Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2018

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) 2018 (October 1, 2017, through September 30, 2018), to provide the combined data received over the last five fiscal years, and to compare the FY2018 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 2017, 10.6 million whole blood and red cells, 1.8 million apheresis platelets, and 2.4 million plasma components were transfused, with a continued but slowing decline in demand for RBCs compared to 2015. [2,3] During FY2014 there were 56 fatalities that were either transfusion related or transfusion-not-ruled-out cases. The corresponding fatalities were 41 in 2015, 60 in 2016, 44 in 2017, and 43 in 2018. 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 (FY2014 – FY2018) there were 52 reported donation-associated fatalities (associated with a variety of donated products), with 11 cases since 2014 having an imputability of definite, probable, 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, https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/transfusiondonation-fatalities. 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 - FY2013 data are not discussed in this report, but are available at: http://wayback.archive-it.org/7993/20171114012113/https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/default.htm

[2] Jones et al. Slowing decline in blood collection and transfusion in the United States–2017.Transfusion 2020;60: S1-S6.

[3] NBCUS: https://www.hhs.gov/oidp/topics/blood-tissue-safety/surveys/national-blood-collection-and-utilization-survey/index.html

[4] Plasma Protein Therapeutics Association at https://www.pptaglobal.org/images/Data/Plasma_Collection/2009-2018_US_TC.pdf

[5] https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/transfusiondonation-fatalities

[6] Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/notifying-fda-fatalities-related-blood-collection-or-transfusion

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, we have modified our approach to the review and classification of fatality reports. The annual reports for FY2015 through FY2018 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 Haemovigilance 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, probable, possible, doubtful,* and *not assessable* (Table 1). Fatalities previously defined as *not transfusion/donation related* continue to be classified as *ruled out*.

To achieve a more comprehensive review, we added three new categories of transfusion reactions beginning with FY2016: No Transfusion Reaction, Possible TRALI (previously tallied with TRALI), and Transfusion Reaction, Type Not Determined (Table 2). In FY18, we added Unlikely Transfusion Reaction.

[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 Haemovigilance 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 haemovigilance systems.

Table 1: Imputability Definitions[7,8], FY2015 - FY2018

Imputability	Definition
Definite	Conclusive evidence beyond reasonable doubt for attributing the fatality to the transfusion/donation
Probable	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	Evidence in favor of attributing the fatality to an alternative cause, but transfusion/donation cannot be excluded.
Ruled Out	Conclusive evidence beyond reasonable doubt for attributing the fatality to cause other than transfusion/donation
Not Assessable	Insufficient information/relationship unknown

III. FY2018 Results

During FY2018, we received a total of 70 fatality reports. Of these reports, 51 were potentially associated with transfusion recipient fatalities, and 19 were potentially associated with donation.

Of the 51 potentially transfusion-associated fatality reports, we concluded the imputability of the transfusions to the fatalities as follows:

a) Thirty-one (61%) of the fatalities were classified as either *definite, probable,* or *possible* imputability.
b) Twelve (23%) of the fatalities were classified as either *doubtful*, or *not assessable* imputability.
c) Eight (16%) of the fatalities were classified as *ruled out* imputability.

Of the 19 potentially donation-associated fatality reports, we concluded the imputability of the donations to the fatalities as follows:

a) Four (21%) of the fatalities were classified as *probable, or possible* imputability.
b) Six (32%) of the fatalities were classified as either *doubtful*, or *not assessable* imputability.
c) Nine (47%) of the fatalities were classified as *ruled out* imputability.

We summarize the results of our review in Table 2.

Table 2: Fatality Complication Breakdown by Imputability, FY2018

CATEGORY	Definite	Probable	Possible	Doubtful	Ruled Out	Not Assessable	TOTAL REPORTS
Transfusion							
Allergy/Anaphylaxis	1	1	-	1	-	-	3
Contamination (Bacterial)	2	4	-	-	-	-	6
Contamination (Parasitic)	-	-	1	-	-	-	1
HTR (ABO)	2	-	-	-	-	-	2
HTR (non-ABO)	2	1	1	1	-	-	5
No Transfusion Reaction	-	-	-	-	8	-	8
Possible TRALI	-	2	2	1	-	-	5
TACO	1	4	7	2	-	-	14
Transfusion Reaction, Type Not Determined	-	-	-	1	-	-	1
Unlikely Transfusion Reaction	-	-	-	5	-	-	5
						1*	
Donation							
Donor Fatality	-	-	4	5	9	1	19

TRALI = Transfusion Related Acute Lung Injury; TACO = Transfusion Associated Circulatory Overload; HTR = Hemolytic Transfusion Reactions
The Row Header refers to Imputablility to Death
*Category and Imputability Not Assessable

For the purpose of comparison with previous fiscal years, the FY2015 through FY2018 imputabilities of *definite*, *probable*, and *possible* transfusion fatalities in the tables and figures of sections A through E of this document would most accurately compare with fatalities classified in previous years as *transfusion-related*. Sections F and G present the transfusion fatalities classified as *doubtful*, or *not assessable*, which would most accurately compare with fatalities classified in previous years as *transfusion not ruled out.* Section H presents the transfusion fatality reports classified as *ruled out*, which would compare with fatalities classified in previous years as *not transfusion related*. Section I presents the reported fatalities associated with donation.[12]

A. Overall Comparison of Transfusion-Associated Fatalities Reported from FY2014 through FY2018

In combined FYs 2014 through 2018, TACO[11,13] cases caused the highest number of reported fatalities (32%), followed by the combined TRALI and Possible TRALI (26%), microbial contamination (14%), HTR due to non-ABO incompatibilities (11%). HTRs due to ABO incompatibilities (7%), anaphylaxis reactions (8%), 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/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/transfusiondonation-fatalities

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

TACO was the leading cause of reported transfusion-associated deaths for FY16 through FY18 and is currently the leading cause of transfusion-associated fatalities over the 5-year reporting period (FY2014 - FY2018). 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 FY2014 through FY2018, 14 anaphylactic reactions were identified. Six 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 seven cases. Anaphylactic reactions may also be associated with haptoglobin-deficient patients with serum haptoglobin antibodies.[20] Of the two anaphylaxis cases investigated in FY2018, no haptoglobin levels were reported. (Table 2)

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 and FY2018. 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, FY2014 – FY2018

Complication	FY14 No.	FY14 %	FY15 No.	FY15 %	FY16 No.	FY16 %	FY17 No.	FY17 %	FY18 No.	FY18 %	Total No.	Total %
Anaphylaxis	2	7%	2	5%	5	12%	3	8%	2	6%	**14**	**8%**
Contamination	1	3%	5	14%	5	12%	7	19%	7	23%	**25**	**14%**
HTR (ABO)	4	13%	2	5%	4	9%	1	3%	2	6%	**13**	**7%**
HTR (non-ABO)	4	13%	4	11%	1	2%	6	16%	4	13%	**19**	**11%**
Hypotensive Reaction	1	3%	1	3%	1	2%	0	0%	0	0%	**3**	**2%**
TACO	5	17%	11	30%	19	44%	11	30%	12	39%	**58**	**32%**
TRALI*	13	43%	12	32%	8	19%	9	24%	4	13%	**46**	**26%**

Note: FY2014-FY2018 only includes cases with an imputability of *definite*, *probable*, or *possible*, and FY2014 only includes cases classified as transfusion-related.
*FY2014-FY2018 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 FY2018, there were two cases of Possible TRALI classified with an imputability to death of *probable*, and two cases classified with an imputability of *possible*. There were no cases classified as TRALI. For FY2018, 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 26% of transfusion-associated fatalities reported to CBER over the last five fiscal years, and 13% in FY2018 (Table 3). Figure 1 shows a rise in TRALI cases between FY2004 and FY2007, followed by an abrupt decline in FY 2008 and an overall downward trend between FY2010 and FY2018. Red blood cells continue to be the most frequently implicated product since 2014 (Figure 2).

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, FY2004 - FY2018

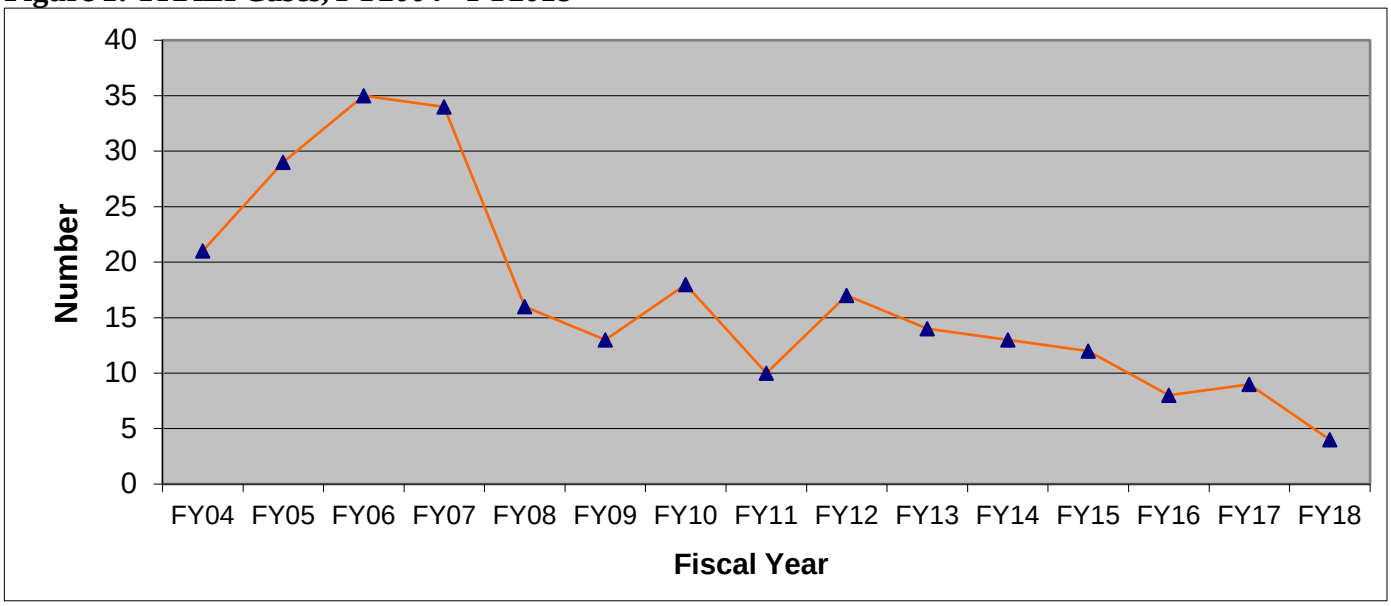
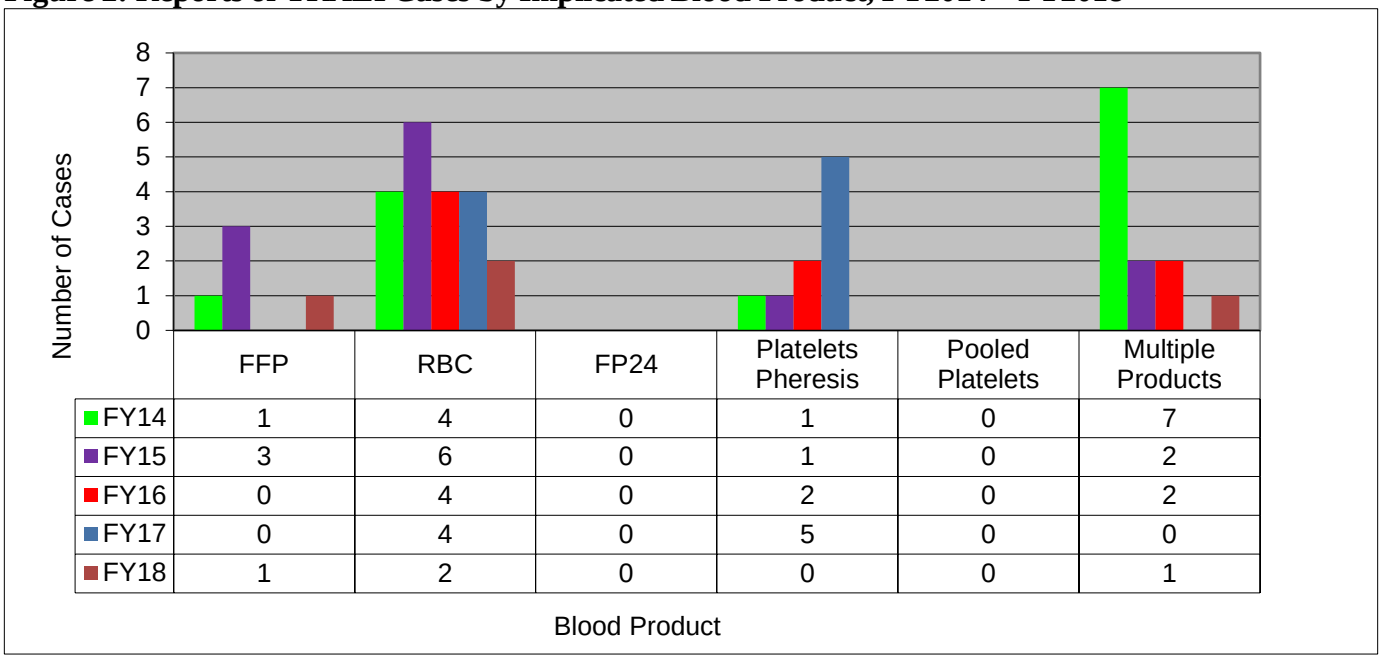


Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2014 – FY2018



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
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
FY18	1	2	0	0	0	1

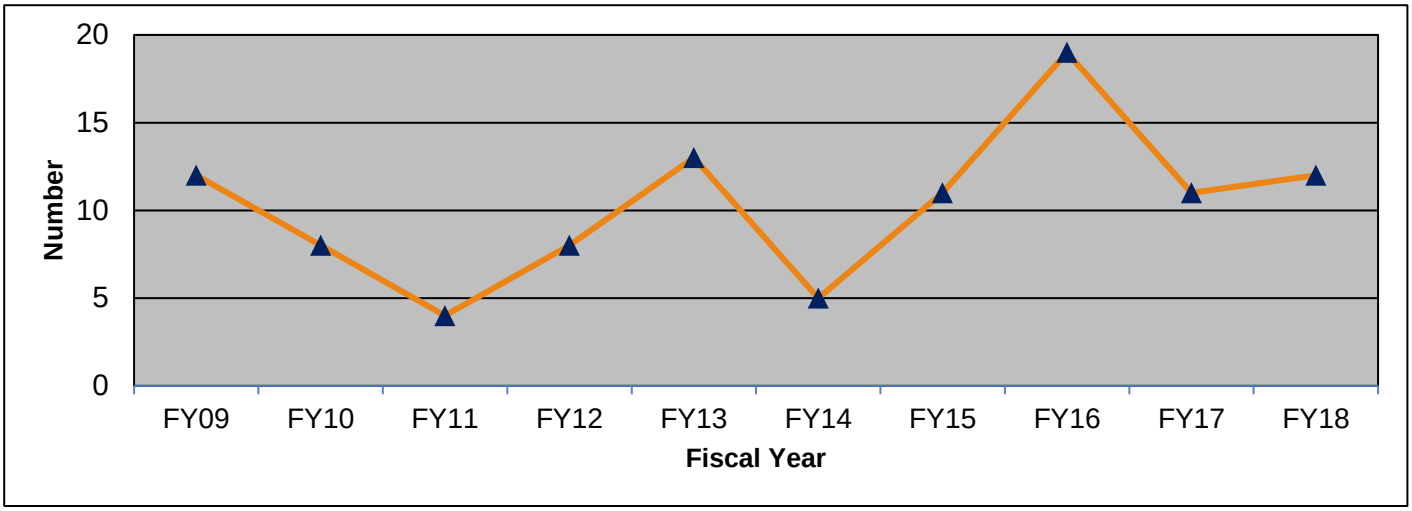
FFP – Fresh Frozen Plasma
RBC – Red Blood Cells
FP24 – Plasma Frozen within 24 hours

C. Transfusion Associated Circulatory Overload (TACO)

In FY2018, there were 12 cases of TACO with an imputability of d*efinite*, *probable*, or *possible*, and TACO was the leading cause of transfusion-associated fatality reported to FDA. Among these 12 reports, one was associated with plasma transfusion, one was associated with platelet transfusion, five were associated with RBC transfusion, and five were associated with multiple products.

TACO has been the leading cause of transfusion-associated fatality reported to FDA in the last three annual reports (FY2016-FY2018), and while the number of TRALI fatalities has showed a downward trend (see section B), the number TACO fatalities (Figure 3) has not seen a similar decline. Active surveillance systems found the incidence of TACO to be approximately one case per 100 patients transfused,[38] and risk factors include cardiac, pulmonary or renal disease, older age, and pre-transfusion positive fluid balance. A revised international surveillance case definition was recently described,[39] and it is anticipated that a standardized definition may facilitate clinicians to better identify, understand, and prevent TACO. The National Healthcare Safety Network expects to incorporate a new definition for TACO in the Hemovigilance Module in January 2021 to reflect the international effort to standardize reporting.[40]

Figure 3: TACO Cases, FY2009 – FY2018



D. Hemolytic Transfusion Reactions (HTR)

In FY2018, there were two reported ABO hemolytic transfusion fatalities classified as d*efinite* (6% of confirmed transfusion-associated fatalities), and four non-ABO hemolytic transfusion fatalities; two with an imputability of *definite*, one with an imputability of *probable*, and one with an imputability of *possible* (13% of confirmed transfusion-associated fatalities) (Tables 3 and 4).

[38]Roubinian NH, Hendrickson JE, Triulzi DJ, et al. Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. Vox Sang. 2017;112(1):56–63. doi:10.1111/vox.12466.
[39]Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study Wiersum-Osselton, Johanna C et al. The Lancet Haematology, Volume 6, Issue 7, e350 - e358.
[40]National Healthcare Safety Network E-Newsletter. Volume 14, Issue 4, December 2019.

HTR (ABO)

1. **HTR (ABO) – *Definite***
   An AB Pos recipient was transfused a group O unit of apheresis platelets. The patient experienced a hemolytic transfusion reaction. It was subsequently determined that isohemagglutinin titers for the platelet product were 1:32000.

2. **HTR (ABO) – *Definite***
   A patient was given an ABO-incompatible RBC product in the Operating Room (OR) that was labeled and intended for another patient. Both patients were in the OR for the same type of procedure, and an RBC product was prepared for each patient and labeled appropriately. The incorrect RBC product (A Pos) was taken from the OR refrigerator and inadvertently given to the incorrect patient (O Pos).

HTR (non-ABO)

1. **HTR (non-ABO) – *Definite***
   A patient with warm autoantibody and history of multiple alloantibodies received two units of RBCs and experienced a hemolytic transfusion reaction with acute and delayed manifestations. The patient had anti-Jk(b), anti-S, anti-E, and anti-D (due to potential variant D antigen). The patient's worsening anemia and severe hemolysis was also suggestive of acute hyperhemolysis syndrome.

2. **HTR (non-ABO) – *Definite***
   A patient received two RBC units and experienced a reaction during transfusion of the second unit. It was subsequently determined that the patient had an antibody to a low-frequency antibody [anti-Wr(a)] that was not detected during pre-transfusion testing.

3. **HTR (non-ABO) – *Probable***
   A patient with a history suggestive of a cold autoimmune hemolytic anemia was premedicated and transfused two crossmatch compatible RBC units using a blood warmer. The patient subsequently developed widespread agglutination of RBCs and evidence of a hemolytic transfusion reaction. Findings were consistent with exacerbation of hemolysis after transfusion in a patient with cold autoimmune anemia.

4. **HTR (non-ABO) – *Possible***
   A patient with a history of a warm autoimmune hemolytic anemia was transfused an uncrossmatched RBC unit under emergency release and prior to completion of pre-transfusion antibody identification. She was subsequently determined to have an anti-C and anti-Fy(a), and the transfused unit was C antigen negative, but was Fy(a) antigen positive. The patient had multiple co-morbidities which may have also contributed to the death.

The number of hemolytic transfusion reactions has remained low in recent years, particularly ABO HTRs, where the error is most frequently preventable misidentification of the patient or the patient's sample. 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 4).

Table 4: Antibodies identified in the Hemolytic Transfusion Reactions FY2014 – FY2018

Antibody	FY14 No.	FY15 No.	FY16 No.	FY17 No.	FY18 No.	Total No.
ABO	4	2	4	1	2	**13**
Multiple Antibodies	-	2	-	1	-	**3**
Other**	2	1	-	2	2	**7**
Jk^a	1	-	-	-	-	**1**
Jk^b	-	-	-	-	1	**1**
c	-	1	1	-	-	**2**
C	1	-	-	-	-	**1**
U	-	-	-	1	-	**1**
Fy^a	-	-	-	1	1	**2**
e	-	-	-	1	-	**1**
Wr^a	-	-	-	-	1	**1**
Total	**8**	**6**	**5**	**7**	**7**	**33**

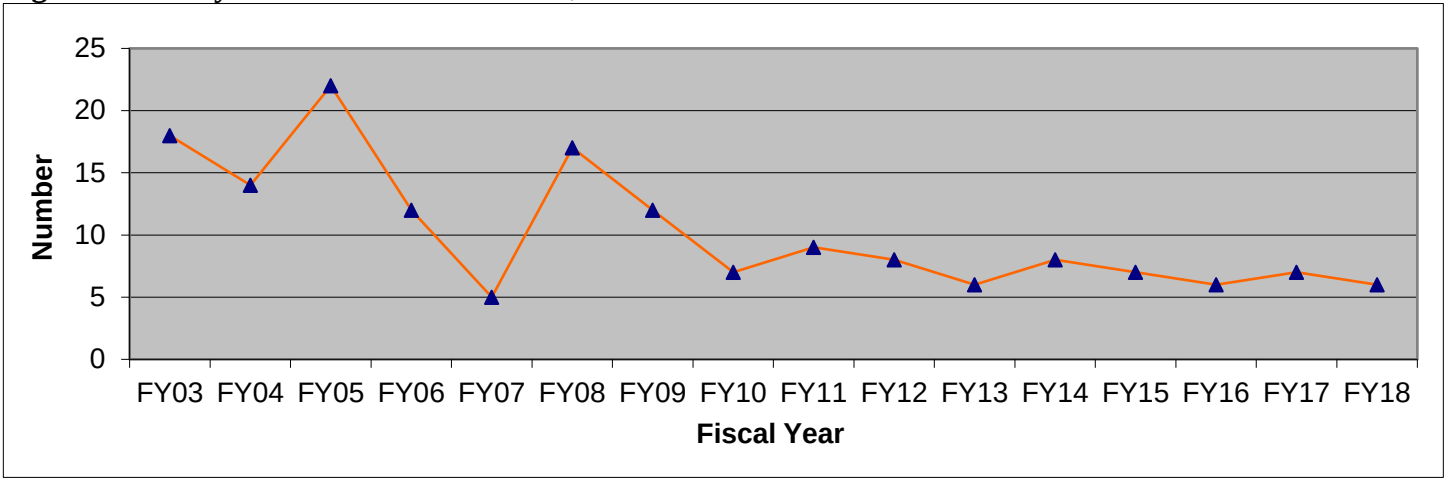
*Multiple Antibodies: FY2015: antibody combinations include: E+K+Jk^a+M+Co^b+Cw**;** C+E+S+Jk^b+Fy^a+Fy^b
FY2017: antibody combinations include: Jk^a+M

**Other: FY2014: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified[41,42]
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
FY2018: 1) The case with anti Jk^b, also demonstrated anti-S and a Hyperhemolysis Syndrome 2) A case of transfused Cold Autoimmune Hemolytic Anemia

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

[42] 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 4 Hemolytic Transfusion Reactions, FY2003 – FY2018



E. Microbial Contamination

In FY2018, there were seven contamination-related fatalities, with six attributed to bacterial contamination, and one attributed to parasitic contamination (Table 5 & 6). The bacterial contamination cases were associated with four apheresis platelet collections (*Staphylococcus aureus* (2), *Acinetobacter pittii*, *Clostridium perfringens*), one associated with red blood cells (*Pseudomonas veronii*), and one associated with multiple products with unknown specific product source (*Pseudomonas aeruginosa*). The parasitic contamination case was associated with red blood cells (*Babesia microti*).

Table 5: Contamination Breakdown, FY2018

Product	Organism	Imputability
Apheresis platelets	*Staphylococcus aureus*	Definite
Apheresis platelets	*Staphylococcus aureus*	Probable
Apheresis platelets	*Acinetobacter pittii*	Definite
Apheresis platelets	*Clostridium perfringens*	Probable
Red Blood Cells	*Pseudomonas veronii*	Possible
Red Blood Cells	*Babesia microti*	Possible
Multiple Products	*Pseudomonas aeruginosa*	Probable

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

2. **Contamination (*Acinetobacter pittii*) - *Definite***
   The patient received an apheresis platelet product and *Acinetobacter pittii* (belonging to *Acinetobacter calcoaceticus-baumannii* complex) was identified in both the product and the patient. No other sources for the contamination were identified, and the patient was not infected with *Acinetobacter pittii* prior to transfusion. Molecular testing confirmed that the strains in the patient and platelet product were related.

3. **Contamination (*Staphylococcus aureus*) – *Probable***
   A patient received an apheresis platelet unit and *Staphylococcus aureus* was identified in the apheresis platelet product and in the patient. Although the patient's underlying condition was a contributing factor, it was probable that the death was due to bacterial sepsis from the implicated product.

4. **Contamination (*Clostridium perfringens*) – *Probable***
   A patient received both splits of an apheresis platelet product, and *Clostridium perfringens* was identified in the product. Blood cultures performed on the recipient were negative, but this was likely due to on-going antibiotic therapy. Although the patient's underlying condition was a contributing factor, it was probable that the death was due to bacterial sepsis from the implicated product.

5. **Contamination (*Pseudomonas aeruginosa*) – *Probable***
   A patient received multiple products including platelets, fresh frozen plasma, and red blood cells. *Pseudomonas aeruginosa* was identified in the patient. Although the blood product containers were unavailable for culture, there was evidence of a temporal association and there were no other notable sources of *Pseudomonas aeruginosa*.

6. **Contamination (*Pseudomonas veronii*) – *Possible***
   A patient received two red blood cell products and *Pseudomonas veronii* was identified in one of the products. The patient's blood cultures were negative; however, this was possibly due to antimicrobial therapy received by the patient. The patient had many underlying comorbidities, therefore imputability of the reaction to death was classified as possibly due to bacterial sepsis from the implicated product.

7. **Contamination (*Babesia microti*) – *Possible***
   A patient received multiple red blood cell products and *Babesia microti* was identified in the patient and in one donor. However, the recipient had multiple co-morbidities and significant clinical deterioration; therefore, imputability of the reaction to death was classified as possibly due to *Babesia microti* from the implicated product.

Staphylococcus aureus was the most frequently identified infectious agent over the past five years (Table 6).

Figure 5 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.[43,44] The WNV infections were associated with both apheresis platelets and thawed plasma.

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

[44]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.

The five *Staphylococcus aureus* infections were associated with transfusion of apheresis platelets. (Figure 5). Recent articles provide additional information about bacterial contamination of platelet products.[45, 46, 47,48]

Figure 6 shows the trend of contamination (bacterial) associated with apheresis platelets from FY 2004 to FY2018. Bacterial contamination of platelet components remains a public health concern which FDA has addressed in a recently published Final Guidance (https://www.fda.gov/media/123448/download) on controlling the risk of bacterial contamination to enhance the safety and availability of platelets for transfusion.[49] Refer to Title 21, Code of Federal Regulations 606.145 for requirements regarding control of bacterial contamination of platelets.

Table 6: Contamination by Implicated Organism, FY2014 - FY2018

Organism	FY14	FY15	FY16	FY17	FY18	TOTAL
Acinetobacter pittii	-	-	-	-	1	**1**
Anaplasma phagocytophilum	-	-	-	1	-	**1**
Babesia microti	-	-	2	-	1	**3**
Clostridium perfringens	-	-	-	2	1	**3**
Coagulase-negative staphylococci	-	1	1	-	-	**2**
Enterobacter aerogenes	-	-	1	-	-	**1**
Enterococcus faecium	-	1	-	-	-	**1**
Klebsiella pneumoniae	-	-	-	1	-	**1**
Pseudomonas fluorescens	-	-	1	-	-	**1**
Pseudomonas veronii	-	-	-	-	1	**1**
Pseudomonas aeruginosa	-	-	-	-	1	**1**
Serratia marcescens	1	-	-	-	-	**1**
Staphylococcus aureus	-	3	-	-	2	**5**
Staphylococcus epidermidis	-	-	-	1	-	**1**
West Nile virus	-	-	-	2	-	**2**
TOTAL	**1**	**5**	**5**	**7**	**7**	**25**

[45]Rollins MD, Molofsky AB, Nambiar A, et al. Two Septic transfusion reactions presenting as transfusion-related acute lung injury from a split

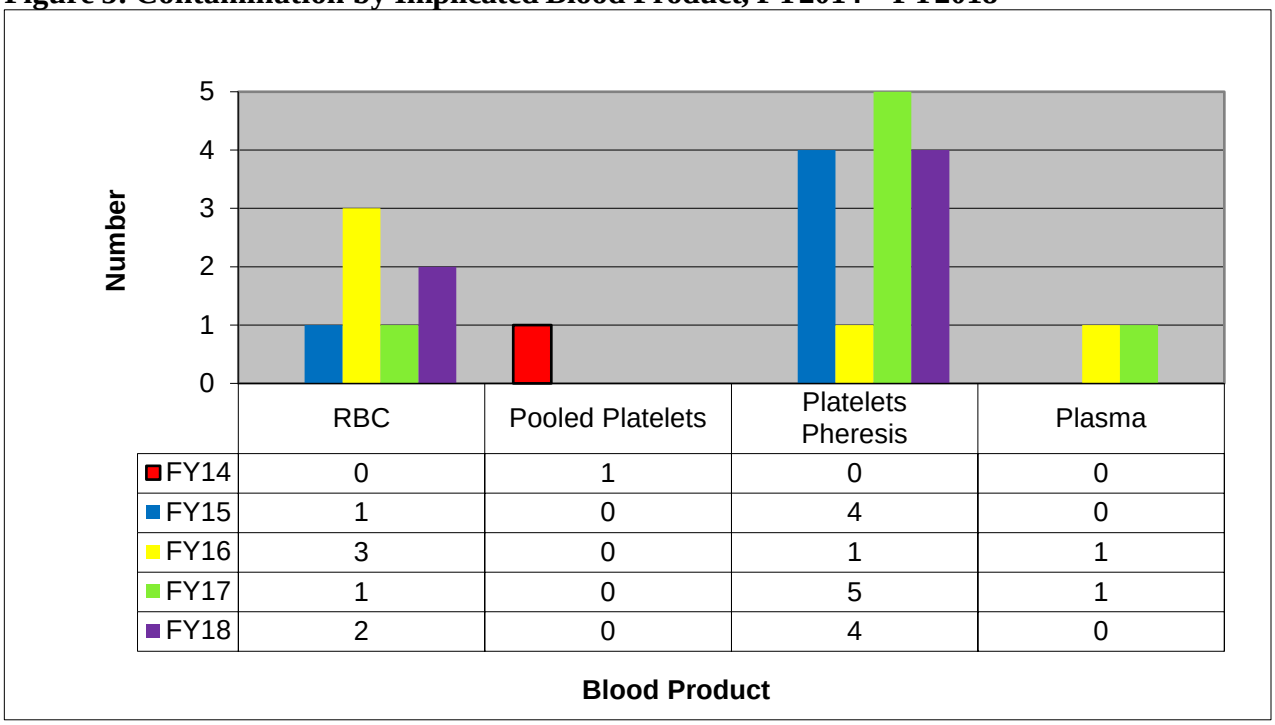
[46]Plateletpheresis unit. Crit Care Med 2012;40:2488-2491.

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

[48]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.

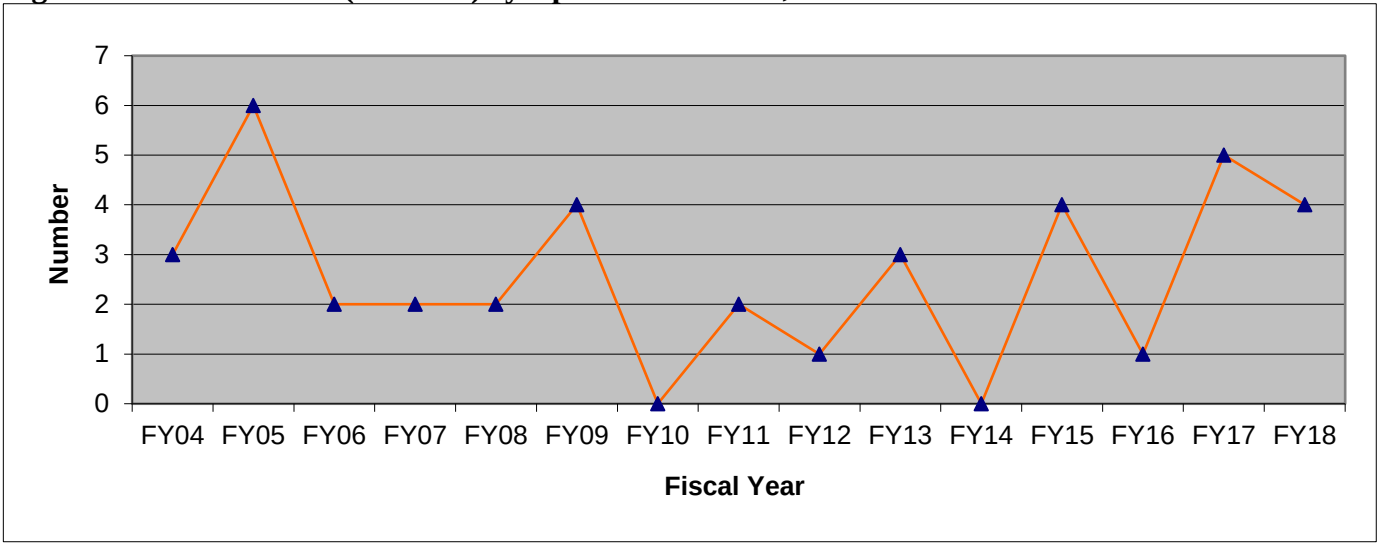
[49]Hong et al., Blood 2016.28;127:496-502.

Figure 5: Contamination by Implicated Blood Product, FY2014 – FY2018



Red Blood Cells microorganisms: *B. microti (3), P. fluorescens (1), E. faecium (1), Anaplasma phagocytophilum (1), P. veronii (1)*
Pooled Platelets microorganisms: *S. Marcescens (1)*
Plasma: (TPE) coagulase-negative staphylococci (1), (thawed plasma) West Nile Virus (1)
Platelets Pheresis microorganisms: *S. aureus (5), S. epidermidis (1),* coagulase-negative staphylococci *(1),* West Nile virus *(1), A. pitti (1), E. aerogenes (1), K. pneumoniae (1), C. perfringens (3)*
Multiple products (specific product source unknown): *P. aeruginosa (1)* (not included in figure)

Figure 6: Contamination (bacterial) by Apheresis Platelets, FY2004 – FY2018



F. Transfusion Doubtful as Cause of Death

We classified 11 (21%) of the 51 cases described earlier as potentially associated with transfusion recipient fatalities in FY2018 as *doubtful*, including one anaphylaxis case, one HTR (non-ABO), one Possible TRALI, two TACO cases, one Transfusion Reaction, Type Not Determined, and five Unlikely Transfusion Reaction cases. 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.E.

G. Transfusion Not Assessable as Cause of Death

We classified one (2%) of the 51 cases described as potentially associated with transfusion recipient fatalities in FY2018 as *not assessable*. In this case, there was insufficient information submitted/available to determine the type of reaction and the extent of the relation between the transfusion and the death. Thus, this reported fatality was also not included in the analysis in Sections III.A through III.E.

H. Transfusion Ruled Out as Cause of Death

We classified 8 (16%) of the 51 cases described as potentially associated with transfusion recipient fatalities in FY2018 as *ruled out*. 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.E.

I. Donation Fatalities

The processes of blood and plasma donation are generally safe and determining that a causal link exists between a donation and the fatality remains uncommon among reported donation fatalities. For FY2018, there were no donation fatalities classified as *definite* or pr*obable,* and there were four donations classified as *possible.* There were five donation fatalities classified as *doubtful,* nine donation fatalities classified as *ruled out,* and one donation fatality classified as *not assessable* (Table 7).

- **Donation – *Possible***
  There were four fatalities following 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***
  There were four fatalities following Source Plasma donations and one fatality following Whole Blood donation, in which the relationship between the donation and subsequent death was classified as *doubtful.* In these five 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 – *Ruled Out***
  There were nine fatalities following Source Plasma donation in which the donations were classified as *ruled out.* 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 Assessable***
  There was one fatality following Source Plasma donation in which the donation was classified as *not assessable*. 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, FY2018

DONATION TYPE	Definite	Probable	Possible	Doubtful	Ruled Out	Not Assessable	TOTAL REPORTS
Source Plasma	-	-	4	4	9	-	**17**
Whole Blood	-	-	-	1	-	1	**2**
Apheresis Platelets	-	-	-	-	-	-	-
Apheresis Red Cells	-	-	-	-	-	-	-
Total	**-**	**-**	**4**	**5**	**9**	**1**	**19**

The Row Header refers to Imputablility to Death

The changes in our review and classification process presented a challenge in terms of comparing FY2015 through FY2018 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, nor did the available evidence support a causal relationship between the donation and the donor's death.

For FY2018, the cases classified as *doubtful*, and *not assessable* would most accurately compare to the *donation not ruled out* cases from previous years (Table 8).

Table 8: Donation "Not Ruled Out" by Product, FY2014- FY2018*

Donated Product	FY14	FY15	FY16	FY17	FY18	TOTAL REPORTS
Source Plasma	4	12	5	6	4	**31**
Whole Blood	1	1	2	1	2	**7**
Apheresis Platelets	1	1	0	0	0	**2**
Apheresis Red Blood Cells	-	-	1	0	0	**1**
Total	**6**	**14**	**8**	**7**	**6**	**41**

*FY2015 - FY2018 numbers include *doubtful* and *not assessable.*

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*, and *not assessable* in FY2014 to FY2018. These reported donation fatality cases have been classified in years past as *donation ruled out* (Table 9).

Table 9: Donation "Ruled Out" by Product, FY2014-FY2018*

Donated Product	FY14	FY15	FY16	FY17	FY18	TOTAL REPORTS
Source Plasma	2	4	3	5	9	**23**
Whole Blood	-	1	-	-	-	**1**
Apheresis Platelets	-	-	-	-	-	**-**
Apheresis Red Blood Cells	-	-	-	-	-	**-**
Total	**2**	**5**	**3**	**5**	9	**24**

*FY2015 - FY2018 numbers include *ruled out*.