

**SUMMARY OF THE 2017 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS
FOR BLOOD AND BLOOD COMPONENTS
(DATA COLLECTED FROM 01/01/2016 TO 31/12/2016)**

1. EXECUTIVE SUMMARY

Blood transfusion is an essential medical procedure supporting many different healthcare specialities across the European Union (EU), with millions of EU citizens receiving donated blood and blood components every year. However, the use of any substance of human origin carries some risk, notably the possible transmission of diseases from the donor. These risks can be controlled and minimised by the application of a comprehensive set of safety and quality measures such as are laid down in the EU Blood legislation. Despite these measures, rare adverse outcomes can occur, and in line with the legislation¹, these must be monitored and reported at national and EU level through vigilance and surveillance programmes.

Since 2008, in line with obligations defined in the legislation², the EU Member States, Iceland, Liechtenstein and Norway have submitted to the European Commission (hereinafter referred to as the Commission) annual vigilance reports on the notification of Serious Adverse Reactions (SAR) which occur in recipients of blood and blood components and Serious Adverse Events (SAE) which occur in the chain from donation to clinical application.

The Commission works with national Competent Authorities to verify the consistency and clarity of the information submitted on Serious Adverse Reactions and Events (SARE) and to improve the data collection procedure. The completeness and comparability of the data collected in the blood field has improved over time. The SARE exercise has also facilitated the development and consolidation of the Member States' national vigilance programmes.

This report summarises the data submitted by the Member States during 2017, for the year 2016, and assesses the data in light of the information submitted in previous years.

Some key results of the 2017 reporting exercise are:

- Overall, 30 countries (28 EU Member States, Iceland and Norway) reported in the SARE annual exercise. Of these, 24 countries indicated receiving complete data from their reporting establishments³. This is an increase compared to the previous exercise, showing the great efforts made by parties, improving the accuracy and completeness of reported data.

¹ Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.

² Article 8 of Directive 2005/61/EC provides that Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events (SARE) received by the competent authority using the formats in Part D of Annex II and C of Annex III.

³ Article 1 of Directive 2005/61/EC defines a "reporting establishment" as "the blood establishment, the hospital blood bank or facilities where transfusion takes place that reports serious adverse reactions and/or serious adverse events to the competent authority".

- In relation to the number of units issued for transfusion and/or transfused⁴, 24.8 million units of blood or blood components were reported by 29 countries. Partial data reported by 20 countries indicated that over 3 million patients were transfused (3.13 million).
- Concerning SAR in recipients, 1,737 cases were reported for 2016 with imputability level 2 or 3 (likely or certain to have been caused by the transfusion), which are the focus of further analysis in this report. The total number of SAR has slightly increased compared with previous exercises. Anaphylaxis, transfusion-associated circulatory overload and febrile non-haemolytic transfusion reaction were the most frequent SAR.
- The results also show that there were 16 deaths likely or certainly resulting from blood transfusions in 2016. Compared with previous exercises this number has moderately decreased. It is worth noting that the majority of deaths were not directly attributable to the quality and safety of blood components, but rather to clinical practice or to unforeseeable reactions.
- Concerning SAE, which amounted to 2,599 cases for 2016, the reported figures have also slightly increased compared to those of the previous year. Most of the SAE occurred due to human error (73%). This fact emphasises the importance of root-cause analysis to determine the best measures to avoid the repetition of SAE. It should also be mentioned that SAE reporting rates vary considerably between countries.

The reports submitted by 23 of the countries included information not only on recipients but also donors, for whom 7,658 reactions were reported on a voluntary basis. It is important to collect these data and to further assess the underlying causes in order to better protect those citizens who volunteer to donate blood and thus make transfusion possible.

Before publishing the summary report, the data contained in this report was presented at the meeting of the Competent Authorities for Blood and Blood Components in February 2018. This gave the reporting countries the opportunity to interact and share experience and knowledge on haemovigilance, hence supporting the development of their national systems and improving the safety of blood transfusion.

2. DATA COLLECTION METHODOLOGY

This document provides a summary report of the data collected during 2016 (from 1st January to 31st December) and submitted to the Commission in 2017 by Iceland, Norway and all EU Member States. It also includes a comparison with the data from previous years and draws general conclusions. The Commission provided the following tools to the participating authorities to promote a standardised approach to data reporting:

⁴ It should be taken into account that in the data from 2 countries, only the units reported as transfused have been included. It is evident that the number of units transfused must also have been issued prior to transfusion.

- 1) An electronic reporting template to be sent to a DG SANTE hosted database. The electronic reporting template used in 2017 (for 2016 data) was version 2.5.7;
- 2) The Common Approach document for the definition of reportable SAR and SAE (“Common Approach”) attached to the electronic reporting template. The aim of the document, although not legally binding, is to provide guidance to Member States when reporting. First published in 2008, the Common Approach has been regularly updated to clarify points of ambiguity and inconsistency. This has in turn resulted in a gradual increase in the quality and accuracy of the data collected from the Member States. In 2017, version 5.3 of the Common Approach document was available to those countries reporting 2016 SARE data.

In December 2017 a service contract agreement was signed between the Commission and the Council of Europe/European Directorate for the Quality of Medicines and HealthCare (EDQM) to carry out the verification and analysis of the 2017 SARE exercise. Therefore, since the beginning of 2018, the EDQM started contacting reporting countries when needed in order to clarify and verify the accuracy of the data, and performed the detailed analysis of the information presented in this report.

3. MAIN FINDINGS OF THE 2016 DATA COLLECTION

3.1. General comments

For the 2017 exercise (data reported in 2016), the electronic reporting template was unchanged. A revised version of the Common Approach document had been developed by the Commission, together with experts of the Vigilance Expert Sub-group.

Country reports were received from all 28 EU Member States, Iceland and Norway, comprising aggregated data from 4,118 reporting facilities. Not all countries provided complete data on all denominators (i.e. blood units issued, blood units transfused and number of recipients), raising questions about the availability and accuracy of the data. Despite this, denominator data have improved overall in comparison with previous exercises.

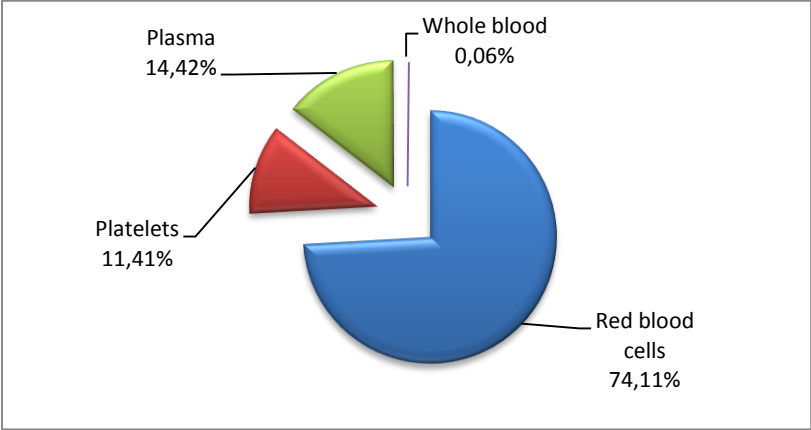
Regarding data completeness, 24 countries reported receiving complete data, 5 countries received 80-98% of the expected data and one received 29%. Although data quality has continued to improve, the data presented here are considered partial and still do not represent the entire picture. Therefore, conclusions should be interpreted with caution.

The data were presented at the February 2018 meeting of the Competent Authorities for Blood and Blood Components. Additionally, clarification and verification of the data between the EDQM, the Commission and Member States was carried out on various occasions.

3.2. Denominators

All 28 EU Member States, Iceland and Norway submitted replies to the questionnaire, thereby complying with the annual report submission requirement established by Article 8 of Directive 2005/61/EC.

As regards the **units of blood components issued**, 27 Member States (AT, BE, BG, CY, CZ, DE, DK, EE, EL, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK and UK) provided data. Two of the remaining countries (ES and NO) did not report the number of units issued, but did provide the number of units transfused. As all units transfused must have first been issued, their numbers for units transfused have been included in the total number of units reported issued. A total of 24,827,516 units of blood and blood components were reported as issued in 2016. Figure 1 shows the breakdown of units issued by component type (including the transfused data from ES and NO).

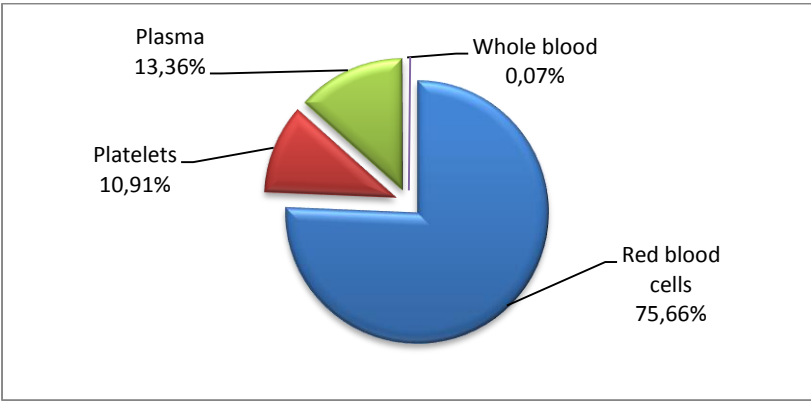


Component type	Units issued
Red Blood Cells	18,399,866
Platelets ⁵	2,833,635
Plasma	3,578,993
Whole blood	15,022
Total	24,827,516

Figure 1: Units issued⁶ (per blood component); data 2016.

Twenty-eight countries (all but DK, HU) also provided the total number of whole blood collections made during the year, amounting to 18,213,325, and the number of apheresis collections, amounting to 5,524,877, similar to the numbers provided in previous exercises.

Concerning the **units of blood components transfused**, there were 20,910,579 units reported as transfused by EU and EEA countries. It should be noted that this is not the total number of units transfused, as only 25 countries (AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FR, HR, IE, IT, LT, LU, LV, MT, NL, PT, RO, SE, SK, UK and NO) reported this figure for at least one blood component. The data for units transfused per blood component are shown in Figure 2.

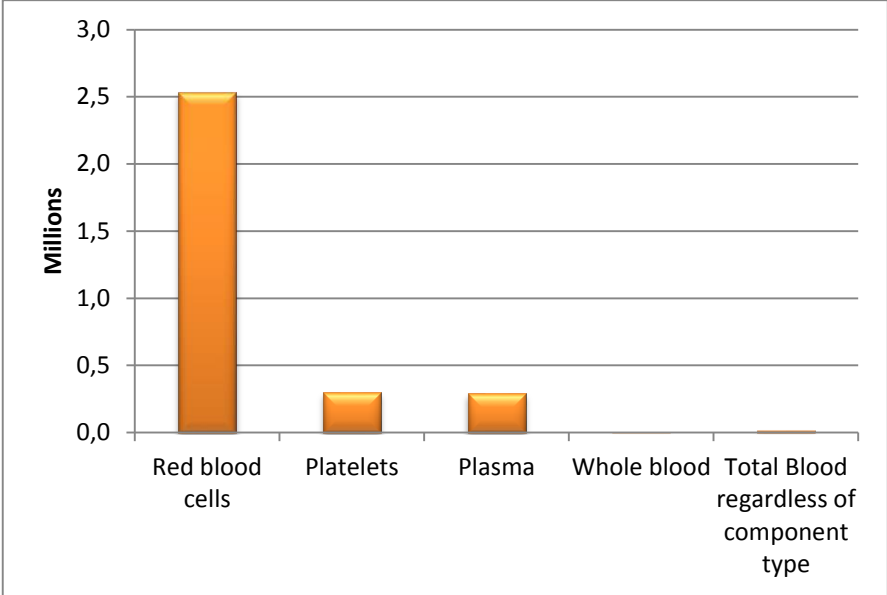


Component	Units transfused
Red Blood Cells	15,820,902
Platelets ⁵	2,280,838
Plasma	2,794,554
Whole blood	14,285
Total	20,910,579

Figure 2. Units transfused (per blood component); data 2016.

⁵ Note that one platelet unit is normally prepared from several donations.
⁶ Including data on units transfused from ES and NO.

Regarding **recipients transfused**, 3,134,944 patients were transfused in 2016 according to the reports. These are partial figures provided by 20 countries (AT, BE, BG, CY, CZ, EE, ES, FR, IS, IE, IT, HR, LT, LU, MT, NL, PT, RO, SE and UK) which reported the number of recipients transfused by blood component type. The breakdown of the transfused recipients is shown in Figures 3 and 4.



Component	Recipients transfused
Red Blood Cells	2,533,837
Platelets	297,732
Plasma	289,922
Whole blood	1,656
Total blood regardless of component type ⁷	11,797
Total	3,134,944

Figure 3. Recipients transfused (per blood component) in millions; data 2016.

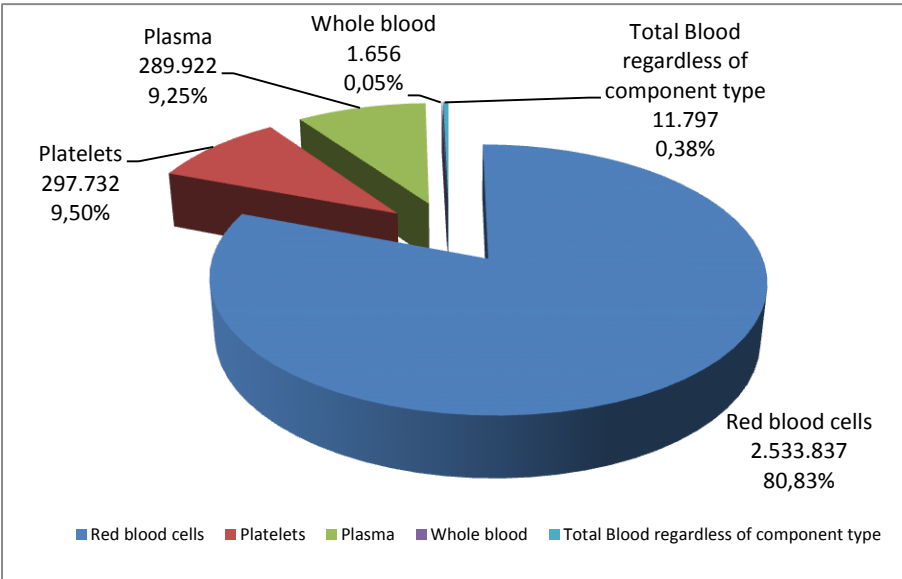


Figure 4. Recipients transfused per blood component; data 2016.

⁷ Two countries were not able to provide the number of recipients transfused per type of component, but provided the total number of patients transfused regardless of the type of component.

3.3. Serious Adverse Reactions

3.3.1. Information by country

In 2016, a total of 2,950 SAR with imputability level of 1 to 3 were reported in the exercise. Seven countries (EE, ES, IT, LU, LT, RO and SE) did not report any SAR of imputability level 1.

Directive 2005/61/EC provides that reporting establishments notify to the Competent Authority all relevant information about SAR of imputability level 2 or 3⁸. Further analysis of SAR in this report relates only to the reporting of SAR at imputability levels 2 and 3. During 2016, a total of 1,737 SAR at imputability level 2 or 3 were reported. Of those, 16 resulted in death.

For the 30 countries that provided data for the number of SAR and units transfused per blood component, there were 11,847 units transfused per SAR imputability level 2 or 3.

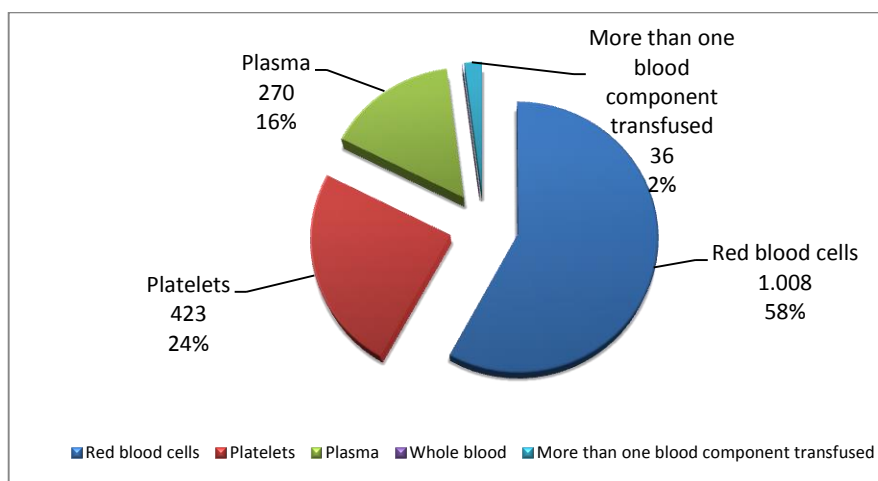
These figures should also be interpreted with caution as many reports are still partial and differences between countries do not necessarily indicate a safer system. In fact, a higher number of SAR reported may indicate a more reliable and accurate reporting system, and a lower number of SAR may indicate underreporting.

3.3.2. Information by blood component

Of the 1,737 SAR of imputability level 2 or 3 reported:

- 1008 SAR were related to **red blood cells**,
- 423 SAR were related to **platelets**,
- 270 SAR were related to **plasma**, and,
- 36 SAR were related to **more than one blood component**.

Figure 5 shows the percentage of SAR and number of units transfused per blood component.



Component type	Units transfused per SAR
Red Blood Cells	15,405
Platelets	5,308
Plasma	10,337

Figure 5. Percentage of SAR per blood component and units transfused per SAR.

⁸ Where it is likely or certain that the reaction is attributable to the blood or blood component. Article 5, para 3a of Directive 2005/61/EC.

3.3.3. Information by category of SAR

The 1,737 SAR (inputability level 2 or 3) reported were classified as follows:

- Anaphylaxis/hypersensitivity: 703 cases
- Febrile non-haemolytic transfusion reaction (FNHTR): 404 cases
- Transfusion-associated circulatory overload (TACO): 222 cases
- Immunological haemolysis: 172 cases, of which
 - 60 cases due to ABO incompatibility and
 - 112 cases due to other alloantibodies
- Delayed haemolytic reaction: 7 cases
- Transfusion-associated dyspnoea (TAD): 44 cases
- Transfusion-related acute lung injury (TRALI): 54 cases
- Transfusion-transmitted infections: 21 cases, of which
 - 12 bacterial infections, and
 - 9 viral infections, of which 7 were hepatitis E and 2 hepatitis B virus respectively.
- Hypotension: 6 cases
- Non-immunological haemolysis: 9 cases
- Post-transfusion purpura: 6 cases
- Acute haemolytic transfusion reaction: 1 case
- Other: 88

The percentage of SAR per category is shown in Figure 6.

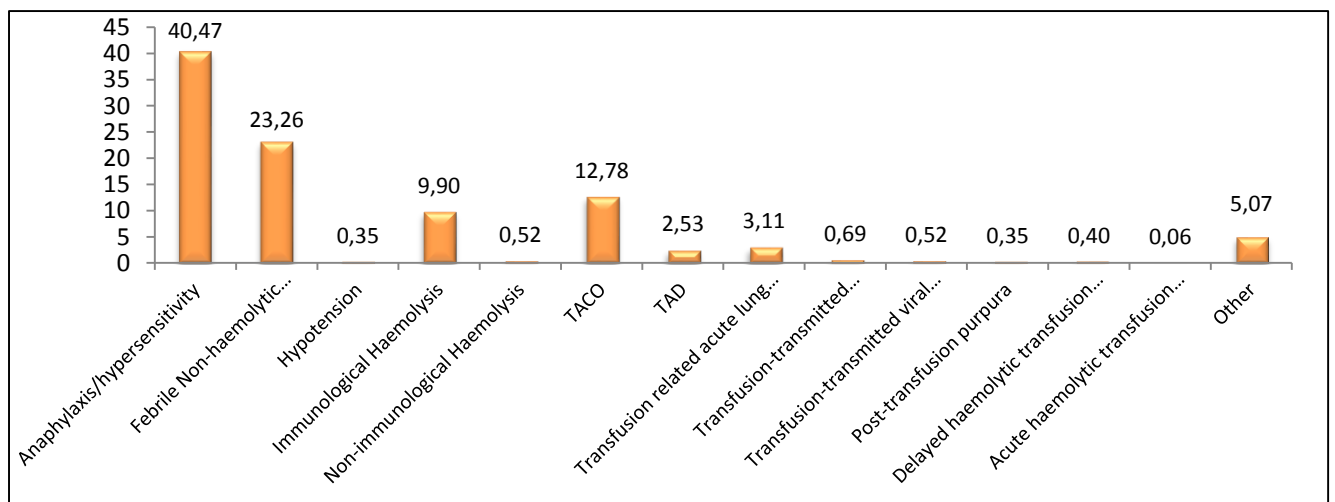


Figure 6. Percentage of SAR per category; data 2016.

3.3.4. Recipient deaths

Over the 1,737 cases of SAR reported, there were 16 deaths, as follows:

- 1 was associated with immunological haemolysis due to ABO incompatibility associated with red blood cell transfusion. This number represents 6.25% of all reported deaths.

- 8 were associated with TACO following red blood cell transfusion. This number represents 50% of all reported deaths.
- 1 was associated with TRALI following platelet transfusion. This number represents 6.25% of all reported deaths.
- 2 were associated with bacterial transmission, 1 following red blood cell transfusion and 1 following platelet transfusion. This number represents 12.5% of all reported deaths.
- 2 were associated with anaphylaxis/hypersensitivity. This number represents 12.5% of all reported deaths.
- 1 was associated with viral transmission (HEV) following platelet transfusion. This number represents 6.25% of all reported deaths.
- 1 was reported under the “other” category, following the transfusion of platelets. This number represents 6.25% of all reported deaths.

It should be highlighted that even though Directive 2005/64/EC does not require to provide data concerning serious adverse reactions of imputability 1, nine countries voluntarily reported 28 deaths within this level. Imputability 1 considers that evidence is indeterminate for attributing adverse reaction either to the quality and safety of blood and blood components or to alternative causes. Although these are partial data, and should be interpreted with caution, it was deemed appropriate to include them within this section, as safety of the transfused patients is considered paramount for the Commission and all reporting countries.

The United States Food and Drug Administration (FDA) publishes an annual summary of “Fatalities reported to FDA following blood collection and transfusion”⁹. The statistics provided in that report allow some broad comparisons to be made with the annual vigilance reports on SARE submitted by EU and EEA countries to the Commission. During 2016, there were 60 transfusion-related fatalities reported to the FDA. TRALI and TACO caused the highest number of reported fatalities, followed by anaphylaxis and contamination. In Europe, the information submitted in the SARE reporting exercise for 2017 (data from 2016) shows similar conclusions; the highest number of deaths related to the transfusion of blood and blood components was due to TACO, followed by anaphylaxis/hypersensitivity and transmission of bacterial infection.

3.3.5. SAR in donors

Twenty-three countries (AT, BE, BG, CY, CZ, DE, DK, EE, FI, FR, HR, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, SK and UK) reported, on a voluntary basis, a total of 7,658 SAR in donors.

A subset of countries also provided additional information to the Commission on SAR in donors. Based on these reports, it can be seen that many of the reactions in donors were related to blood vessel and nerve injuries, vasovagal episodes or cardiovascular reactions.

It should be noted that there is considerable variability between countries in the reporting of SAR in donors, with one country reporting 50% of the total. However, in contrast to SAR in recipients,

⁹ Annual summary for 2016: “Fatalities reported to FDA following blood collection and transfusion” <https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM598243.pdf>

countries are not requested to report the imputability level of SAR in donors and, as stated above, there is no legally binding requirement to report this denominator. Therefore, there are no homogeneous criteria for reporting.

3.4. Serious Adverse Events

3.4.1. Information by country

SAE were reported by 30 countries; the total number of SAE reported for 2016 was 2,599. It should be noted that nine countries (BG, CY, HU, IS, LT, LU, MT, RO and SK) reported that in 2016 there had been no reportable SAE.

It is worth noting that the number of SAE reported varied substantially between reporting countries, both in terms of rates and the criteria for inclusion. For instance, two countries submitted 62% of all SAE whereas 7 countries reported less than 10 SAE each. This suggests that further improvements should be made to the reporting criteria, with the collaboration of the Competent Authorities, to achieve a greater comparability of data.

As regards the denominator for SAE, the total number of units processed, 28 countries (all but DK, and HU) reported a total of 25,177,727 units processed during 2016.

3.4.2. Information by type of SAE

Overall, of the 2,599 SAE reported, incidents were linked to the following activity steps:

- **Whole blood collection:** 611 SAE (24 %)
- **Apheresis collection:** 55 SAE (2 %)
- **Testing of donations:** 78 SAE (3 %)
- **Processing:** 63 SAE (2 %)
- **Storage:** 267 SAE (10 %)
- **Distribution:** 298 SAE (12 %)
- **Materials:** 23 SAE (1 %)
- **Other activity steps:** 1024 events (46 % of reported SAE).

These data are presented in Figure 7.

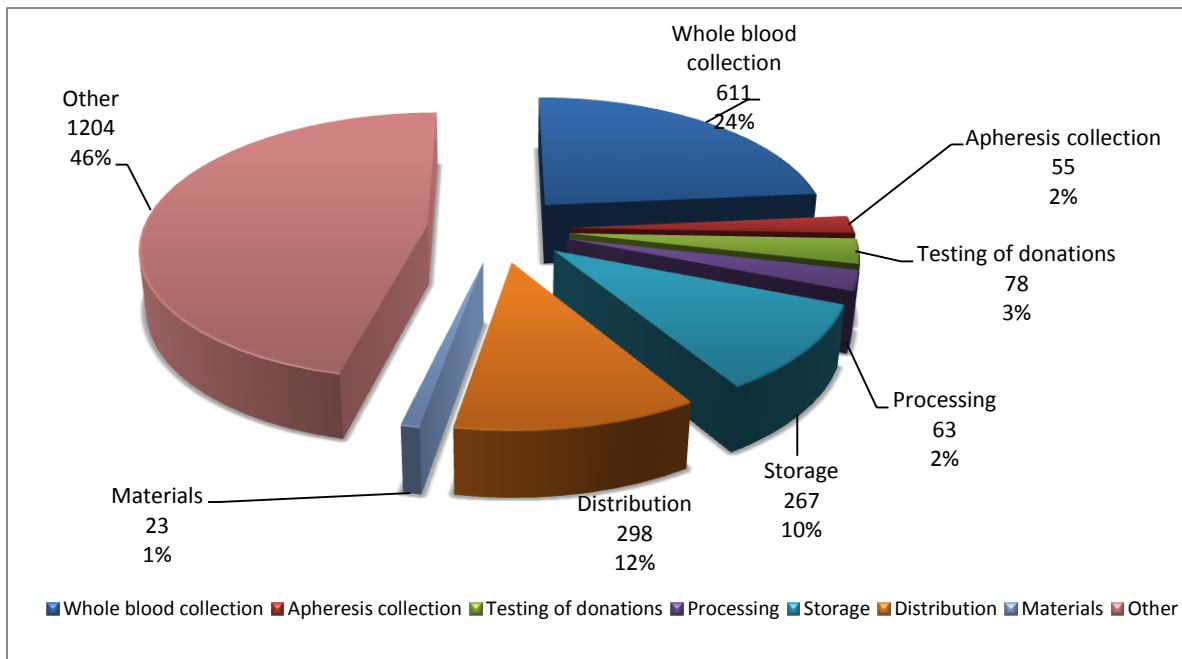


Figure 7. SAE per activity step; data 2016.

3.4.3. Information by specification of SAE

The 2,599 SAE were attributed to one of the following specifications:

- **Human Error:** 1,896 SAE (73%)
- **Equipment failure:** 387 SAE (15%)
- **Product defect:** 128 SAE (5%)
- **Other:** 188 SAE (7%)

These data are shown in Figure 8.

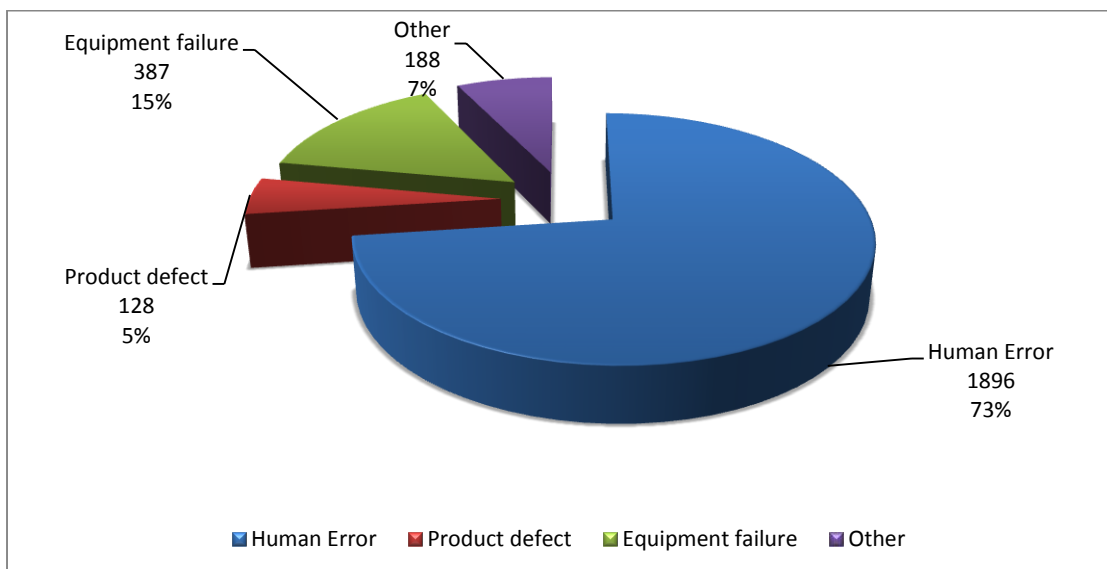


Figure 8. SAE by specification; data 2016.

Most of the SAE (73%) were reported within the category of *Human error* without any further detail, and the process step most associated with SAE was the *Other* category. In order to facilitate improvement through learning from vigilance, consideration should be given to gathering more information in future exercises.

4. COMPARISON OF SARE REPORTING 2011-2016

Table 1 gives an overview of SARE reporting for 2011 to 2017 (data from 2010 to 2016).

In general, the numbers for each denominator have fluctuated from year to year: 23–25 million units issued, 12–21 million units transfused (with a slight decrease in the current exercise) and 2–4 million recipients transfused, which has also slightly decreased this year.

The number of SAR (at imputability level 2 or 3) reported increased from 2011 to 2014 (data from 2010 to 2013), decreased during the next 2 years, and now remains stable. The same trend occurs for SAR of imputability 1 to 3. This reflects the efforts made by all participating countries to implement and improve their biovigilance systems year by year.

The number of deaths has remained relatively stable, at around 20, with a slight decrease in recent years, showing the efficacy of the preventive measures implemented in the different systems.

For SAE, the numbers reported have varied over the years; this is probably the result of improved reporting by establishments and better training and education of staff involved in the process.

Finally, although SAR in donors is voluntarily reportable, the number has increased over the years, reflecting the increased awareness among countries about the safety of the EU citizens who voluntarily decide to donate their blood in order to save others.

	2011		2012		2013		2014		2015		2016		2017	
	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number
Units issued	26	22,817,166	29	24,821,809	27	25,129,344	27	24,043,766	27	25,717,028	26	25,324,888	29 ¹⁰	24,827,516
Units transfused	19	16,718,258	17	12,311,691	20	13,351,948	22	16,564,817	25	21,425,047	25	21,443,125	25	20,910,579
Recipients transfused	11	2,298,304	16	2,964,839	19	3,595,155	20	3,216,938	18	4,190,835	18	4,246,978	20	3,134,944
SAR (1-3)	30	2,449	30	3,133	30	3,519	30	2,831	30	2,441	31	2,587	30	2,950
SAR (2-3)	30	1,259	30	1,574	30	1,831	30	1,739	30	1,410	31	1,349	30	1,737
SAR death (2-3)	30	20	30	14	30	22	28	22	30	27	31	25	30	16
SAE	28	16,360	25	4,113	28	2,953	30	2,972	30	4,460	24	2,338	30	2,599
SAR in donors					18	2,494	23	2,470	20	3,723	23	7,769	23	7,658

Table 1. Overview of the 2011-2017 SARE reporting exercises (2010-2016 data).

¹⁰ This figure includes the data of the 2 countries that reported only number of units transfused. It was considered that the number of units transfused must also have been issued prior to transfusion.

5. CONCLUSIONS

In the SARE 2017 annual reporting exercise, complete data was provided by 80% of the reporting countries (i.e. 24 out of 30). This represents a steady state improvement in reporting by Member States compared to previous years. It also reflects the continuous work by the EDQM and the Commission to improve data collection, to assist those countries which have difficulties in collecting reliable data and to improve the data analysis.

The *number of SAR* in recipients (imputability level 2 or 3) reported for 2016 was 1,737. Anaphylaxis, TACO and FNHTR were the most frequent SAR. This figure has slightly increased in comparison with the previous reporting exercise. The majority of the SAR were related to the transfusion of red blood cells and platelets. However, as mentioned in previous exercises, considering that the data reported are partial, year-on-year comparisons should be interpreted with caution.

The *number of deaths* likely or certain to have resulted from blood transfusion in 2016 was 16. This figure has decreased compared with previous years. It should be noted that of the 16 deaths reported, the majority were not attributable to the quality and safety of the blood component, but rather to clinical practice or to unforeseen reactions including TACO and anaphylaxis/hypersensitivity.

In the case of *number of SAE*, the reported figures have increased compared with previous exercises. It should be noted that, on an individual Member State basis, a higher number of reported SAE may not necessarily imply an increased incidence of SAE but rather indicate a more reliable and accurate reporting system whereas a lower number may indicate underreporting. The large number of SAE reported as due to human error calls for a word of caution and highlights the importance of performing root-cause analysis to determine the ultimate cause of these SAE and to implement adequate preventive and corrective measures.

The process step most associated with SAE was within the *Other activity steps* category. Reporting of SAE has revealed that there is a need to further clarify and improve the collection of SAE data overall to ensure that the reporting criteria are consistently applied.

Voluntary reporting on donors, which was introduced in 2012 and undertaken by a majority of countries in this reporting exercise, highlights a significant increase in reported SAR *in donors* from 2,494 in 2013 to 7,658 in 2017 (see table 1); (see table 1). Performing this exercise has allowed Member States to increase awareness of the importance of monitoring the safety and quality of care of those persons who make transfusion medicine possible. The availability of these data provides the opportunity for further assessment of the underlying reasons for donor reactions and for the implementation of preventive measures to reduce them, assuring the safety of those EU citizens who generously decide to help others by donating blood.

Overall, the available data indicate that reporting is consistent with known effects and expected trends, with no new safety concerns regarding blood and blood components identified from national monitoring programmes.

Since 2016, through a service grant agreement signed with the Commission, the EDQM is carrying out the verification and analysis of the blood and tissues and cells SARE exercises and drafting the final summary reports. Due to the expertise of the EDQM in the field of biovigilance and with international data collection activities, this collaboration has greatly contributed to improving the EU SARE exercise by helping refine the Common Approach document and reporting templates, increasing the quality of the data reported by the Member States through extensive data curation and verification and going deeper into the data analysis and interpretation.

In January 2017, a Vigilance Expert Sub-Group (a subgroup of the Competent Authorities on Substances of Human Origin Expert Group) was established by the Commission. This group was created with the aim of supporting the development and improvement of the SARE reporting system. The work of the Sub-Group has helped to improve and harmonise the exercise and support the development of national SoHO vigilance systems. The resulting outcomes of this work will contribute not only to the improvement of the SARE exercise and the development of vigilance systems in the Member States but also to the ongoing evaluation by the Commission of the legal frameworks on blood, tissues and cells.¹¹

Finally, at European level the SARE exercise has allowed Member States to share experience and knowledge on haemovigilance. Individual countries should continue to use this exercise to evaluate the safety of their national blood sectors and to identify where issues occur and need to be addressed in order to improve the safety and quality of blood components across the EU.

¹¹ https://ec.europa.eu/health/blood_tissues_organ/policy/evaluation_en