through September 30, 2008), we received a total of 82 fatality reports. Of these reports, 72 were transfusion recipient fatalities and 10 were post-donation fatalities.

Of the 72 transfusion recipient fatality reports, we concluded:

- a) 46 of the fatalities were transfusion-related,
- b) in 8 cases we were unable to rule out transfusion as the cause of the fatality,
- c) 18 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 from FY2005 through FY2008
- B. Transfusion Related Acute Lung Injury (TRALI)
- C. Hemolytic Transfusion Reactions (HTR)
- D. Microbial Infection
- E. Transfusion Not Ruled Out as Cause of Fatality
- F. Not Transfusion Related
- G. Post-Donation Fatalities

A. Overall Comparison of Transfusion-Related Fatalities Reported from FY2005 through FY2008

In combined FY2005, FY2006, FY2007, and FY2008, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (51%), followed by hemolytic transfusion reactions (25%) due to non-ABO (15%) and ABO (10%) incompatibilities. Complications of microbial infection, Transfusion Associated Circulatory Overload (TACO),

and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1 and Figure 1).

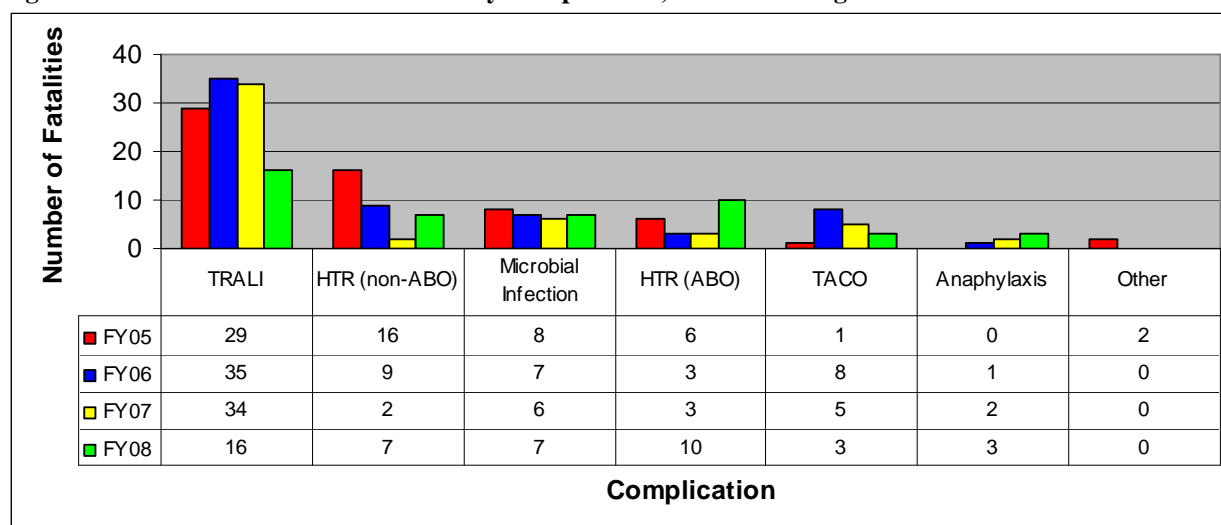
Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2008

Complication	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56%	34*	65%	16*	35%	114	51%
HTR (non-ABO)	16	26%	9	14%	2	4%	7	15%	34	15%
Microbial Infection	8	13%	7	11%	6	12%	7	15%	28	13%
HTR (ABO)	6	10%	3	5%	3	6%	10	22%	22	10%
TACO	1	2%	8	13%	5	10%	3	7%	17	8%
Anaphylaxis	0	0%	1	2%	2	4%	3	7%	6	3%
Other	2**	3%	0	0%	0	0%	0	0	2	1%
Totals	62	100%	63	100%	52	100%	46	100%	223	100%

*In FY2007, our review committee began using the Canadian Consensus Conference criteria^{3,4} for evaluating TRALI cases – these numbers 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 FY2008



B. Transfusion Related Acute Lung Injury (TRALI)

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.

While TRALI represented 51% of confirmed transfusion related fatalities reported to CBER over the last four fiscal years, in FY2008 fatalities due to TRALI decreased to 35% of confirmed transfusion related fatalities, compared to 65% in FY2007, 56% in FY2006, and 47% in FY2005. 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 TRALI cases) in FY2007 to 4 (25% of TRALI cases) in FY2008 (Figure 2). TRALI fatalities associated with receipt of Apheresis Platelets increased from 1 (3% of TRALI cases) in FY2007 to 5 (31% of TRALI cases) in FY2008. The percentage of FY2008 TRALI fatalities associated with receipt of Red Blood Cells (31% of TRALI cases) was comparable to that reported in FY2007 (35% of TRALI cases).

In Calendar Year 2006, 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 2005-2008, FFP and other plasma accounted for 48% (55/114) of reported TRALI fatalities, apheresis platelets accounted for 10% (12/114), and RBC's accounted for 24% (27/114).

In FY2008, the 16 TRALI cases were temporally associated with products from 20 donors. Of these donors, 17 (85%) were tested for white blood cell (WBC) antibodies (Table 2). Antibody tests were negative in 18% of those tested. Of those tested, Human Leukocyte Antibodies (HLA) were present in 58% of donors. Human Neutrophil Antibodies (HNA) were present in 12% of donors, but these reactions were weak and non-specific. Some of the donors had multiple antibodies. Reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens in 4 of the 16 cases, implicating 4 female donors. In two cases, reporters were able to identify **recipient** antibodies that matched or were a probable match to **donor** cognate antigens. In another case, both donor and recipient antibodies were identified which matched cognate antigens in the corresponding recipient and donor.

Of the 20 implicated donors, reports identified 13 females (65%) and 7 males (35%).

Although the transfusion community has taken voluntary measures to reduce the risk of TRALI, this complication of transfusion continues to be one of the leading causes of transfusion-related fatalities reported to the FDA. 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 (#06-07), 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

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

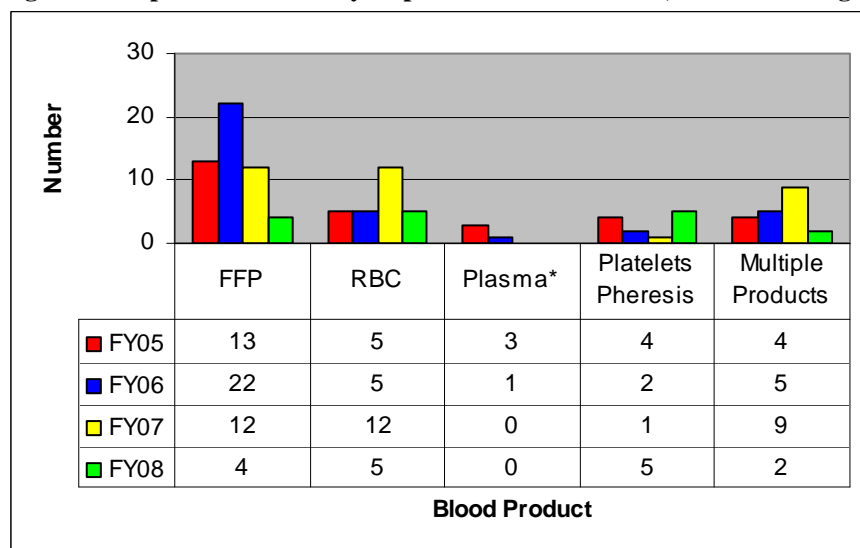
⁶ Curtis, BR, Mcfarland JG. Mechanisms of transfusion-related acute lung injury (TRALI): anti-leukocyte antibodies. Crit Care Med 2006;34(5 Suppl):S118-S123.

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.

have white blood cell antibodies or who are at increased risk for developing these antibodies.⁹ Some of the more current literature further describes efforts to reduce the use of plasma for transfusion prepared from female donors.^{10,11}

Figure 2: Reports of TRALI by Implicated Blood Product, FY2005 through FY2008



*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 and FY2008

Donor Leukocyte Antibodies	FY07 No.	FY07%	FY08 No.	FY08%
HLA Class I	18	17%	3	18%
HLA Class II	6	6%	2	12%
HLA Class I and II	15	14%	6	35%
HNA	17	16%	2	12%
HLA and HNA	6	6%	2	12%
Negative	42	41%	2	12%
Total Donors Tested	104	100%	17	100%

This table does not include the 59 donors that were not tested for WBC antibodies in FY07 and the 3 donors that were not tested in FY08.

⁹ Transfusion-related acute lung injury. AABB Association Bulletin (#06-07). Bethesda: American Association of Blood Banks;2006 Nov 3.

¹⁰ Wright S, Athey S, Leaver A, et al. The effect of male-donor-only fresh frozen plasma on the incidence of acute lung injury following ruptured abdominal aortic aneurysm repair. Crit Care 2007;11:374.

¹¹ Chapman CE, Stainsby D, Jones H, et al. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion ;doi:10.1111/j.1537-2995.2008.01948.x

C. Hemolytic Transfusion Reactions

In FY2008, hemolytic transfusion reactions were the leading cause of transfusion related fatalities reported to CBER, representing 37% of confirmed transfusion related fatalities. The number of reported fatal hemolytic transfusion reactions increased to 17 in FY2008, as compared to 5 in FY2007, and 12 in FY2006. The recent increase is due to an increase in reports of ABO hemolytic reactions, with reports of 10 in FY2008, as compared to 3 in both FY2007 and FY2006. Reports of non-ABO hemolytic transfusion reactions also increased from 2 in FY2007 to 7 in FY2008 (Figure 1 and Table 3). Despite the FY2008 increase in the number of reported fatalities due to hemolytic transfusion reactions, we have seen an overall decrease in this number since FY2001 (Figure 3).

Table 3: Hemolytic Transfusion Reactions by Implicated Antibody, FY2005 through FY2008

Antibody	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%
ABO	6	27%	3	25%	3	60%	10	59%	22	39%
Multiple Antibodies*	6	27%	4	33%	1	20%	1	6%	12	21%
Jk ^b	3	14%	0	0%	0	0%	2	12%	5	9%
Other**	3	14%	0	0%	0	0%	0	0%	3	5%
Kell	1	5%	1	8%	0	0%	2	12%	4	7%
Jk ^a	1	5%	1	8%	1	20%	0	0%	3	5%
Fy ^a	0	0%	1	8%	0	0%	2	12%	3	5%
Fy ^b	0	0%	1	8%	0	0%	0	0%	1	2%
E	1	5%	0	0%	0	0%	0	0%	1	2%
I	1	5%	0	0%	0	0%	0	0%	1	2%
Js ^a	0	0%	1	8%	0	0%	0	0%	1	2%
Totals	22	100%	12	100%	5	100%	17	100%	56	100%

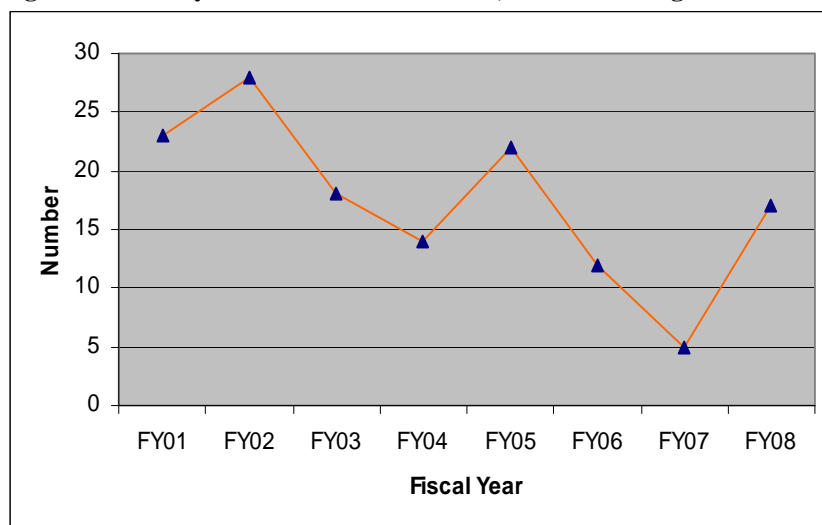
*FY2005 antibody combinations included E+c, Fy^a+K, Fy^a+Jk^b, E+I+A₁, possible C+E+K, Wr^a+warm autoantibody.

*FY2006 antibody combinations included E+c, S+K, Jk^b+cold agglutinin, unidentified auto- and alloantibodies.

*FY2007: anti-M+C

*FY2008: anti-C+K+Fy^b+S+N+V+Js^a+Go^a+warm autoantibody.

**FY2005: 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 FY2008

In FY2008, there were ten reports of fatal hemolytic transfusion reactions due to ABO-incompatible blood transfusions:

- 5 cases: recipient identification error at the time of transfusion
- 1 case: blood bank clerical error (incorrect sample used for testing)
- 3 cases: sample collected from incorrect patient¹²
- 1 case: transfusion of high-titer anti-B in group O Apheresis Platelets following group B bone marrow transplant

¹² MacIvor D, Triulzi DJ. Enhanced detection of blood bank sample collection errors with a centralized patient database. *Transfusion* 2009;49:40-43.

D. Microbial Infection

In FY2008, there were 7 reported fatalities attributed to microbial infection compared with reports of 6 in FY2007, 7 in FY2006, and 8 in FY2005. Two different bacteria were implicated in two fatalities, and five other fatalities resulted from *Babesia* transmission following Red Blood Cell transfusions from donors who subsequently tested positive for *Babesia*. The babesiosis cases accounted for 71% (5/7) of the microbial infections associated with transfusion fatalities in FY2008, as compared to 50% (3/6) in FY2007, 29% (2/7) in FY2006, and none reported in FY2005. *Babesia* accounted for 36% (10/28) of reported cases over the last four fiscal years, followed by *Staphylococcus aureus*, which accounted for 18% (5/28) (Table 4).

After seven years with no reported deaths due to transfusion-transmitted Babesiosis, CBER received reports of 10 transfusion-transmitted Babesiosis deaths during the four-year reporting period. For additional information, see the CBER article published in January 2009 describing fatal Babesiosis cases received by CBER from 1997-2007.¹³

There was one strict anaerobe, *Eubacterium limosum*, implicated in a fatal bacterial infection during the 4-year reporting period; this fatality occurred in FY2005. The remaining bacteria are facultative anaerobes.

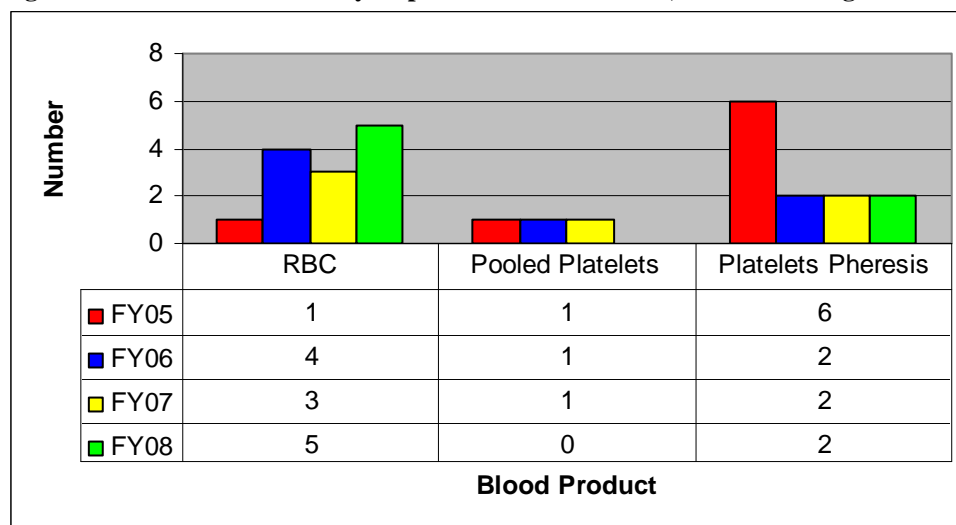
Since FY2006, the number of reports of fatal microbial infections associated with apheresis platelets has remained unchanged (Figure 4). This finding is consistent with an overall decrease in the number of bacterial infections associated with apheresis platelets since FY2001 (Figure 5).

Table 4: Microbial Infection by Implicated Organism, FY2005 through FY2008

Organism	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Babesia</i> *	0	0%	2	29%	3	50%	5*	63%	10	36%
<i>Staphylococcus aureus</i>	3	37%	0	0%	1	17%	1	13%	5	18%
<i>Escherichia coli</i>	0	0%	3	43%	0	0%	0	0%	3	11%
<i>Serratia marcescens</i>	2	24%	0	0%	0	0%	0	0%	2	7%
<i>Staphylococcus epidermidis</i>	1	13%	0	0%	0	0%	1	13%	2	7%
<i>Staphylococcus lugdunensis</i>	1	13%	0	0%	0	0%	0	0%	1	4%
<i>Eubacterium limosum</i>	1	13%	0	0%	0	0%	0	0%	1	4%
<i>Morganella morganii</i>	0	0%	1	14%	0	0%	0	0%	1	4%
<i>Yersinia enterocolitica</i>	0	0%	1	14%	0	0%	0	0%	1	4%
<i>Group C Streptococcus</i>	0	0%	0	0%	1	17%	0	0%	1	4%
<i>Klebsiella oxytoca</i>	0	0%	0	0%	1	17%	0	0%	1	4%
Total	8	100%	7	100%	6	100%	7	100%	28	100%

*Four *Babesia microti* and one probable *Babesia MO-1* species

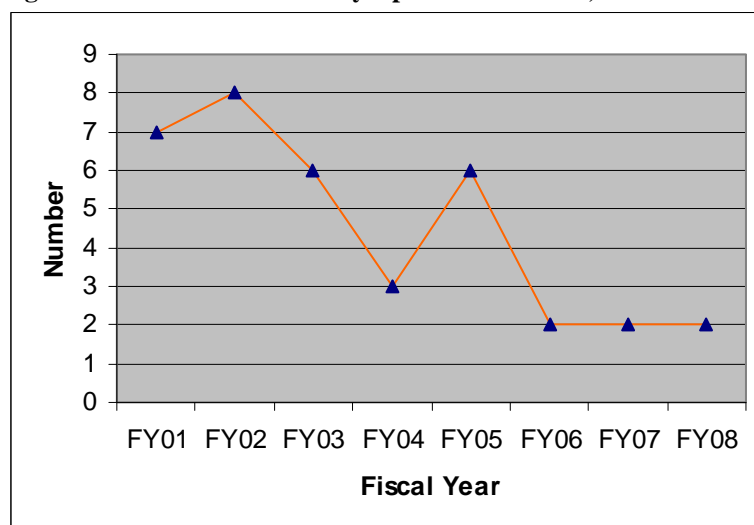
¹³ Gubernot DM, Lucey CT, Lee KC et al. *Babesia* Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997-2007. Clin Infect Dis 2009;48:000-000, electronically published, 26 November 2008.

Figure 4: Microbial Infection by Implicated Blood Product, FY2005 through FY2008

Red Blood Cells microorganisms: *S. marcescens* (1), *E. coli* (1), *Y. enterocolitica* (1), *B. microti* (9), *B. MOI*(1)

Pooled Platelets microorganisms: *S. aureus* (1), *E. coli* (1), *Streptococcus dysgalactiae* (1)

Platelets Pheresis microorganisms: *S. aureus* (4), *S. marcescens* (1), *S. lugdunensis* (1), *S. epidermidis* (2), *E. limosum* (1), *E. coli* (1), *M. morgani* (1), *K. oxytoca* (1)

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2008

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 63 in FY2007 to 55 in FY2008.

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 FY2008

	FY05	FY06	FY07	FY08
Not Transfusion Related	21	8	13	18
Not Ruled Out	14	10	11	8
Totals	35	18	24	26

G. Post-Donation Fatalities

There was a small decrease in FY2008 in the number of reported fatalities following Source Plasma donation, and one fatality following donation of Apheresis Red Blood Cells (Table 6). In all of these cases, 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 donations and subsequent death of the donors.

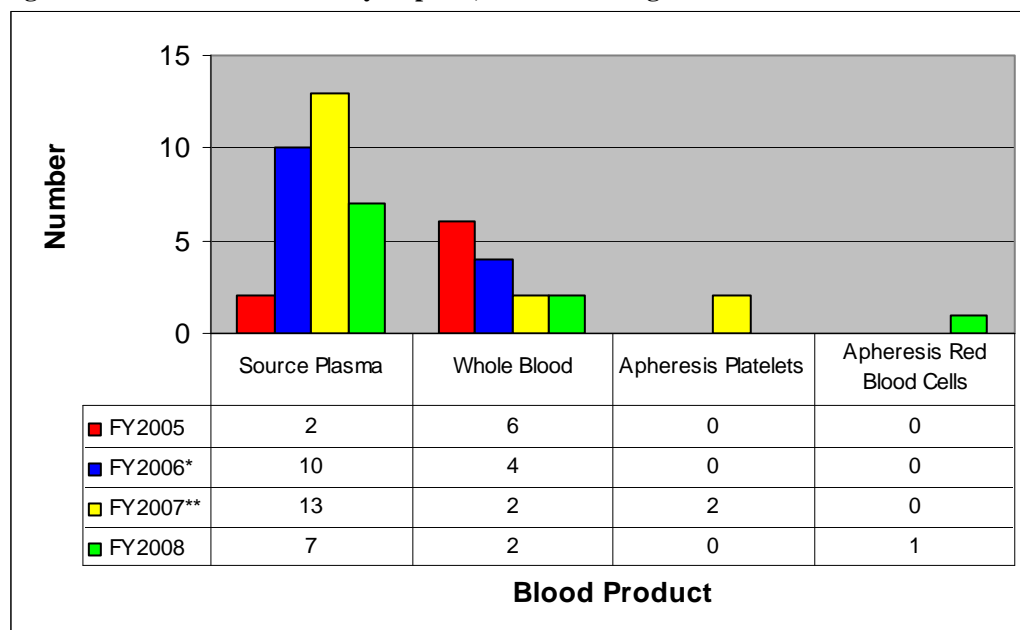
In FY2008, we received reports of two fatalities following Whole Blood donation collected by manual methods. In both cases, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

Table 6: Post-Donation Fatality Reports by Donated Product, FY2005 through FY2008

Donated Product	FY05	FY06	FY07	FY08
Source Plasma	2	10	13	7
Whole Blood	6	4*	2**	2
Apheresis Platelets	0	0	2	0
Apheresis Red Blood Cells	0	0	0	1
Total	8	14	17	10

*Includes 2 autologous donations

**Autologous donations

Figure 6: Post-Donation Fatality Reports, FY2005 through FY2008

*Includes 2 autologous Whole Blood donations

**Both Whole Blood donations in FY07 were autologous