Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2017

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) 2017 (October 1, 2016, through September 30, 2017), to provide the combined data received over the last five fiscal years, and to compare the FY2017 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. In calendar year 2015, 11.3 million whole blood and red blood cells, 2.1 million apheresis platelets, and 3.6 million plasma components were transfused, a decrease of 14% in transfusions of red blood cells and whole blood since 2013.[2,3] During FY2013, there were 59 reported transfusion-associated fatalities, with subsequent reports of 56 in 2014, 41 in 2015, 60 in 2016, and 44 in 2017. 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 greater than what the numbers would otherwise suggest.

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. In 2016, there were 38.3 million source plasma donations made in the U.S.[4] Over the combined five-year reporting period (FY2013 – FY2017) there were 47 reported donation-associated fatalities (associated with a variety of donated products), with seven cases since 2014 having an imputability of definite/certain, probable/likely, or possible.[5]

Fatality reporting requirements can be found under Title 21, Code of Federal Regulations 606.170(b). 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]

[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] NBCUS: https://www.hhs.gov/ohaidp/initiatives/blood-tissue-safety/initiatives/national-blood-collection-and-utilization-survey/index.html

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

[5] https://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 through FY2017 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 (transfusion complications) beginning with FY2016: No Transfusion Reaction, Possible TRALI (previously tallied with TRALI), and Transfusion Reaction, Type Not Determined (Table 2).

[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 - FY2017

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. FY2017 Results

During FY2017, 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) Thirty-seven (55%) of the fatalities were classified as either *definite/certain, probably/likely,* or *possible.*
b) Seven (11%) of the fatalities were classified as either *doubtful/unlikely/improbable*, or *not determined/assessable/evaluable*.
c) Twenty-three (34%) of the fatalities were classified as *ruled out/excluded*.

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

a) Two (14%) of the fatalities were classified as *probable/likely, or possible*.
b) Seven (50%) of the fatalities were classified as either *doubtful/unlikely/improbable*, or *not determined/assessable/evaluable*.
c) Five (36%) 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, FY2017

CATEGORY	Definite/ Certain	Probable/ Likely	Possible	Doubtful/ Unlikely/ Improbable	Ruled Out/ Excluded	Not Determined/ Assessable/ Evaluable	TOTAL REPORTS
Transfusion							
Allergy/Anaphylaxis	2	1	-	1	-	-	**4**
Contamination (Bacterial)	4	1	-	-	-	-	**5**
Contamination (Viral)	-	2	-	-	-	-	**2**
HTR (ABO)	-	1	-	-	-	-	**1**
HTR (non-ABO)	4	-	2	-	-	-	**6**
Hypotensive Reaction[18]	-	-	-	1	-	-	**1**
Other*	-	-	-	-	2	-	**2**
No Transfusion Reaction	-	-	-	-	21	-	**21**
TACO	-	6	5	1	-	-	**12**
TRALI	-	2	3	-	-	-	**5**
Possible TRALI	-	-	4	-	-	-	**4**
Transfusion Reaction, Type Not Determined	-	-	-	-	-	1	**1**
Donation							
Donor Fatality	-	1	1	6	5	1	**14**

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

Note: Three cases concluded as *not determined/assessable/evaluable* were not included in Table 2.

*Febrile non-hemolytic reaction; Flushing and Pulmonary symptoms

For the purpose of comparison with previous fiscal years, the FY2015, FY2016 and FY2017 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.[12]

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

In combined FYs 2013 through 2017, TACO[11,13] cases caused the highest number of reported fatalities (32%), followed by the combined TRALI and Possible TRALI (30%), microbial contamination (12%), HTR due to non-ABO incompatibilities (11%). HTRs due to ABO incompatibilities (7%), anaphylaxis reactions (6%), and hypotensive reactions (2%) each accounted for a relatively smaller number of reported fatalities (Table 3).

[11] 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.

[12] https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/default.htm

[13] http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2598362

TACO was the leading cause of reported transfusion-associated deaths for FY2016 and FY2017 and is currently the leading cause of transfusion-associated fatalities over the 5-year reporting period (FY2013 - FY2017). Prior to FY2016, TRALI was the consistent leading cause of transfusion-associated fatalities.

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 FY2013 through FY2017, 12 anaphylactic reactions were investigated for IgA deficiency. Five 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] Of the three anaphylaxis cases investigated in FY2017, one haptoglobin level was reported as low, and no haptoglobin was reported in the remaining two 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 each of FY2014, FY2015, and FY2016, and none in FY2017. 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, all other adverse reactions presenting with hypotension were excluded.

Table 3: Transfusion-Associated Fatalities by Complication, FY2013 – FY2017

Complication	FY13 No.	FY13 %	FY14 No.	FY14 %	FY15 No.	FY15 %	FY16 No.	FY16 %	FY17 No.	FY17 %	Total No.	Total %
Anaphylaxis	-	0%	2	7%	2	5%	5	12%	3	8%	**12**	**6%**
Contamination	5	13%	1	3%	5	14%	5	12%	7	19%	**23**	**12%**
HTR (ABO)	1	3%	4	13%	2	5%	4	9%	1	3%	**12**	**7%**
HTR (non-ABO)	5	13%	4	13%	4	11%	1	2%	6	16%	**20**	**11%**
Hypotensive Reaction	-	0%	1	3%	1	3%	1	2%	0	0%	**3**	**2%**
TACO	13	34%	5	17%	11	30%	19	44%	11	30%	**59**	**32%**
TRALI*	14	37%	13	43%	12	32%	8	19%	9	24%	**56**	**30%**

Note: FY2015-FY2017 only includes cases with an imputability of *Definite/Certain, Probable/Likely,* or *Possible*, and FY2013-FY2014 only include cases classified as transfusion-related.
*FY2013-FY2017 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 FY2017, there were two cases of TRALI classified as *probable/likely*, and three cases of TRALI that were classified as *possible*. There were four cases of Possible TRALI classified with an imputability of *possible*. For FY2017, there were no cases where testing matched donor antibodies with recipient cognate antigens, due to either negative or incomplete donor/recipient 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 30% of transfusion-associated fatalities reported to CBER over the last five fiscal years, and 24% in FY2017 (Table 3). Figure 1 shows a rise in TRALI cases between FY2003 and FY2007, followed by an abrupt decline and a downward trend between FY2010 and FY2017. 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 was paralleled with a reduction in the number of TRALI deaths. Current literature describes the results of continued international efforts 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, FY2003 - FY2017

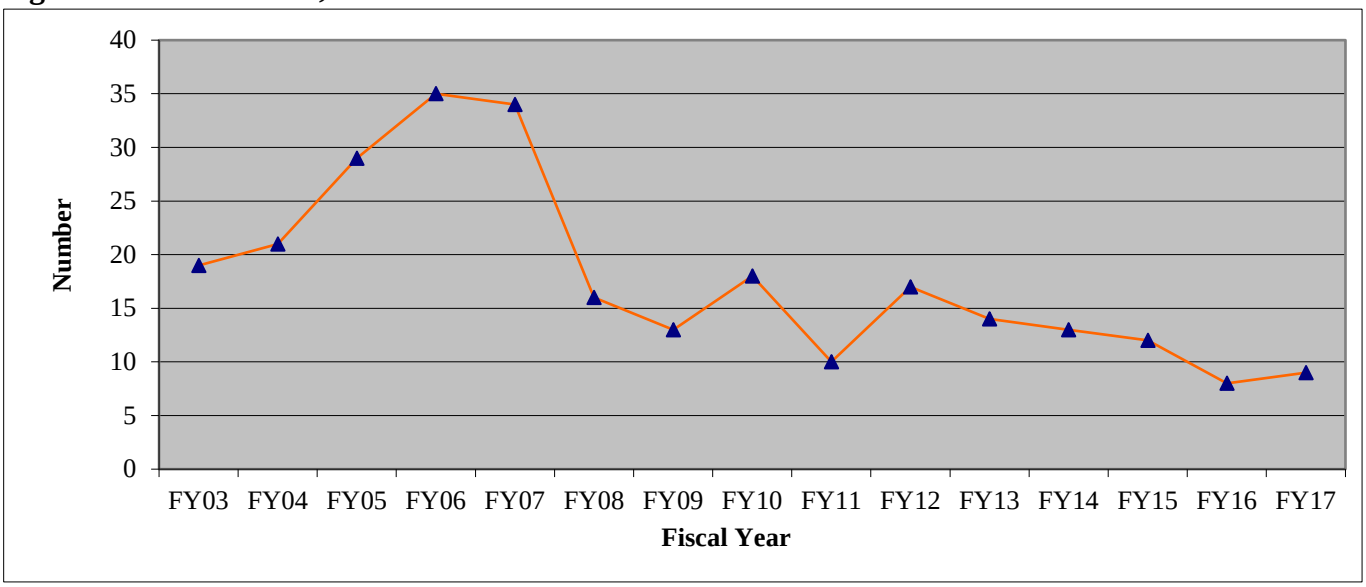
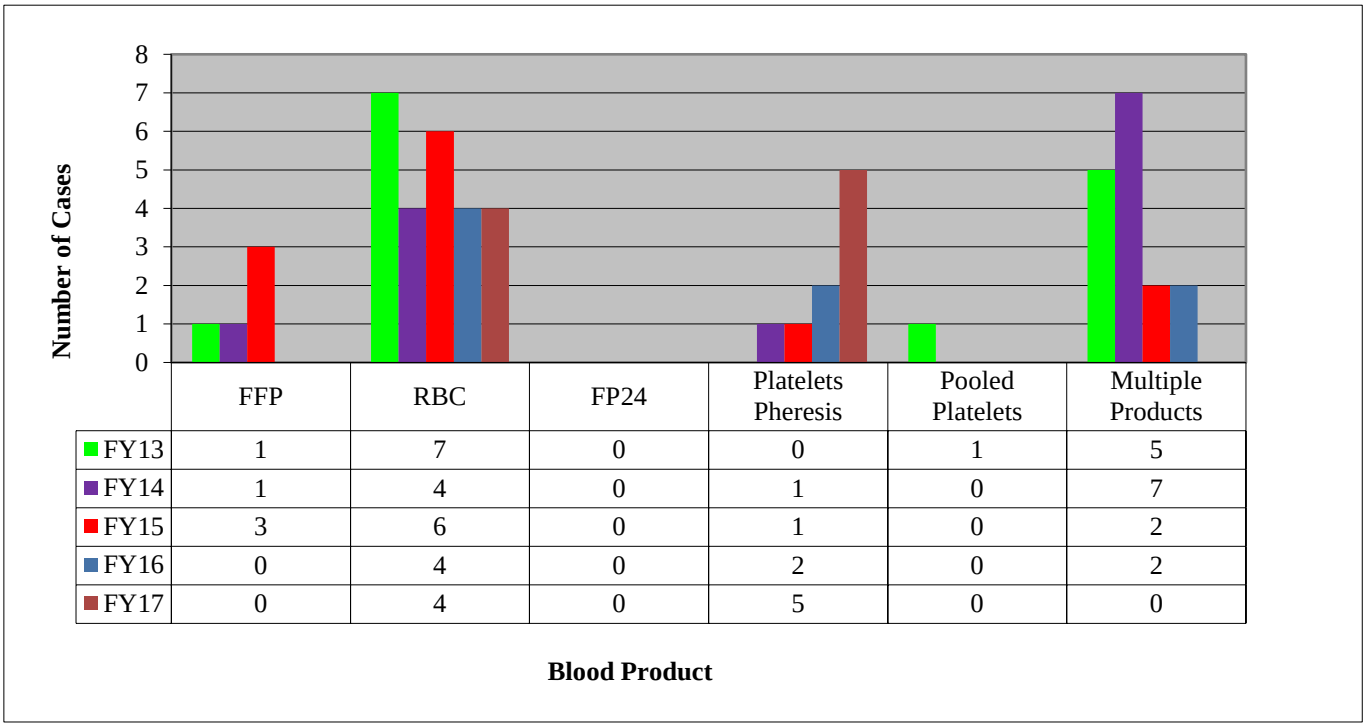


Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2013 – FY2017



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
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
FY17	0	4	0	5	0	0

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

C. Hemolytic Transfusion Reactions (HTR)

In FY2017, there was one reported ABO hemolytic transfusion fatality classified as *probable/likely* (3% of confirmed transfusion-associated fatalities), and six non-ABO hemolytic transfusion fatalities; four with an imputability of *definite/certain*, and two with an imputability of *possible* (16% of confirmed transfusion-associated fatalities) (Tables 3 and 4).

The one report of a fatal hemolytic transfusion reaction which was found to be related to ABO-incompatible transfusion was determined to be the result of an error in patient testing.

HTR (ABO) – *Probable/Likely*
Multiple group B red blood cell units were transfused to a group O Pos patient who initially typed as B Pos due to microscopic interpretation of the B forward type, and absence of anti-B in the back type. Upon retest of the original samples, the patient was determined to be O Pos, although the back type of the patient's plasma with B cells was markedly weak.

The six reports of non-ABO fatal hemolytic transfusion reactions involve emergently released products subsequently determined to be positive for cognate antigens, a case of hyperhemolysis, and possibly undetectable antibody(s) in pre- and post-transfusion testing.

1. **HTR (non-ABO) – *Definite/Certain***
   The patient received units released with an initially positive antibody screen according to an emergency release least- incompatible procedure. Subsequent testing confirmed the patient had an anti-C, anti-Jk(a), and anti-M reactive at AHG phase. All units transfused were C negative, however all were Jk(a) positive and one unit was M positive.

2. **HTR (non-ABO) – *Definite/Certain***
   A patient with sickle cell disease had known alloantibodies including anti-C, anti-E, anti-Fy(a), anti-Jk(b), anti-S, anti-Js(a), as well as an HTLA-like antibody and a warm autoantibody. Units were negative for cognate antigens and were compatible using adsorbed plasma; however, the transfusion findings were consistent with a hemolytic transfusion reaction. Clerical check was negative, and the transfusion reaction investigation showed no new antibodies.

3. **HTR (non-ABO) – *Definite/Certain***
   The patient received units released under an emergency release procedure due to an acute intra-abdominal hemorrhage. The patient was found to have a positive antibody screen due to anti-e, and units emergently released were discovered to be e antigen positive. The patient experienced disseminated intravascular coagulation (DIC), secondary to a non-ABO hemolytic transfusion reaction due to anti-e.

4. **HTR (non-ABO) – *Definite/Certain***
   A patient with sickle cell disease presented with a history of anti-U and required transfusion. A national search was initiated, however the patient required units that were emergently released as least incompatible due to the patient's severe clinical deterioration. The patient experienced an acute hemolytic transfusion reaction due to anti-U.

5. **HTR (non-ABO) – *Possible***
   A patient with a history of sickle beta thalassemia and anti-Fy(a) required a massive transfusion where uncrossmatched units positive for Fy(a) were provided. The patient suffered from suspected DIC and severe sickle cell crisis in addition to the non-ABO hemolytic transfusion reaction.

6. HTR (non-ABO) – *Possible*
   The patient was a sickle cell patient with no detectable alloantibodies who possibly experienced hyperhemolysis, which was complicated by sickle cell crisis, veno-occlusive disease and congestive heart failure.

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 was one (3%) reported fatality due to an ABO hemolytic transfusion reaction in FY2017, compared to four (9%) in FY2016. There were six (16%) fatalities due to non-ABO hemolytic transfusion reactions in FY2017, compared to one (2%) in FY2016 (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 FY2003, and numbers have stabilized in recent years (Figure 3).

Table 4: Hemolytic Transfusion Reactions by Implicated Antibody, FY2013 – FY2017

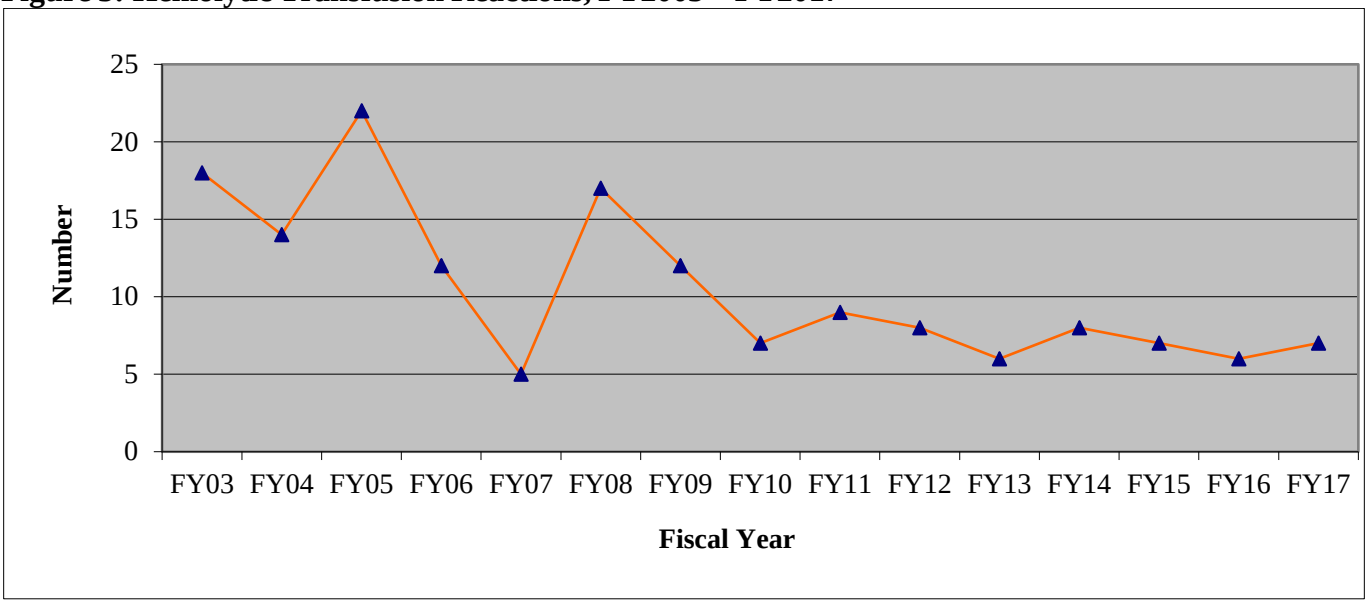
Antibody	FY13 No.	FY14 No.	FY15 No.	FY16 No.	FY17 No.	Total No.
ABO	1	4	2	4	1	**12**
Multiple Antibodies	1	-	2	-	1	**4**
Other**	-	2	1	-	2	**5**
K	2	-	-	-	-	**2**
Jk^a	1	1	-	-	-	**2**
Jk^b	1	-	-	-	-	**1**
c	-	-	1	1	-	**2**
C	-	1	-	-	-	**1**
U	-	-	-	-	1	**1**
Fy^a	-	-	-	-	1	**1**
e	-	-	-	-	1	**1**
Total	**6**	**8**	**6**	**5**	**7**	**32**

*Multiple Antibodies: FY2012: antibody combinations include: S+E; C+K. FY2013: anti-c+E
FY2015: antibody combinations include: $E+K+Jk^a+M+Co^b+Cw$**;**
$C+E+S+Jk^b+Fy^a+Fy^b$
FY2017: antibody combinations include: Jk^a+M

**Other: FY2014: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified[38, 39]
FY2015: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified
FY2017: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was indentified, and one case of a hemolytic transfusion reaction where 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.

Figure 3: Hemolytic Transfusion Reactions, FY2003 – FY2017



D. Microbial Contamination

In FY2017, there were seven contamination-related fatalities, with five attributed to bacterial contamination, and two attributed to viral contamination (Table 5 & 6). The bacterial contamination cases were associated with three apheresis platelet collections (*Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Clostridium perfringens*), one of which was split (*Clostridium perfringens*), and one red cell unit contaminated with *Anaplasma phagocytophilum.* Two viral cases involved products (thawed plasma and apheresis platelet) contaminated with West Nile Virus (WNV).

Table 5: Contamination Breakdown, FY2017

Product	Organism	Imputability
Apheresis platelets	*Staphylococcus epidermidis*	Probable/Likely
Apheresis platelets	West Nile Virus	Probable/Likely
Apheresis platelets	*Klebsiella pneumoniae*	Definite/Certain
Apheresis platelets	*Clostridium perfringens*	Definite/Certain
Red Blood Cells	*Anaplasma phagocytophilum*	Definite/Certain
Thawed Plasma	West Nile Virus	Probable/Likely

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

2. **Contamination (*Clostridium perfringens*) - *Definite/Certain***
   Two patients received part of a split apheresis platelet product derived from the same donor collection. *Clostridium perfringens* was identified from isolates in patient A's blood culture, two isolates from the platelet bag transfused to patient B, and isolates from the donor's skin. Analysis submitted using whole genome sequencing demonstrated all isolates were found to be highly related.

3. **Contamination (*Anaplasma phagocytophilum*) – *Definite/Certain***
   A patient received a red blood cell unit and *Anaplasma phagocytoplilum* was identified in the red blood cell product, and in the patient. No other sources for the contamination were identified, and the patient was not infected with *Anaplasma phagocytophilum* prior to transfusion.

4. **Contamination (*Staphylococcus epidermidis*) – *Probable/Likely***
   A patient received an apheresis platelet product and *Staphylococcus epidermidis* was identified in the product. No information was received regarding blood cultures performed on the recipient. Although the patient's underlying condition was a contributing factor, it was likely that the death was due to bacterial sepsis from the implicated product.

5. **Contamination (West Nile Virus) – *Probable/Likely***
   A patient received a thawed plasma product and West Nile Virus was identified in the patient's CSF and serum, and in the donor's follow-up sample. Although it was possible that the recipient was infected by a mosquito after his hospital discharge, it is more likely that his WNV infection was due to transfusion of the plasma unit.

6. **Contamination (West Nile Virus) – *Probable/Likely***
   A patient received an apheresis platelet product and West Nile Virus was identified in the patient's CSF and serum, and in the donor's repeat donation. However, because the donor lived in a relatively high prevalence area for WNV, other potential exposure could not be ruled out.

Reviewing data from the last five years, *Babesia microti, Staphylococcus aureus* and West Nile Virus were the most frequently identified infectious agents (Table 6).

Figure 4 shows the microorganisms implicated by product type. *Babesia microti* infections were associated with three of the seven 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.[40,41]

The three *Staphylococcus aureus* infections were associated with transfusion of apheresis platelets, and the WNV infections were associated with both apheresis platelets and thawed plasma. (Figure 4). Recent articles provide additional information about bacterial contamination of platelet products.[42, 43, 44,45]

Figure 5 shows the trend of contamination (bacterial) associated with apheresis platelets from FY 2003 to FY2017. 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.[46] Refer to Title 21, Code of Federal Regulations 606.145 for requirements regarding control of bacterial contamination of platelets.

[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.

[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.

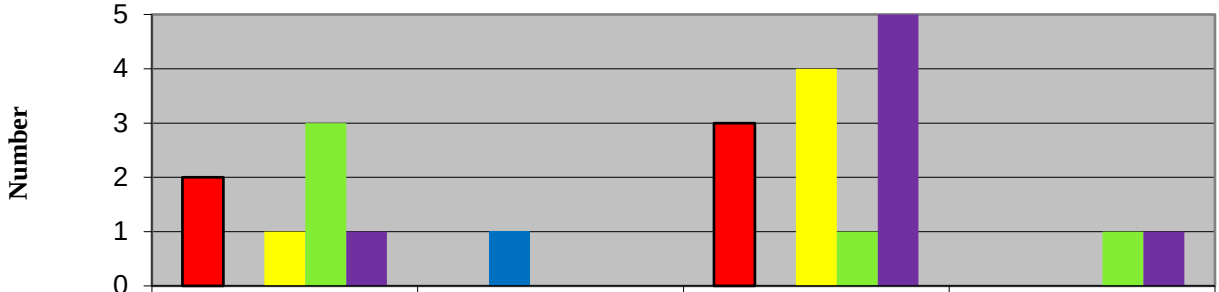
[45] Hong et al., Blood 2016.28;127:496-502

[46] Bacterial Risk Control Strategies for Blood Collections Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion; Draft Guidance for Industry December 2018

Table 6: Contamination by Implicated Organism, FY2013 - FY2017

Organism	FY13	FY14	FY15	FY16	FY17	TOTAL
Staphylococcus aureus	-	-	3	-	-	**3**
Babesia microti	1	-	-	2	-	**3**
Serratia marcescens	-	1	-	-	-	**1**
Coagulase-negative staphylococci	-	-	1	1	-	**2**
Pseudomonas fluorescens	1	-	-	1	-	**2**
Staphylococcus epidermidis	1	-	-	-	1	**2**
Acinetobacter species	1	-	-	-	-	**1**
Enterococcus faecium	-	-	1	-	-	**1**
Enterobacter aerogenes	-	-	-	1	-	**1**
Klebsiella pneumoniae	-	-	-	-	1	**1**
Clostridium perfringens	-	-	-	-	2	**2**
Anaplasma phagocytophilum	-	-	-	-	1	**1**
West Nile virus	1	-	-	-	2	**3**
TOTAL	**5**	**1**	**5**	**5**	**7**	**23**

Figure 4: Contamination by Implicated Blood Product, FY2013 – FY2017

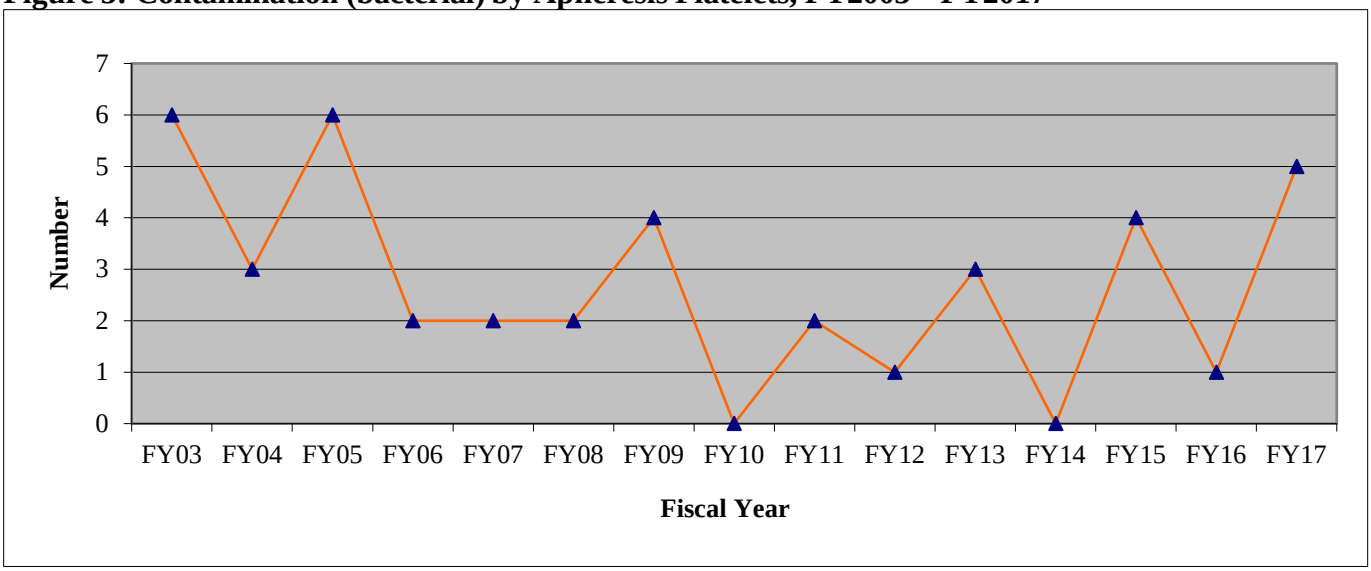


	RBC	Pooled Platelets	Platelets Pheresis	Plasma
FY13	2	0	3	0
FY14	0	1	0	0
FY15	1	0	4	0
FY16	3	0	1	1
FY17	1	0	5	1

Blood Product

Red Blood Cells microorganisms: *B. microti (3), P. fluorescens (2), E. faecium (1), Anaplasma phagocytophilum (1)*
Pooled Platelets microorganisms: *S. Marcescens (1)*
Plasma: (TPE) coagulase-negative staphylococci (1), (thawed plasma) West Nile Virus (1)
Platelets Pheresis microorganisms: *S. aureus (3), S. epidermidis (2),* coagulase-negative staphylococci *(1),* West Nile virus *(2), Acinetobacter sp. (1), E. aerogenes (1), K. pneumoniae (1)*

Figure 5: Contamination (bacterial) by Apheresis Platelets, FY2003 – FY2017



E. Transfusion Doubtful/Unlikely/Improbable as Cause of Death

We classified three (5%) of the 67 reported transfusion fatalities in FY2017 as *doubtful/unlikely/improbable,* including one hypotensive case, one TACO, and one Allergic/Anaphylaxis reaction. Although 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 as Cause of Death

We classified four (6 %) of the 67 reported transfusion fatalities in FY2017 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 between the transfusion and the death. Thus, these reported fatalities were also not included in the analysis in Sections III.A through III.D.

G. Transfusion Ruled Out/Excluded as Cause of Death

We classified 23 (34%) of the 67 reported transfusion fatalities in FY2017 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 FY2017, there were no donation fatalities classified as *definite/certain,* one donation fatality classified as pr*obable/likely,* and one classified as *possible.* There were six donation fatalities classified as *doubtful/unlikely/improbable,* five donation fatalities classified as *ruled out/excluded,* and one donation fatality classified as *not determined/assessable/evaluable* (Table 7).

- **Donation – *Probable/Likely***
  There was one fatality following a Whole Blood donation where the evidence was in favor of attributing the complication to the donation as the cause of the fatality. This was a case where the donor had a history of heart disease, and approximately six hours after donation, the donor lost consciousness and fell, sustaining a head injury and intracranial hemorrhage.

- **Donation – *Possible***
  There was one fatality following a Source Plasma donation where the complication was possibly related to the donation; however, the evidence was indeterminate for attributing the fatality to the donation or an alternative cause.

- **Donation – *Doubtful/Unlikely/Improbable***
  There was a total of six fatalities following five Source Plasma donations, and one Whole Blood 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 five 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).

- **Donation – *Not Determined/Assessable/Evaluable***
  There was one fatality following Source Plasma donation in which the donation was classified as *not determined/assessable/evaluable*. In this case, there was insufficient information submitted/available to determine the extent of the relation between the donation and the cause of death.

Table 7: Donation Fatalities with Imputability by Product, FY2017

	Definite/ Certain	Probable/ Likely	Possible	Doubtful/ Unlikely/ Improbable	Ruled Out/ Excluded	Not Determined/ Assessable/ Evaluable	TOTAL REPORTS
Source Plasma	-	-	1	5	5	1	**12**
Whole Blood	-	1	-	1	-	-	**2**
Apheresis Platelets	-	-	-	-	-	-	-
Apheresis Red Cells	-	-	-	-	-	-	-
Total	**-**	**1**	**1**	**6**	**5**	**1**	**14**

The changes in our review and classification process presented a challenge in terms of comparing FY2015 through FY2017 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 because thorough medical review determined that the available evidence did not definitively rule out the donation as 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 FY2017, 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, FY2013- FY2017*

Donated Product	FY13	FY14	FY15	FY16	FY17	TOTAL REPORTS
Source Plasma	4	4	12	5	6	**31**
Whole Blood	1	1	1	2	1	**6**
Apheresis Platelets	-	1	1	0	0	**2**
Apheresis Red Blood Cells	-	-	-	1	0	**1**
Total	**5**	**6**	**14**	**8**	**7**	**40**

*FY2015 - FY2017 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 FY2013 to FY2017. These reported donation fatality cases have been classified in years past as *donation ruled out*.

For FY2017, 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, FY2013-FY2017*

Donated Product	FY13	FY14	FY15	FY16	FY17	TOTAL REPORTS
Source Plasma	1	2	4	3	5	**15**
Whole Blood	1	-	1	-	-	**2**
Apheresis Platelets	-	-	-	-	-	**-**
Apheresis Red Blood Cells	-	-	-	-	-	**-**
Total	**2**	**2**	**5**	**3**	**5**	**17**

*FY2015 - FY2017 numbers include *ruled out/excluded*.