Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2016

I. Background

FDA's Center for Biologics Evaluation and Research (CBER) is issuing this summary of fatality reports received by the FDA to make public the data received in Fiscal Year (FY) 2016 (October 1, 2015, through September 30, 2016), to provide the combined data received over the last five fiscal years, and to compare the FY2016 summary to the fatality reports received in the previous four fiscal years.[1] As mentioned in the previous annual summaries of fatalities reported to the Food and Drug Administration (FDA), the blood supply is safer today than at any time in history. Due to advances in donor screening, improved testing, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion remain low. Overall, the number of transfusion-associated fatalities reported to the FDA remains small, but relatively constant, in comparison to the total number of transfusions. Calendar year 2015 in which transfusions of red blood cells and whole blood decreased 14% since 2013, comprised 11.3 million whole blood and red blood cells, 2.1 million apheresis platelets, and 3.6 million plasma transfusions. During the proximate period of FY2012, there were 65 reported transfusion-associated fatalities, with subsequent reports of 59 in 2013, 56 in 2014, 41in 2015, and 60 in 2016.[5] Throughout this report we note changes over time in the number of reported fatalities, 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.

Although blood donations are generally safe, we also include information on the infrequent reports of donation-associated fatalities submitted to the Agency. The number of donation-associated fatalities reported to the FDA also remains small in comparison to the total number of donations. In 2015, allogeneic blood donations provided 12.0 million whole blood and apheresis red blood cell components, 2.4 million platelet components, and 3.7 million plasma components for distribution. Also, in 2016, there were 38.3 million source plasma donations made in the U.S.[3] Over the combined five-year reporting period (FY2012 – FY2016), there were 43 reported donation-associated fatalities (associated with a variety of donated products)[2], with only one conclusively linked to the donation occurring in 2014 .[4]

Refer to Title 21, Code of Federal Regulations 606.170(b) 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/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm. For further information, see our *Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion*, September 2003.[6]

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[1] The FY2005 - FY2010 data are not discussed in this report, but are available at: http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm.

[2] Katherine D. Ellingson, et al. continued decline in blood collection and transfusion in the United States-2015. Transfusion 2017;57;1588-1598.

[3] Plasma Protein Therapeutics Association at http://pptaglobal.org/plasma/plasma-collection

[4] http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf

[5] The FY2005 - FY2010 data are not discussed in this report, but are available at: http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm.

[6] Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074947.htm.

If you have questions concerning this summary, you may contact us using the following options:

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II. Changes in Our Evaluation Approach:

Starting with the annual report of FY2015, and in support of the FDA's international harmonization efforts and to provide consistency between US government agencies (http://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm298576.htm), we have modified our approach to the review and classification of fatality reports. The annual reports for FY2015 and FY2016 align with the case definitions and imputability criteria used by the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network,[7] (http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf), the International Society of Blood Transfusion (ISBT) in collaboration with the International Haemovigilance Network (IHN) and the AABB Donor Haemovigilance Working Group[8] (https://www.aabb.org/research/hemovigilance/Documents/Donor-Standard-Definitions.pdf), the British Serious Hazards of Transfusion (SHOT)[9], and the Hemovigilance activity report of the French National Agency for Medicines and Health Products Safety (ANSM)[10] .

In fiscal years prior to FY2015, we classified fatalities in one of three imputability groups that define the strength of the evidence (causality) between the transfusion/donation and the fatality: *transfusion/donation-related, not ruled out, or not related*. Beginning in FY2015, fatalities that were previously classified either as *transfusion/donation-related*, or *not ruled out* are assigned a level of imputability, specifically *definite/certain, probable/likely, possible, doubtful/unlikely/improbable,* and *not determined/assessable/evaluable* (Table 1). Fatalities previously defined as *not transfusion/donation related* continue to be classified as *ruled out/excluded*.

To achieve a more comprehensive review, we added three new categories (complications) for FY2016: No Transfusion Reaction, Possible TRALI, and Transfusion Reaction, Type Not Determined.

[7] Center for Disease Control and Prevention National Healthcare Safety Network, Biovigilance Component, Hemovigilance.
[8] International Society of Blood Transfusion Working Party on Haemovigilance in collaboration with the International Haemovigilance Network and the AABB Donor Haemovigilance Working Group, Standard for Surveillance of Complications Related to Blood Donation, December 2014.
[9] Annual Serious Hazards of Transfusion Report, 2014.
[10] French National Agency for Medicine and Health Product Safety (ANSM), 2013 Hemovigilance Activity Report.

Our review process continues to include a team of CBER medical officers who conduct a detailed review of the documentation submitted by the reporting facilities and obtained by FDA investigators to assess the relationship, if any, between the blood donation or transfusion, and the fatality. Our new classification approach allows the review team to conduct more effective evaluations, and improves consistency in case classifications. These changes add clarity, and allow comparability with other domestic and international hemovigilance systems.

Table 1: Imputability Definitions[7,8], FY2015 & FY2016

Imputability	Definition
Definite/Certain	Conclusive evidence beyond reasonable doubt for attributing the fatality to the transfusion/donation
Probable/Likely	Evidence clearly in favor of the transfusion/donation as the cause of the fatality
Possible	Evidence is indeterminate for attributing the fatality to the transfusion/donation or alternative cause
Doubtful/Unlikely/Improbable	Evidence in favor of attributing the fatality to an alternative cause, but transfusion/donation cannot be excluded.
Ruled Out/Excluded	Conclusive evidence beyond reasonable doubt for attributing the fatality to cause other than transfusion/donation
Not Determined/Assessable/Evaluable	Insufficient information/relationship unknown

III. FY2016 Results

During FY2016, we received a total of 81 fatality reports. Of these reports, 67 were potentially associated with transfusion recipient fatalities, and 14 were potentially associated with donation.

Of the 67 potentially transfusion-associated fatality reports, we concluded:

a) Forty-three (64%) of the fatalities were classified as either *definite/certain, probably/likely,* or *possible.*
b) Seventeen (25%) of the fatalities were classified as either *doubtful/unlikely/improbable,* or *not determined/assessable/evaluable*.
c) Seven (11%) of the fatalities were classified as *ruled out/excluded.*

Of the 14 potentially donation-associated fatality reports, we concluded:

a) Three (21%) of the fatalities were classified as *probable/likely, or possible*.
b) Eight (57%) of the fatalities were classified as either *doubtful/unlikely/improbable*, or *not determined/assessable/evaluable*.
c) Three (22%) of the fatalities were classified as *ruled out/excluded.*

We summarize the results of our review in Table 2.

Table 2: Fatality Complication Breakdown by Imputability, FY2016

CATEGORY	Definite/ Certain	Probable/ Likely	Possible	Doubtful/ Unlikely/ Improbable	Ruled Out/ Excluded	Not Determined/ Assessable/ Evaluable	TOTAL
Transfusion							
Allergy/Anaphylaxis	4	1	-	-	-	-	**5**
Contamination (Bacterial)	2	-	1	1	-	-	**4**
Contamination (Viral)	-	-	-	-	-	1	**1**
Contamination ((Parasitic)	-	2	-	-	-	-	**2**
HTR (ABO)	2	-	2	1	-	-	**5**
HTR (non-ABO)	-	-	1	2	-	-	**3**
Hypotensive Reaction[18]	-	-	1	-	-	-	**1**
Other*	-	-	-	-	1	-	**1**
No Transfusion	-	-	-	-	5	-	**5**
TACO	3	11	5	1	-	1	**21**
TRALI	2	-	1	2	-	-	**5**
Possible TRALI	-	-	5	1	-	-	**6**
Transfusion Reaction, Type Not Determined	-	-	-	7	1	-	**8**
Donation							
Donor Fatality	-	1	2	8	3	-	**14**

TRALI = Transfusion Related Acute Lung Injury; TACO = Transfusion Associated Circulatory Overload; HTR = Hemolytic Transfusion Reactions

*Febrile non-hemolytic reaction

For the purpose of comparison with previous fiscal years, the FY2015 and FY2016 imputabilities of *definite/certain*, *probable/likely*, and *possible* transfusion fatalities in the tables and figures of sections A through D of this document would most accurately compare with fatalities classified in previous years as *transfusion-related*. Sections E and F present the transfusion fatalities classified as *doubtful/unlikely/improbable*, or *not determined/assessable/evaluable*, which would most accurately compare with fatalities classified in previous years as *transfusion not ruled out.* Section G presents the transfusion fatality reports classified as *ruled out/excluded*, which would compare with fatalities classified in previous years as *not transfusion related*. Section H presents the reported fatalities associated with donation.

A. Overall Comparison of Transfusion-Associated Fatalities Reported from FY2012 through FY2016

In combined FYs 2012 through 2016, the combined TRALI[11] and Possible TRALI cases caused the highest number of reported fatalities (34%), followed by TACO[12,13] (30%), HTR due to non-ABO incompatibilities (10%), and microbial contamination (10%). HTRs due to ABO incompatibilities (8%), anaphylaxis reactions (6%), and hypotensive reactions (2%) each accounted for a relatively smaller number of reported fatalities (Table 3).

[11] http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/ucm110327.htm

[12] https://reds-iii.rti.org/REDSProgram.aspx.

[13] Kleinman S, Busch MP, Murphy EL et al. The National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study (REDS-III): a research program striving to improve blood donor and transfusion recipient outcomes. Transfusion. 2014 Mar;54(3 Pt 2):942-55.

While the number of fatalities attributed to TACO has varied, TACO was the leading cause of reported transfusion-associated deaths for FY2016, and the second leading cause of transfusion-associated fatalities over the 5-year reporting period.

The number of reported transfusion-associated deaths attributable to anaphylaxis[14,15,16,17,18,19] has remained small over the last five fiscal years. For FY2012 through FY2016, 11 anaphylactic reactions were investigated for IgA deficiency; however, four of 11 cases were found to have normal IgA levels, one case had a slightly low IgA level, and IgA levels were not tested in the remaining six cases. Anaphylactic reactions may also be associated with haptoglobin-deficient patients with serum haptoglobin antibodies.[20] However, of the five anaphylaxis cases investigated in FY2016, one haptoglobin level was reported as slightly elevated, and no haptoglobin was measured in the remaining four cases.

The number of reported transfusion-associated deaths attributable to hypotensive reactions[21] has also remained small over the last five fiscal years, with one case in FY2014, FY2015, and FY2016. Since hypotension may be an element of the clinical presentation for other types of transfusion reactions, recognizing it as the primary cause can be challenging. In each of the reported cases, there was no supportive evidence to conclude that hypotension was secondary to another condition.

Table 3: Transfusion-Associated Fatalities by Complication, FY2012 – FY2016

Complication	FY12 No.	FY12 %	FY13 No.	FY13 %	FY14 No.	FY14 %	FY15 No.	FY15 %	FY16 No.	FY16 %	Total No.	Total %
Anaphylaxis	2	5%	-	0%	2	7%	2	5%	5	12%	**11**	**6%**
Contamination	3	8%	5	13%	1	3%	5	14%	5	12%	**19**	**10%**
HTR (ABO)	3	8%	1	3%	4	13%	2	5%	4	9%	**14**	**8%**
HTR (non-ABO)	5	13%	5	13%	4	13%	4	11%	1	2%	**19**	**10%**
Hypotensive Reaction	-	0%	-	0%	1	3%	1	3%	1	2%	**3**	**2%**
TACO	8	21%	13	34%	5	17%	11	30%	19	44%	**56**	**30%**
TRALI*	17	45%	14	37%	13	43%	12	32%	8	19%	**64**	**34%**

Note: FY2015-FY2016 only includes cases with an imputability of *Definite/Certain, Probable/Likely,* or *Possible.*

FY2012-FY2014 only include cases classified as transfusion-related.

*FY2012-FY2016 numbers combine both *TRALI* and *Possible TRALI* cases[22,23]

[14] Lindsted G, Larsen R, Kriegaard M, et al. Transfusion-Associated Anaphylaxis during anaesthesia and surgery – a retrospective study. Vox Sanguinis 2014;107(2):158-65.

[15] Hirayama F. Current Understanding of allergic transfusion reactions: incidence, pathogenesis, laboratory tests, prevention and treatment. British Journal of Haematology 2013;160:434-444.

[16] Savage W, Tobian A, Savage J, et al. Scratching the surface of allergic transfusion reactions. Transfusion 2013;53:1361- 1371.

[17] Sandler SG1, Eder AF, Goldman M, Winters JL. The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based. Transfusion. 2015 Jan;55(1):199-204.

[18] Savage WJ, Tobian AA, Savage J, et al. Transfusion and component characteristics are not associated with allergic transfusion reactions to apheresis platelets. Transfusion 2015;55:296-300.

[19] Sandler SG1, Eder AF, Goldman M, Winters JL. The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based. Transfusion. 2015 Jan;55(1):199-204.

[20] Shimada E, Tadokoro K, Watanabe Y, et al. Anaphylactic transfusion reactions in haptoglobin-deficient patients with IgE and IgG haptoglobin antibodies. Transfusion 2002;42:766-773.

[21] http://www.captodayonline.com/tuning-in-to-hypotensive-transfusion-reactions/

[22] 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.

[23] 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.

B. Transfusion Related Acute Lung Injury (TRALI)

In FY2016, two of the reported TRALI cases were classified as TRALI with an imputability of *definite/certain*, and one case was classified as TRALI with an imputability of *possible*. Beginning in FY2016, we added a separate category (complication) for Possible TRALI, and five of these cases were classified with an imputability of *possible*. For FY16, there was only one case where the reporter who obtained patient testing was able to match donor antibodies with recipient cognate antigens (HLA Class II). In the remaining cases, either no HLA testing was performed, or only donor testing was performed without recipient antigen testing. The limited data provided to FDA do not elucidate the role of particular donor antibodies or donor gender in the etiology of the TRALI reactions.

TRALI represented 34% of transfusion-associated fatalities reported to CBER over the last five fiscal years, and 19% in FY2016 (Table 3). Figure 2 shows a steady rise in TRALI cases between FY2002 and FY2007, and an abrupt decline to a relatively consistent plateau over the last seven fiscal years. Red blood cells continue to be the most frequently implicated product since 2012.

Although TRALI continues to be one of the leading causes of transfusion-associated fatalities reported to the FDA, the voluntary measures taken by the transfusion community to reduce the risk of TRALI have coincided with a reduction in the number of TRALI deaths. Current literature describes the results of continued international efforts to reduce the use of high-volume plasma products for transfusion prepared from female donors, and other strategies to reduce the incidence of TRALI.[24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37]

[24] Muller MCA, Juffermans NP. Transfusion-related acute lung injury: a preventable syndrome? Expert Rev. Hematol. 2012;5(1):97-106.

[25] Wiersum-Osselton JC, Middleburg RA, Beckers EAM, et al. Male-only fresh frozen plasma for transfusion-related acute lung injury prevention: before-and-after comparative cohort study. Transfusion 2011;51:1278-1283.

[26] Schmidt AE, Adamski J. Pathology Consultation on Transfusion-Related Acute Lung Injury. Am J Clin Pathol 2012;138:498-503

[27] Saidenberg E, Petraszko T, et al. Transfusion-Related Acute Lung Injury (TRALI): A Canadian Blood Services Research and Development Symposium. Transfusion Medicine Reviews 2010;24:305-324.

[28] Arinsburg SA, Skerrett DL, Karp JK, et al. Conversion to low transfusion-related acute lung injury (TRALI)-risk plasma significantly reduces TRALI. Transfusion 2012;52:946-952.

[29] Reesink HW, Lee J, Keller A, et al. Measures to prevent transfusion-related acute lung injury (TRALI). Vox Sanguinis 2012;103:231-259.

[30] Toy P, Ognjen G, Bacchetti P, et al. Transfusion-related lung injury: incidence and risk factors. Blood 2012;119:1757-1767.

[31] Eder A, Herron Jr R, Strupp A, et al. Effective reduction of transfusion-related lung injury risk with male-predominant plasma strategy in the American Red Cross (2006-2008). Transfusion 2010;50:1732-1742.

[32] Clifford L, Singh A, Wilson G, et al. Electronic health record surveillance algorithms facilitate the detection of transfusion-related pulmonary complications. Transfusion 2013;53:1205-1216.

[33] Association Bulletin #14-02 – TRALI Risk Mitigation for Plasma and Whole Blood for Allogeneic Transfusion. http://www.aabb.org/resources/publications/bulletins/Pages/abwhatsnew.aspx.

[34] Menis M, Anderson SA, Forshee FA, et al. Transfusion-related acute lung injury and potential risk factors among the inpatient US elderly as recorded in Medicare claims data, during 2007 through 2011. Transfusion 2014;54:2182-2193.

[35] Silliman CC, Kelher MR, Khan SY, et al. Experimental prestorage filtration removes antibodies and decreases lipids in RBC supernatants mitigating TRALI in vivo. Blood 2014;123:3488-3495.

[36] Popovsky MA. Transfusion-related acute lung injury: three decades of progress but miles to go before we sleep. Transfusion 2015;55:930-934.

[37] Peters AL, Van Stein D, Vlaar AP. Antibody-mediated transfusion-related acute lung injury; from discovery to prevention. British Journal of Haematology 2015. DOI 10.1111/bjh.13459.

Figure 1: TRALI Cases, FY2002 - FY2016

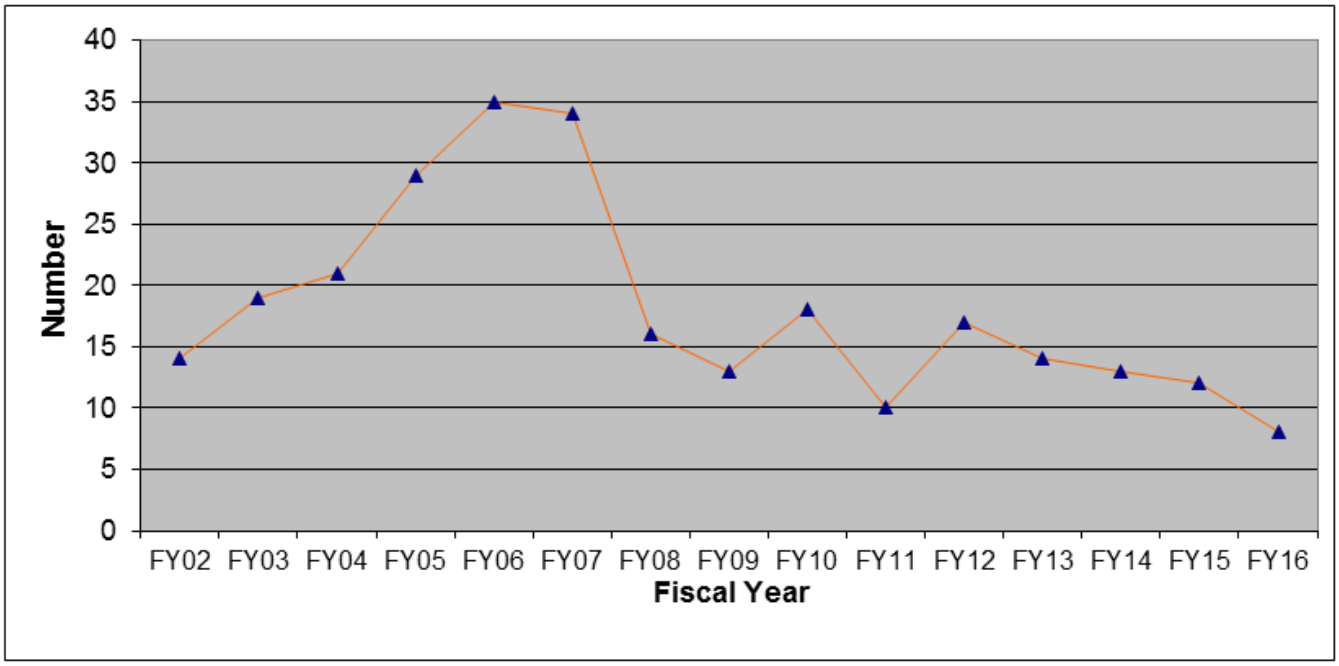
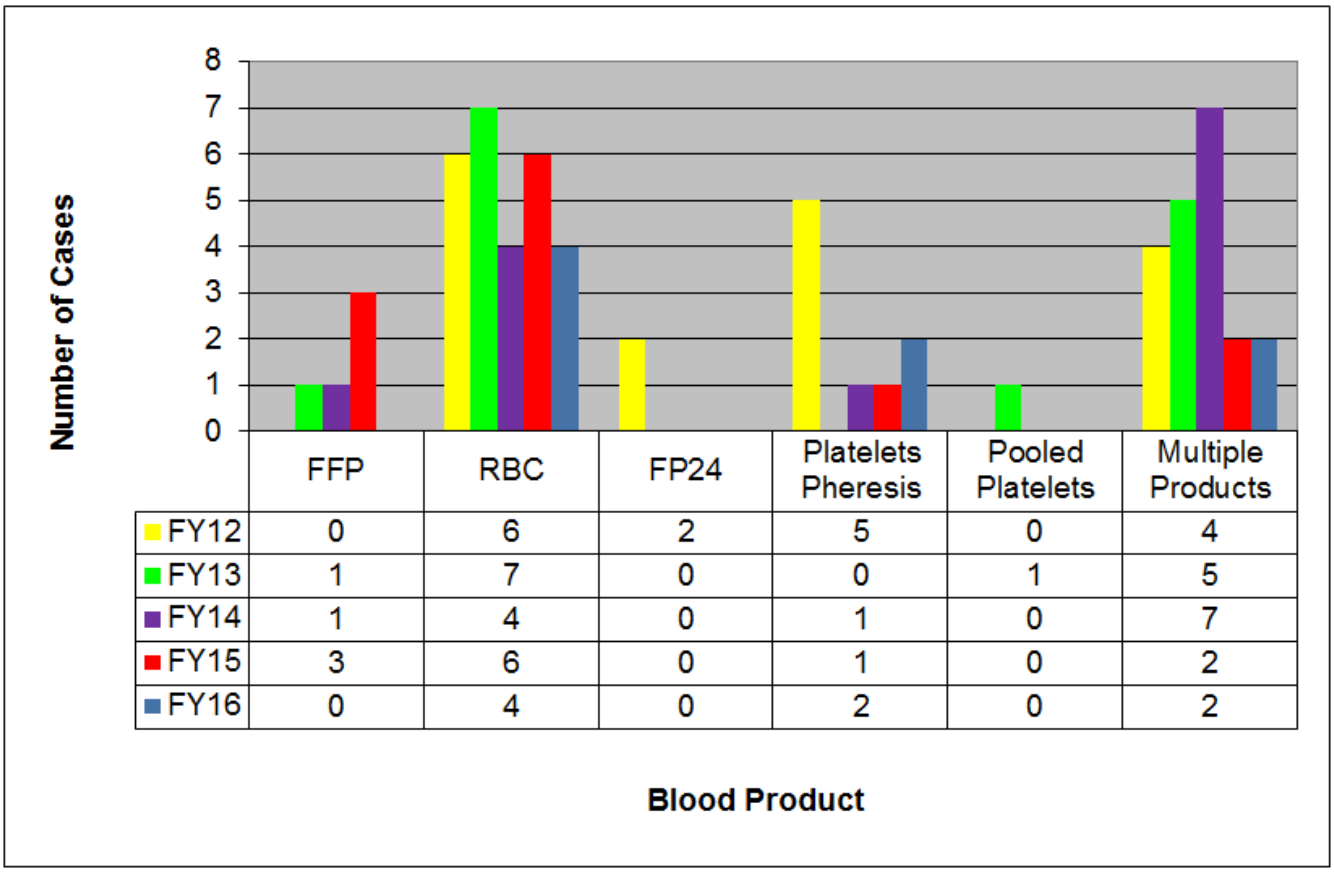


Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2012 – FY2016



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY12	0	6	2	5	0	4
FY13	1	7	0	0	1	5
FY14	1	4	0	1	0	7
FY15	3	6	0	1	0	2
FY16	0	4	0	2	0	2

FFP – Fresh Frozen Plasma
RBC – Red Blood Cells
FP24 – Plasma Frozen within 24 hours

C. Hemolytic Transfusion Reactions (HTR)

In FY2016, there were four (two with an imputability of *definite/certain* and two with an imputability of *possible*) reported ABO hemolytic transfusion fatalities (9% of confirmed transfusion-associated fatalities), and one non-ABO hemolytic transfusion fatality with an imputability of *possible* (2% of confirmed transfusion-associated fatalities) (Tables 3 and 4).

The four reports of fatal hemolytic transfusion reactions which were found to be either definitely, or possibly related to ABO-incompatible transfusions include a sample identification error at the time of specimen collection, an incorrect recipient identification used for product request, and two errors in patient testing.

1. HTR (ABO) – *Definite/Certain*
   Multiple group B red blood cell units were transfused to a patient who initially typed as B Pos. When a subsequent sample was collected, it was determined the patient's correct type was O Pos. There was a failure to properly identify the patient prior to collection, resulting in a case of Wrong Blood in Tube (WBIT).

2. HTR (ABO) – *Definite/Certain*
   A group O Pos recipient was transfused with two units of group B Pos red blood cell units. A label from a previous patient (B Pos) in the operating room was left behind and used to request blood for the group O recipient. In addition, there was a failure to properly identify the recipient prior to transfusion.

3. HTR (ABO) – *Possible*
   A group A Pos recipient was transfused with multiple group AB Pos units due to a test tube reading error. The patient's plasma was icteric and the reverse B cells were read as forward B typing (reagent color was similar to the patient's plasma). The role of the hemolytic transfusion reaction is unclear due to serious underlying co-morbidities.

4. HTR (ABO) – *Possible*
   A group O Pos recipient was transfused with a unit of group A Pos red blood cells due to a manual system testing error. The technologist was testing multiple patient samples and failed to verify specimen identification during testing. Although the patient's symptomatology was consistent with an acute HTR, there was no laboratory evidence of hemolysis.

The one report of a non-ABO fatal hemolytic transfusion reaction involved the presence of a weakly detectable antibody missed on initial testing.

1. HTR (non-ABO) – *Possible*
   A blood bank technologist interpreted the pre-transfusion antibody testing as negative. The patient experienced a hemolytic transfusion reaction and subsequent testing showed the presence of anti-c in the pre-transfusion specimen. Although the patient experienced a hemolytic transfusion reaction, the patient had significant co-morbidities which may also have contributed to their demise.

Reviewing data from previous years, the number of hemolytic transfusion reactions has remained low, particularly with ABO HTRs, where the error is most frequently preventable misidentification of the patient or the patient's sample. There were four reported ABO hemolytic transfusions (9%) that were attributed to the fatalities in FY2016, compared to two (5%) in FY2015. There was one (2%) non-ABO hemolytic transfusion reaction in FY2016, compared to four (11%) in FY2015 (Table 3). There has been an overall downward trend in the total number of reported fatalities due to HTRs (both ABO and non-ABO) since FY2002, and numbers have stabilized in recent years (Figure 3).

Table 4: Hemolytic Transfusion Reactions by Implicated Antibody, FY2012 – FY2016

Antibody	FY12 No.	FY13 No.	FY14 No.	FY15 No.	FY16 No.	Total No.
ABO	3	1	4	2	4	**14**
Multiple Antibodies	2	1	-	2	-	**5**
Other**	-	-	2	1	-	**3**
K	1	2	-	-	-	**3**
Jk^a	-	1	1	-	-	**2**
Jk^b	1	1	-	-	-	**2**
c	-	-	-	1	1	**2**
C	-	-	1	-	-	**1**
Js^b	1	-	-	-	-	**1**
Total	**8**	**6**	**8**	**6**	**5**	**33**

*Multiple Antibodies: FY2012: antibody combinations include: S+E; C+K. FY2013: anti-c+E
FY2015: antibody combinations include: $E+K+Jk^a+M+Co^b+Cw$; $C+E+S+Jk^b+Fy^a+Fy^b$

**Other: FY2014: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified[38, 39, 40]

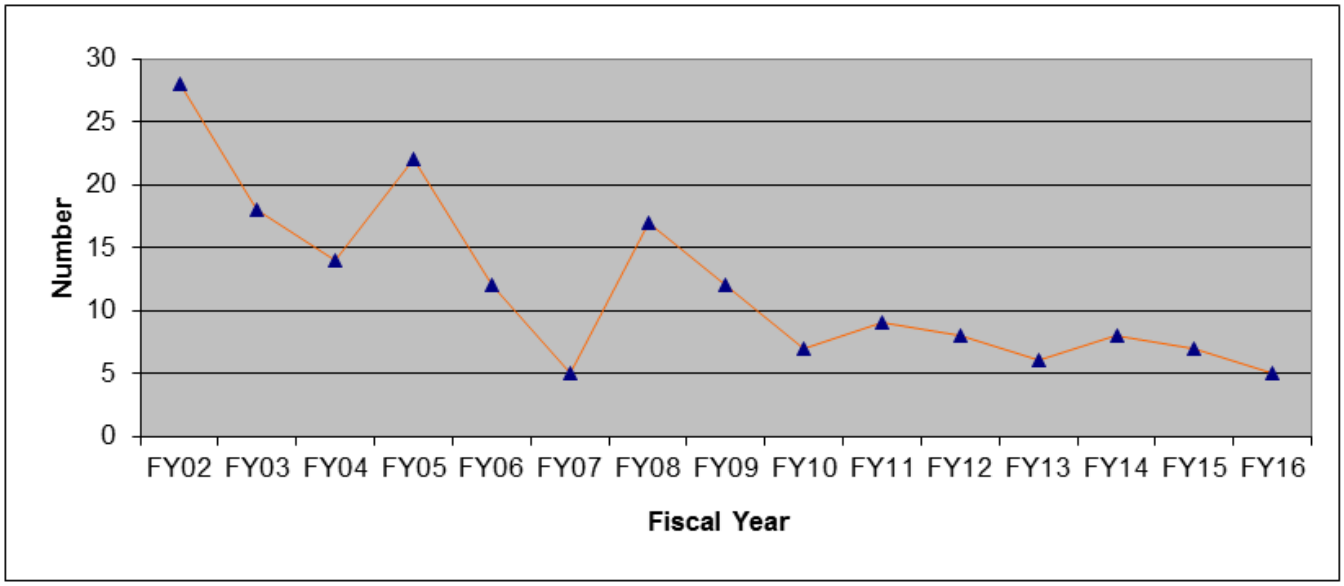
FY2015: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified

[38] Win N, New H, et al. Hyperhemolysis Syndrome in sickle cell disease: case report (recurrent episode) and literature review. Transfusion 2008;48:1231-1238.

[39] Santos B, Portugal R, et al. Hyperhemolysis Syndrome in patients with sickle cell anemia: report of three cases. Transfusion. 2015 Jun;55(6 Pt 2):1394-8.

[40] Erin D. Moritz, et al. Screening for *Babesia microti* in the U.S. Blood Supply. New England Journal of Medicine. 2016;375:2236-45.

Figure 3: Hemolytic Transfusion Reactions, FY2002 – FY2016



C. Microbial Contamination

In FY2016, there were five contamination-related fatalities, with three attributed to bacterial contamination, and two attributed to parasitic contamination (Table 5). One of the FY2016 cases involved transfusion of an apheresis platelet which was contaminated with *Enterobacter aerogenes* (Figure 4). One case involved a therapeutic plasma exchange (TPE) which was contaminated with coagulase-negative staphylococci. One case involved a red cell unit which was contaminated with *Pseudomonas fluorescens*, and two cases involved transfusion of red blood cells contaminated with *Babesia microti* (Table 5, Figure 4).

Table 5: Contamination Breakdown, FY2016

Product	Organism	Imputability
Apheresis platelets	*Enterobacter aerogenes*	Definite/Certain
Plasma (TPE)	Coagulase-negative staphylococci	Possible
Red Blood Cells	*Pseudomonas fluorescens*	Definite/Certain
Red Blood Cells	*Babesia microti*	Probable/Likely
Red Blood Cells	*Babesia microti*	Probable/Likely

1. Contamination (*Enterobacter aerogenes*) - *Definite/Certain*
   The patient received an apheresis platelet product and *Enterobacter aerogenes* was identified in both the product and in the patient. No other sources for the contamination were identified, and the patient was not infected with *Enterobacter aerogenes* prior to transfusion.

2. Contamination (*Pseudomonas fluorescens*) - *Definite/Certain*
   A patient received a red blood cell product and *Pseudomons fluorescens* was identified in both the product and in the patient. No other sources for the contamination were identified, and the patient was not infected with *Pseudomonas fluorescens* prior to transfusion.

3. Contamination (*Babesia microti*) – *Probable/Likely*
   A patient received a red blood cell unit and *Babesia microti* was identified in the red blood cell product, and in the patient. Although there was no molecular testing performed to match the parasites, the patient had no other potential exposures identified.

4. Contamination (*Babesia microti*) – *Probable/Likely*
   A patient received a red blood cell unit and *Babesia microti* was identified in the patient. The donor had the presence of antibodies indicating recent infection, and the patient had no other potential exposures identified.

5. Contamination (Coagulase-negative Staphylococcus) – *Possible*
   A patient received a therapeutic plasma exchange and coagulase-negative stapylococci was identified in the plasma product. Manifestations in the patient shortly after initiation of the transfusion were consistent with a reaction due to bacterial contamination, however the patient's blood cultures exhibited no growth. While the patient had serious underlying conditions potentially causing sepsis, it is possible transfusion-associated sepsis contributed to their demise.

Reviewing data from the last five years, *Staphylococcus aureus* and *Babesia microti* accounted for the greatest number of the reported deaths due to contamination (eight of 18 deaths) (Table 6).

Figure 5 shows the microorganisms implicated by product type. *Babesia microti* infections were associated with five of the eight RBC transfusions implicated in reported fatalities. Recent articles provide additional information about transfusion transmitted *Babesia* and the current effort to screen the blood supply using investigation tests in endemic states.[41]

The two *Serratia marcescens* infections were associated with transfusion of pooled platelets, and coagulase-negative staphylococci infection was associated with TPE. The nine deaths associated with transfusion of apheresis platelets were distributed among six organisms (Figure 4). Recent articles provide additional information about bacterial contamination of platelet products.[42, 43, 44]

Figure 5 shows the trend of contamination (bacterial) associated with apheresis platelets from FY 2002 to FY2016. These data show that the number of bacterial infections has been trending downward since FY2002, when eight were identified. Bacterial contamination of platelet components remains a public health concern which FDA has addressed in a recently published Draft Guidance on controlling the risk of bacterial contamination to enhance the safety and availability of platelets for transfusion.[45] Refer to Title 21, Code of Federal Regulations 606.145 for requirements regarding control of bacterial contamination of platelets.

[41] Young C, Chawla A, et al. Preventing transfusion-transmitted babesiosis: preliminary experience of the first laboratory- based blood donor screening program. Transfusion 2012;52:1523-1529.

[42] Rollins MD, Molofsky AB, Nambiar A, et al. Two Septic transfusion reactions presenting as transfusion-related acute lung injury from a split plateletpheresis unit. Crit Care Med 2012;40:2488-2491.

[43] Palavecino EL, Yomtovian RA, Jacobs MR. Bacterial contamination of platelets. Transfus Apher Sci 2010;42:71-82.

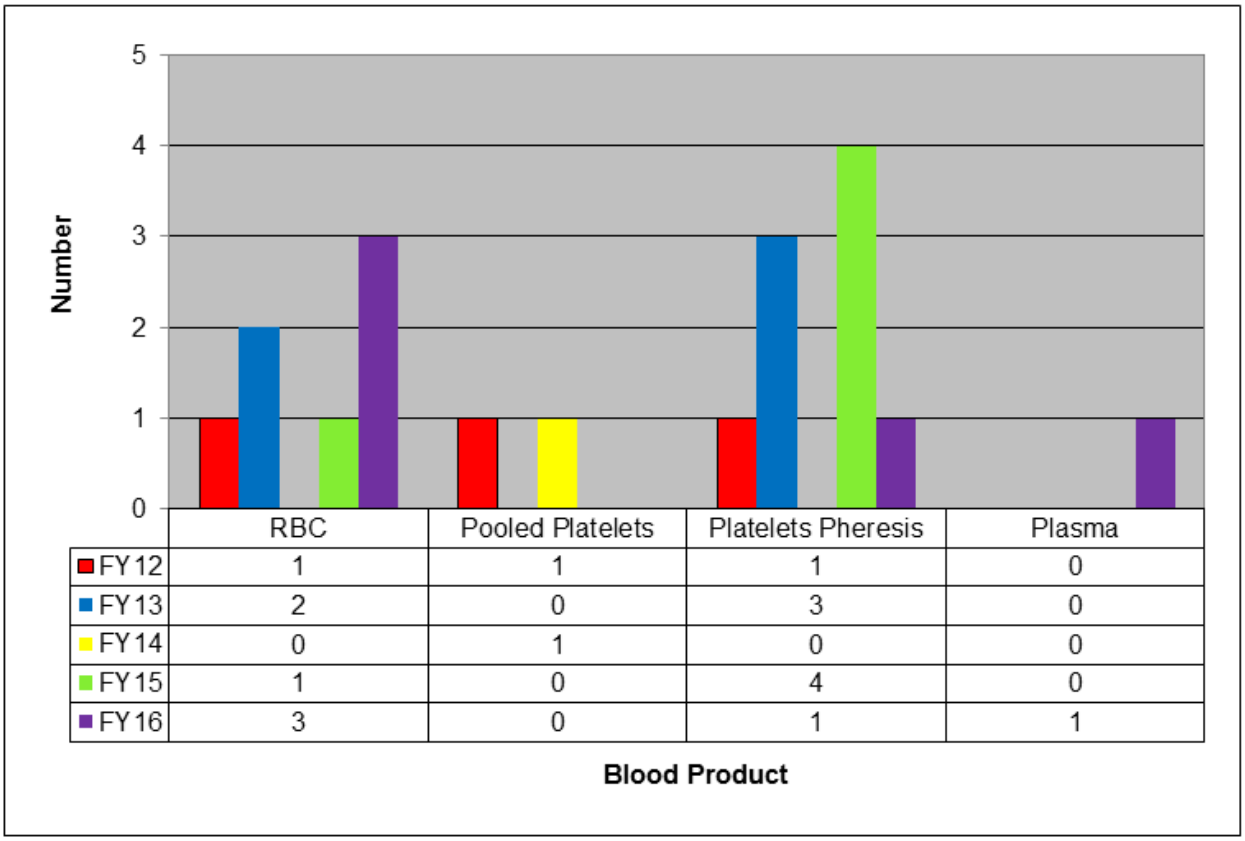
[44] Eder AF, et al. Apheresis technology correlates with bacterial contamination of platelets and reported septic transfusion reactions. Transfusion 2017;00;00-00. 2009;49:1554-1563.

[45] http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf

Table 6: Contamination by Implicated Organism, FY2012 - FY2016

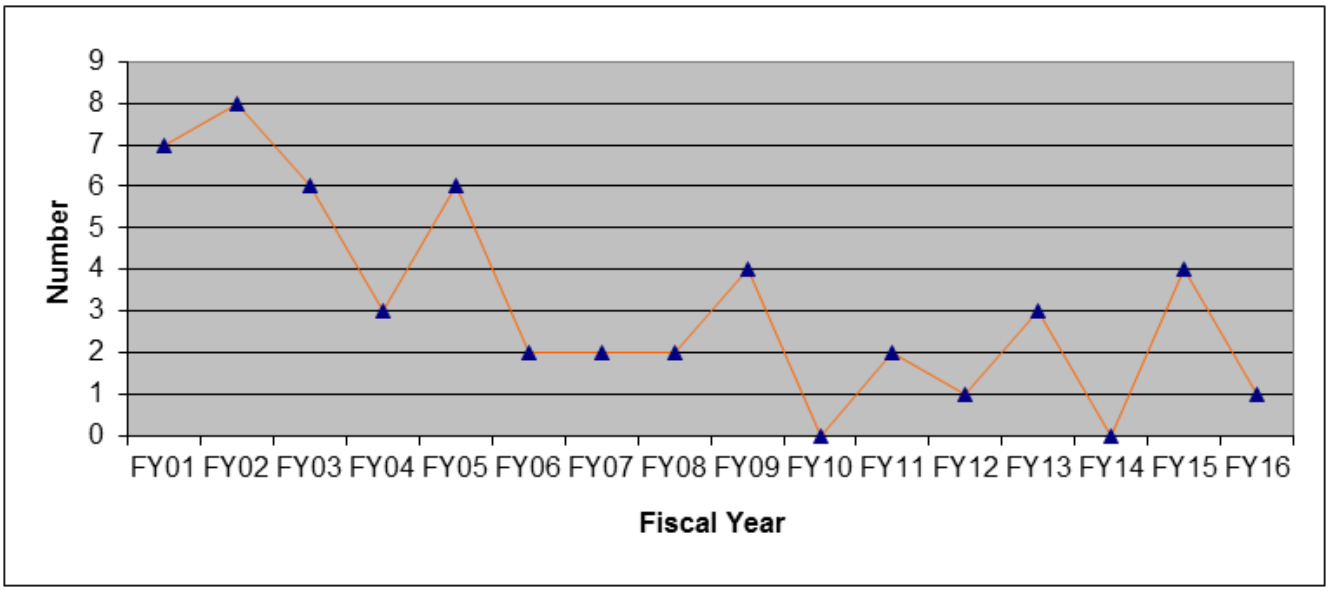
Organism	FY12	FY13	FY14	FY15	FY16	TOTAL
Staphylococcus aureus	1	-	-	3	-	**4**
Babesia microti	1	1	-	-	2	**4**
Serratia marcescens	1	-	1	-	-	**2**
Coagulase-negative staphylococci	-	-	-	1	1	**2**
Pseudomonas fluorescens	-	1	-	-	1	**2**
Staphylococcus epidermidis	-	1	-	-	-	**1**
Acinetobacter species	-	1	-	-	-	**1**
Enterococcus faecium	-	-	-	1	-	**1**
Enterobacter aerogenes	-	-	-	-	1	**1**
West Nile virus	-	1	-	-	-	**1**
TOTAL	**3**	**5**	**1**	**5**	**5**	**19**

Figure 4: Contamination by Implicated Blood Product, FY2012 – FY2016



Red Blood Cells microorganisms: *B. microti (4), P. fluorescens (2), E. faecium (1)*
Pooled Platelets microorganisms: *S. Marcescens (2)*
Plasma (TPE): coagulase-negative staphylococci (1)
Platelets Pheresis microorganisms: *S. aureus (4), S. epidermidis (1),* coagulase-negative staphylococci *(1),*
West Nile virus *(1), Acinetobacter sp. (1), E. aerogenes (1)*

Figure 5: Contamination (bacterial) by Apheresis Platelets, FY2001 – FY2016



E. Transfusion Doubtful/Unlikely/Improbable

We classified 15 (22%) of the 67 reported transfusion fatalities in FY2016 as *doubtful/unlikely/improbable*, including one contamination (bacterial), one HTR (ABO), two HTR (non-ABO), one TACO, two TRALI, one Possible TRALI, and seven Transfusion Reaction, Type Not Determined. Although the transfusion could not be excluded as a contributing factor, the evidence in each of these cases more strongly favored the patient's underlying medical condition(s). Thus, we did not include these reported fatalities in the analysis in Sections III.A through III.D.

F. Transfusion Not Determined/Assessable/Evaluable

We classified two (3%) of the 67 reported transfusion fatalities in FY2016 as *not determined/assessable/evaluable*. In these cases, the patient either had several underlying conditions, or there was insufficient information submitted/available to determine the extent of the relation due to the reaction occurring outside of the clinical care setting. Thus, these reported fatalities were also not included in the analysis in Sections III.A through III.D.

G. Transfusion Ruled Out/Excluded

We classified seven (11%) of the 67 reported transfusion fatalities in FY2016 as *ruled out/excluded*. Our medical reviewers concluded that either no transfusion reaction occurred, or, while there was a temporal relationship between transfusion and subsequent death of the recipient, there was conclusive evidence beyond a reasonable doubt for attributing the fatality to a cause (e.g., underlying condition) other than transfusion. Thus, we did not include these reported fatalities in the analysis in Sections III.A through III.D.

H. Donation Fatalities

The process of blood donation is generally safe and determining that a causal link exists between a donation and the fatality remains uncommon among reported donation fatalities. For FY2016, there were no donation fatalities classified as *definite/certain,* and there were three donation fatalities classified as either *probable/likely or possible.* There were eight donation fatalities classified as *doubtful/unlikely/improbable,* and three donation fatalities classified as *ruled out/excluded* (Table 7).

- Donation – *Probable/Likely*
  There was one fatality following a Source Plasma donation where the evidence was in favor of attributing the complication to the donation as the cause of the fatality. This was a complex case where the donor likely had a septic thrombophlebitis in the upper extremity following phlebotomy as the initiating factor, and a complicated clinical course.

- Donation – *Possible*
  There were two fatalities following a Source Plasma donation where the evidence was indeterminate for attributing the complication to the donation or an alternative cause (e.g., underlying medical condition, possibly precipitated by donation).

- Donation – *Doubtful/Unlikely/Improbable*
  There was a total of eight fatalities following five Source Plasma donations, two Whole Blood donations, and one double Apheresis Red Cell donation, in which the relationship between the donation and subsequent death of the donor was classified as *doubtful/unlikely/improbable.* In these cases, the evidence was in favor of attributing the death to a cause other than the donation (e.g., underlying medical conditions), but the donation could not be excluded.

- Donation – *Rule Out/Excluded*
  There was a total of three fatalities following Source Plasma donation in which the donations were classified as *ruled out/excluded*. In these cases, there was clear evidence beyond a reasonable doubt for attributing the fatality to causes other than donation (e.g., drug overdoses, or underlying medical conditions).

Table 7: Donation Fatalities with Imputability by Product, FY2016

	Definite/ Certain	Probable/ Likely	Possible	Doubtful/ Unlikely/ Improbable	Ruled Out/ Excluded	Not Determined/ Assessable/ Evaluable	TOTAL
Source Plasma	-	1	2	5	3	-	**11**
Whole Blood	-	-	-	2	-	-	**2**
Apheresis Platelets	-	-	-	-	-	-	-
Apheresis Red Cells	-	-	-	1	-	-	1
Total	**-**	1	**2**	**8**	**3**	**0**	**14**

The changes in our review and classification process presented a challenge in terms of comparing FY2015 and FY2016 donation fatalities with previous years. In most of the cases from FY2011 to FY2014, it was concluded that the donation could not be definitively ruled out as the cause of the donor's death. Thorough medical review determined that the available evidence did not definitively rule out the donation being implicated in the donor's death, nor did the available evidence support a causal relationship between the donation and the donor's death.

For FY2016, the cases classified as *doubtful/unlikely/improbable*, and *not determined/assessable/evaluable* would most accurately compare to the *donation not ruled out* cases from previous years (Table 8).

Table 8: Donation "Not Ruled Out" by Product, FY2012- FY2016*

Donated Product	FY12	FY13	FY14	FY15	FY16	TOTAL
Source Plasma	9	4	4	12	5	**34**
Whole Blood	2	1	1	1	2	**7**
Apheresis Platelets	-	-	1	1	0	**2**
Apheresis Red Blood Cells	-	-	-	-	1	**1**
Total	**11**	**5**	**6**	**14**	**8**	**44**

*FY2015 & FY2016 numbers include *doubtful/unlikely/improbable* and *not determined/assessable/evaluable*.

Finally, the number of donation fatalities definitively ruled out as being implicated in the donor's death is markedly smaller than the combination of cases classified as *donation not ruled out, doubtful/unlikely/improbable,* and *not determined/assessable/evaluable* in FY2012 to FY2016. These reported donation fatality cases have been classified in years past as *donation ruled out*.

For FY2016, the cases classified as *ruled out/excluded* would compare to *donation ruled out* cases from previous years (Table 9).

Table 9: Donation "Ruled Out" by Product, FY2012-FY2016*

Donated Product	FY12	FY13	FY14	FY15	FY16	TOTAL
Source Plasma	3	1	2	4	3	**13**
Whole Blood	-	1	-	1	-	**2**
Apheresis Platelets	-	-	-	-	-	**-**
Apheresis Red Blood Cells	-	-	-	-	-	**-**
Total	**3**	**2**	**2**	**5**	**3**	**15**

*FY2015 & FY2016 numbers include *ruled out/excluded.*