Report on Notifications Pursuant to §21 German Transfusion Act for 2008 and 2009

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Keywords

Blood donations · Erythrocyte concentrates · Plasma for fractionation · Blood coagulation factors · Supply situation

Summary

This report contains the data collected in 2008 and 2009, pursuant to Section 21 German Transfusion Act as well as an overview of the supply situation during the last 10 years. In 2009, blood donation services reported a total of 7.5 million donations – the largest amount since 2000. At the same time, more than 4.7 million red blood cell (RBC) concentrates and more than 500,000 platelet concentrates were available. The number of therapeutic single plasma units decreased to 1.1 million units in 2009. The loss rate for RBC concentrates is still between 3 and 4% for the users while for the manufacturers it has decreased slightly to 1.4%. The loss rate, for platelet concentrates, on the other hand, increased in 2009, especially – what is noteworthy – for manufacturers of pooled platelet concentrates. The loss rate for apheresis platelet concentrates accounted for 5.2% compared to 17.5% for pooled platelet concentrates. As far as the users were concerned, loss rates for platelet concentrates largely remained unchanged with rates between 5 and 6%. Based on the data collected, the supply with blood components for transfusion can be regarded as assured. Nearly 2.9 million l of plasma for fractionation were collected in Germany in 2009. According to reports from the pharmaceutical industry, out of these, 2.6 million l remained on the German market, out of which only 56% were fractionated in this country. Many plasma derivatives are not manufactured in Germany, despite the large amounts of plasma collected. The supply with these products, however, is assured by imports. Overall, 16,409 autologous and 9,435 allogeneic stem cell preparations were manufactured in 2009, out of which 3,382 allogeneic preparations were exported. 3,181 autologous and 2,374 allogeneic preparations were transplanted; 187 of these products from imports. The large number of exported stem cells and the small number of imported ones suggest that no serious shortages are to be expected for the supply with these products.

Schlüsselwörter

Blutspenden · Erythrozytenkonzentrate · Plasma zur Fraktionierung · Gerinnungsfaktoren · Versorgungslage

Zusammenfassung

Dieser Bericht enthält die nach §21 Transfusionsgesetz erhobenen Daten der Jahre 2008 und 2009 sowie Auswertungen zur Versorgungssituation im Verlauf der letzten 10 Jahre. Die Blutspendedienste meldeten im Jahr 2009 insgesamt 7,5 Millionen Spenden – die größte Zahl seit dem Jahr 2000. Damit einhergehend wurden auch mehr Erythrozyten- und Thrombozytenkonzentrate (EK, TK) hergestellt; jeweils über 4,7 Millionen EK und mehr als 500 000 TK standen 2008 und 2009 zur Verfügung. Die Zahl der therapeutischen Einzelplasmen ist wieder gesunken auf 1,1 Millionen Einheiten im Jahr 2009. Die Verfallsrate von EK bei den Anwendern liegt nach wie vor zwischen 3 und 4%, bei den Herstellern ist sie leicht gesunken auf 1,4%. Dagegen stieg die Verfallsrate bei den TK, besonders auffällig bei den Herstellern von Pool-TK im Jahr 2009. Einem Verfallsanteil von 5,2% der Apherese-TK standen 17,5% verfallene Pool-TK gegenüber. Bei den Anwendern verliefen weitgehend unverändert zwischen 5 und 6% der TK. Auf Basis der erhobenen Daten kann die Versorgung mit Blutkomponenten zur Transfusion als gesichert angesehen werden. Fast 2,9 Millionen l Plasma zur Fraktionierung wurden 2009 in Deutschland gesammelt. Laut den Meldungen der pharmazeutischen Industrie verblieben davon rund 2,6 Millionen l auf dem deutschen Markt, wovon lediglich 56% hierzulande verarbeitet wurden. Über den Verbleib der restlichen Menge kann keine Aussage getroffen werden. Viele Plasmaderivate werden, trotz der großen Menge zur Verfügung stehenden Plasmas, nicht in Deutschland hergestellt. Die Versorgung mit diesen Produkten ist jedoch durch Importe gewährleistet. Insgesamt 16 409 autologe und 9435 allogene Blutstammzellpräparate wurden 2009 hergestellt, davon wurden 3382 allogene Präparate exportiert. Transplantiert wurden 3181 autologe und 2374 allogene Präparate; 187 davon kamen aus dem Ausland. Die große Zahl exportierter Stammzellen und die wenigen importierten Präparate lassen auch bei diesem Produkt keine gravierenden Versorgungsengpässe erwarten.

Introduction

The blood donation services, the pharmaceutical industry, and the health care facilities provide the Paul-Ehrlich-Institut (PEI) with annual data on the extent of the collection of blood and blood components, the manufacture, imports, and exports as well as the loss and expiry of blood products and recombinant plasma proteins for the treatment of haemostasis disorders. In the meantime, data are available from the past 10 years. In addition to the documentation of the current supply situation, these data can be used to derive trends on the provision of blood products in Germany. The results are also published on the PEI website [2] in tabular form and updated regularly. The figures published on that website can therefore deviate from the figures provided in this report.

Methodology

Report Forms

Notifications are submitted exclusively by means of a web application, the online reporting system pursuant to Section 21 Transfusionsgesetz (TFG; German Transfusion Act).

Information on the Collection of Blood and Blood Products

This information comprises the number of collections of allogeneic and autologous blood including plasma as the starting material for fractionation as well as haematopoietic stem cells (HSC). Since 2009, the collection of HSC from bone marrow is also recorded here.

Information on the Manufacture, Consumption, Loss and Expiry

This information includes manufacture, imports, exports (including country of origin and country of export), consumption, loss and expiry of blood components, HSC, medicinal products derived from human plasma, and recombinant coagulation factor products.

Information on Patients with Congenital Haemostasis Disorders

Since the reporting year 2008, data on patients with congenital haemostasis disorders requiring treatment pursuant to Section 21 TFG are collected via the German Haemophilia Register (DHR) [3]. This data is still incomplete because the DHR has only been introduced recently. They will be published in the next report. The data include the number of patients with haemophilia A and B categorised by seriousness of the disorder and age group, the number of patients with von Willebrand's disease as well as the total of the products administered to these groups of individuals.

Facilities for Which Reporting Is Compulsory

Manufacturers of blood products and recombinant plasma proteins for the treatment of haemostasis disorders as well as health care facilities consuming blood products are required to report pursuant to Section 21 TFG.

Donor facilities are classified as follows:

- *Blood donation services of the German and the Bavarian Red Crosses:* As a rule, the institutes of the Red Cross operate independently from hospitals. They not only organise blood donations on a large scale but also the provision of the blood components manufactured from these donations. They have the company structure of a non-profit GmbH (limited liability company).

- *State, local authority, non-commercial and private blood donation services at hospitals:* Apart from local authority blood donation services, these also include donation facilities at university hospitals and at non-commercial or (in the meantime) privatised hospitals.
- *Private donation centres:* Private donations centres are blood donation services and plasmapheresis centres in the corporate form of a GmbH or AG (public limited company) not operating on a charitable basis and, as a rule, not run by the responsible body of hospitals.
- *Plasma processing / pharmaceutical companies:* This category comprises pharmaceutical enterprises that manufacture, import, or export coagulation factors or other medicinal products from blood plasma as well as recombinant coagulation factor products or sell such products in Germany.
- *Bundeswehr (German Army):* The Army maintains its own blood donation service to provide the soldiers with blood components.

Health care organisations which consume blood products are classified as follows:

- Clinics and hospitals providing basic, regular, focused or maximum care.
- Panel doctors, dialysis centres, and outpatient clinics.
- Health-care facilities of the German Army.
- 'Other medical institutions', comprising rheumatology centres, rehabilitation centres, geriatric, and psychiatric facilities.

The above mentioned institutions are required to report the number of blood components transfused, the number of HSC transplanted, and the administration of plasma proteins.

Results and Discussion

Reporting Rates

For 2008, the overall response rate was 81%. 2,300 institutions transmitted their figures in 2009, which is equivalent to around 80% of the institutions registered at the PEI as required to report.

Collection and Manufacture

As in previous years, all blood donation facilities in Germany transmitted their figures. Thus, reliable data are available on the amount of blood components available for transfusion in Germany. Data are missing only on the facilities performing autologous blood collection and on the plasma-processing industry (table 1).

The number of facilities in which pre-operative autologous blood is donated steadily declined from originally 597 to only 241 facilities in 2009.

Consumption

In 2009, altogether 2,299 reports, corresponding to 80% of the facilities registered at the PEI were received from facilities using blood products. The response rate thus rose by 7% compared with 2007. This means, however, that more than 500 health care facilities still do not report their consumption of blood products (table 2).

Collection of Blood and Blood Components

In 2008, more than 7.12 million allogeneic blood donations were provided by donors in Germany corresponding to an increase of 7.2% compared with the previous year. The portion

Table 1. Response from the manufacturers (collection, production, imports, and exports)

Type of organisation	Number of manufacturers	Notifications	
2008			
State-run, municipal or private hospitals, non-profit limited liability company	57	57	(100%)
Red Cross	9	9	(100%)
Plasma processing industry	16	14	(88%)
Private donation centre	10	10	(100%)
German Army	1	1	(100%)
Facilities collecting autologous blood, manufacturing blood components from directed donations or haematopoietic stem cell preparations	322	295	(92%)
Total	415	386	(93%)
2009			
State-run, municipal or private hospitals, non-profit limited liability company	55	55	(100%)
Red Cross	9	9	(100%)
Plasma processing industry	18	17	(94%)
Private donation centre	13	13	(100%)
German Army	1	1	(100%)
Facilities collecting autologous blood, manufacturing blood components from directed donations or haematopoietic stem cell preparations	302	269	(89%)
Total	398	364	(91%)

Table 2. Response from the users (consumption)

Type of organisation	Number of manufacturers	Notifications	
2008			
Hospital	1,672	1,437	(86%)
Panel doctors / dialysis centres / surgery	1,045	797	(76%)
German Army	1	1	(100%)
Other medical facilities	153	77	(50%)
Total	2,871	2,312	(81%)
2009			
Hospital	1,666	1,422	(85%)
Panel doctors / dialysis centres / surgery	1,043	789	(76%)
German Army	1	1	(100%)
Other medical facilities	154	87	(56%)
Total	2,864	2,299	(80%)

of whole blood donations amounted to 68%. In 2009, the German population was even more motivated to donate. More than 7.42 million allogeneic blood donations could be recorded – an increase of 4.2% compared with 2008. The donations were voluntary and gratuitous; expenses associated with blood donations are often compensated conforming to the laws [1, 4].

Whole blood donations form the basis for the supply with blood products, not only for blood components for transfusion but also for plasma for fractionation as the starting product for the manufacture of medicinal products from human plasma. In 2008, the number of whole blood donations rose by 2.2% compared to 2007 accounting for 4.81 million. Again, in 2009, a slight increase by 1.1% to 4.86 million could be recorded compared with the previous year (table 3, fig. 1).

Since 2000, the number of preoperative autologous blood collections declined from 216,000 to 48,000 collections in 2009. The portion of autologous blood collections compared with the total number of whole blood donations thus declined from 4.7% to just below 1% (table 4, fig. 1). Such a downward trend can also be observed in the member states of the Council of Europe. The current report form 2006 shows a medium portion of autologous blood donations of 0.6% compared with the total of the whole blood donations [5].

In 2009, 60 whole blood donations were performed per 1,000 inhabitants [8] – a high number compared with that of the member states of the Council of Europe which amounts to a median of 36 whole blood donations per 1,000 inhabitants (quartile distance: 50–24) in 2006 [5]. During the same time

Table 3. Products from allogeneic blood (whole blood and apheresis donations)

	Unit	No.	Loss	Manufacture	Expiry (manufacturer)	Portion exports from Germany (EEA ^a)	Consumption	Expiry (user)	Calculated consumption
<i>2008</i>									
Total number of whole blood donations	N	4,810,540							
Total number of apheresis donations	N	2,314,508							
Apheresis donations (RBC)	N	10,603							
Apheresis donations (thrombocyte concentrate)	N	171,690							
Apheresis donations (plasma)	N	2,114,910							
Multi-component apheresis donations	N	17,305							
RBC concentrates from whole blood	TU		65,630	4,686,430	62,745 (1.34%)	892			
RBC concentrates from apheresis	TU		874	20,715	112 (0.54%)	0			
RBC concentrates	TU		66,504	4,707,145	62,857 (1.34%)	892	4,172,678	142,504 (3.30%)	4,490,915
Pooled platelet concentrates	TU		4,726	206,962	22,872 (11.05%)	0			
Platelet concentrates from apheresis	TU		5,267	299,503	11,660 (3.89%)	0			
Total platelet concentrates	TU		9,993	506,465	34,532 (6.82%)	0	420,327	18,287 (4.17%)	452,257
Therapeutic single plasma from whole blood	TU ^c		49,297	790,371	12,221 (1.55%)	0	1,072,371	30,864 (2.80%)	
Therapeutic single plasma from apheresis	TU ^d		9,460	440,233	764 (0.17%)	0			
SD-plasma ^e	TU						74,159	829 (1.11%)	
Total therapeutic plasma	TU		58,757	1,230,604	12,985 (1.06%)	0	1,146,530	31,693 (2.69%)	1,257,714
Plasma for fractionation from whole blood	I		15,267	1,014,818	879 (0.09%)	see table 5			
Plasma for fractionation from apheresis	I		4,470	1,483,496	392 (0.03%)	see table 5			
Total plasma for fractionation	I		19,737	2,498,314	1,271 (0.05%)	see table 5			
Hyperimmune plasma from whole blood	I		0	5,020	0 (0.00%)	see table 5			
Hyperimmune plasma from apheresis	I		45	24,589	15 (0.06%)	see table 5			
Total hyperimmune plasma	I		45	29,609	15 (0.05%)	see table 5			
<i>2009</i>									
Total number of whole blood donations	N	4,863,335							
Total number of apheresis donations	N	2,561,226							
Apheresis donations (RBC)	N	84,414							
Apheresis donations (thrombocyte concentrate)	N	173,888							
Apheresis donations (plasma)	N	2,277,441							
Multi-component apheresis donations	N	25,483							
RBC concentrates from whole blood	TU		103,087	4,732,115	64,108 (1.35%)	816			
RBC concentrates from apheresis	TU		645	17,129	259 (1.51%)	0			
RBC concentrates	TU		103,732	4,749,244	64,367 (1.36%)	816	4,113,568	135,742 (3.19%)	4,535,221
Pooled platelet concentrates	TU		4,859	215,468	37,639 (17.47%)	0			
Platelet concentrates from apheresis	TU		5,818	304,447	15,931 (5.23%)	0			
Total platelet concentrates	TU		10,677	519,915	53,570 (10.30%)	0	412,249	21,561 (4.97%)	443,169

Table 3 continued on next page

Table 3. Continued

	Unit	No.	Loss	Manufacture	Expiry (manufacturer)	Portion exports from Germany (EEA ^a)	Consumption	Expiry (user)	Calculated consumption
Therapeutic single plasma from whole blood	TU ^c		58,576	878,615	7,686	0	1,065,380	30,454	(2.79%)
Therapeutic single plasma from apheresis	TU ^d		7,672	259,327	3,433	3,499	64,845	497	(0.76%)
SD-plasma ^e	TU						1,130,225	31,042	(2.67%)
Total therapeutic plasma	TU		66,248	1,137,942	11,119	3,499			1,164,598
Plasma for fractionation from whole blood	1		16,614	1,207,605	216	see table 5			
Plasma for fractionation from apheresis	1		3,959	1,690,792	1,288	see table 5			
Total plasma for fractionation	1		20,573	2,898,397	1,504	see table 5			
Hyperimmune plasma from whole blood	1		0	3,107	1	see table 5			
Hyperimmune plasma from apheresis	1		41	32,841	45	see table 5			
Total hyperimmune plasma	1		41	35,947	46	see table 5			

^aEEA = European Economic Area. (EU, Norway, Iceland, Liechtenstein). Neither imports nor exports (Non-EEA) data were reported.

^bCalculated consumption = Sold preparations [Manufacture - Portion Expiry (manufacturer)] - % Expiry (user) [Expiry (user) ÷ (Consumption + Expiry (user))] × Sold preparations [Manufacture - Portion Expiry (manufacturer)].

^c270 ml.

^d245 ml.

^eSD-Plasma is manufactured by less than three pharmaceutical companies. Therefore it is not published.

period, 58 whole blood donations per 1,000 inhabitants were collected in Germany and 49 in the USA [6, 19] (fig. 2).

The number of apheresis donations rose from 2005 to 2009 by 15% on average by year to 2.56 million, the highest level since 2000 (table 3, fig. 1). Unlike 2003, the year in which less whole blood donations were collected due to the dramatic increase in apheresis donation, this recent increase has no effect on the number of whole blood donations. Plasmapheresis donations constitute the major portion of apheresis donations; the collection of RBCs and platelets by means of apheresis only accounts for roughly 9% of all apheresis donations. More than 90% of all plasmas collected by means of apheresis are used for the manufacture of plasma proteins.

The effects of the demographic changes on the supply with blood products in Germany are currently being discussed intensively. According to calculations by the Federal Statistical Office, the German population will have declined by up to 15% by 2060 compared with 2008. At the same time, a shift in the age structure will be experienced – the portion of old people in the overall population will rise markedly [7, 8]. Especially in those regions where the age structure is changing drastically, dramatic losses are expected in the supply with blood, while the demand is expected to rise [9].

In the Federal Republic of Germany as a whole, the number of whole blood donations rose by nearly 12% during the past 10 years although the number of individuals who have reached the minimum age required for donations [20] declined by around 2% [7]. This development can be understood if we take a look at the donor age groups. Thus, the number of 18- to 34-year-olds, the age group with the largest portion of first-time donors, declined by around 9% while the number of 35- to 54-year-olds, who accounted for a large portion of multiple donors, increased by 4% [7]. Donors in this age group play an important part in contributing to the provision of blood components [10]. At the same time, the number of over 65-year-olds, the age group about which it is assumed that they need the largest portion of blood components, rose by 23%.

Intended steps to be taken such as a more liberal regulation of the upper age limit for donors are designed to moderate a possible downward trend. The course of the future development of donor availability remains to be seen. In Germany, the donor frequency can still be described as very high, also compared with our European neighbours where considerably less blood is donated.

RBC Concentrates

Altogether, 4.7 million transfusion units (TU) of RBC concentrates were produced each in 2008 and in 2009 (fig. 3). The major portion of these RBC concentrates originates from whole blood donations, while only 0.4% was produced from apheresis donations (table 3). With a portion of 72% of the RBC concentrates manufactured, the institutes of the German and Bavarian Red Cross continued to be the major man-

Fig. 1. Development of blood donations.

Fig. 2. Number of whole blood donations per 1,000 inhabitants in 2006 [5, 6].

ufacturers, followed by the group of state, local authority, and other non-profit donor organisations as well as the facilities of private hospital operators with an unchanged portion of 20% over several years. The portion of private donor services rose continuously from 2.2% in 2000 to currently 7.5%. The portion of RBC concentrates provided by the German Army for general use has remained constant with around 0.7%.

Since 2004, the PEI also records the manufacture of irradiated RBC concentrates. The portion of these RBC concentrates compared with the over-all amount of RBC concentrates has risen from 3.2 to 4.0%.

The already low number of RBCs from autologous blood donations, continued to decline. The rate for RBCs from autologous donations compared with the total supply of RBCs

Table 4. Autologous blood and its components

	Unit	No.	Manufacture	Portion expiry (manufacturer)	Consumption	Expiry (user)
2008						
Number of autologous blood collections (whole blood)	N	58,950				
Number of autologous blood collections (apheresis)	N	3,533				
Total number of autologous blood collections	N	62,483				
Left as whole blood for transfusion	TU		12,390	917 (7.40%)	6,280	6,879 (52.28%)
RBC concentrates from whole blood	TU		42,747	2,055 (4.81%)		
RBC concentrates from apheresis	TU		3,426	299 (8.73%)		
Total RBC concentrates	TU		46,173	2,354 (5.10%)	23,811	19,512 (45.04%)
Platelet concentrates from whole blood	TU		402	1 (0.25%)		
Platelet concentrates from apheresis	TU		11	0 (0.00%)		
Total platelet concentrates	TU		413	1 (0.24%)	171	90 (34.48%)
Plasma from whole blood	TU		37,730	1,902 (5.04%)		
Plasma from apheresis	TU		5,556	37 (0.67%)		
Total plasma	TU		43,286	1,939 (4.48%)	23,940	18,262 (43.27%)
2009						
Number of autologous blood collections (whole blood)	N	45,217				
Number of autologous blood collections (apheresis)	N	2,888				
Total number of autologous blood collections	N	48,105				
Left as whole blood for transfusion	TU		7,912	727 (9.19%)	3,909	4,949 (55.87%)
RBC concentrates from whole blood	TU		35,059	1,962 (5.60%)		
RBC concentrates from apheresis	TU		2,941	312 (10.61%)		
Total RBC concentrates	TU		38,000	2,274 (5.98%)	20,556	14,784 (41.83%)
Platelet concentrates from whole blood	TU		406	1 (0.25%)		
Platelet concentrates from apheresis	TU		43	0 (0.00%)		
Total platelet concentrates	TU		449	1 (0.22%)	185	11 (5.61%)
Plasma from whole blood	TU		30,747	1,617 (5.26%)		
Plasma from apheresis	TU		5,340	44 (0.82%)		
Total plasma	TU		36,087	1,661 (4.60%)	21,829	13,802 (38.74%)

decreased from 3.3% in 2000 to 0.7% in 2009. With 44%, the portion of expired autologous RBCs is markedly above that of allogeneic products. An even larger expiry rate was recorded for whole blood for transfusion from autologous blood donations – almost 60% in 2009.

In 2008 and 2009, 978 and 977 RBC concentrates respectively were manufactured per 1,000 whole blood donations. Thus the best yield in the past 10 years could be obtained in 2008 with a loss before release of only 2.2%.

The expiry rate of released RBCs in the donation services, too, continues to decrease and was below the level of previous years in 2009 with 1.36% (fig. 4). It has become clear that manufacturers have made major efforts to minimise the expiry rate for their products. Since the products required for quality and sterility controls must also be recorded as expiry,

if they constitute released products, there is a lower limit of the expiry rate which cannot be exceeded. The latter has obviously been reached in the meantime.

Due to missing reports on the use of blood products from health care facilities, the approximate number of RBCs transfused was estimated on the basis of the products delivered by the donor services and the expiry figures reported by the users [11]. Based on this information, around 4.5 million RBC concentrates were transfused in 2008 and 2009, to an increasing extent also in an out-patient setting in panel doctor's practices and day clinics. While the portion of transfusions of RBC concentrates in these facilities was 4.6% in 2004, it rose to 7.9% in 2009.

Since no reports on expiry figures were available from a part of the facilities performing RBC transfusions, the portion

Fig. 3. RBC concentrates from allogeneic blood: portions accounted for by the manufacturers.

Fig. 4. RBC concentrates from allogeneic blood: portions reported from expired RBC concentrates at the manufactureres and users. Hashed area: the lower limit describes the expiry rate reported, the upper limit describes the corrected expiry rate (see explanations in the text).

of RBC concentrates expired at the user was calculated in two ways: it was calculated i) in comparison with the total of RBC concentrates reported as transfused in assuming that the facilities that did not report any expiry figures in fact did not have any expiry (reported expiry rate) and ii) taking into account only the number of RBC concentrates reported by those facilities that had simultaneously reported expiry (corrected expiry rate) (fig. 4).

The supply level of RBC concentrates for the German population can still be considered as good, with 58 per 1,000 inhabitants, above all compared with the member states of the Council of Europe. The median of these countries was 36 RBC concentrates per 1,000 inhabitants in 2006 (quartile distance: 48–29). The figure of 2006 in Germany was 55 [5]. Detailed studies of the supply of RBC concentrates have shown that the supply can fluctuate by up to 20% during one given

Fig. 5. Manufacture of platelet concentrates from allogeneic blood: portions of manufacture from whole blood and apheresis. *For 2000 and 2001, this also includes single platelet concentrates from whole blood donations.

Fig. 6. Platelet concentrates from allogeneic blood: portions reported for expired platelet concentrates in % at the manufacturers and users. Hashed area: The lower limit describes the expiry rate reported, the upper limit the corrected expiry rate (see explanations in the text).

year [12]. Health care facilities are obviously able to overcome temporary bottle necks in the supply by prioritising and appropriate planning.

Platelet Concentrates

The favourable trend for the manufacturing figures of platelet concentrates continued in 2009, with 520,000 platelet concen-

trates released for transfusion, even though the annual increase has in the meantime become smaller.

The portions accounted for by the different types of manufacture have remained unchanged. Around 60% of the platelet concentrates are manufactured by means of apheresis. One apheresis procedure produces 1.8 platelet concentrates on average. Pooled platelet concentrates are manufactured from

Fig. 7. Therapeutic single plasma from allogeneic blood: portions of manufacture from whole blood and apheresis.

Fig. 8. Ratio of transfused plasmas compared with transfused RBCs (plasma/RBC ratio): The black lines refer to facilities in Germany; the grey line refers to the medium plasma/RBC ratio of member states of the Council of Europe.

around 18% of the whole blood donations (table 3, fig. 5). The portion of irradiated platelet concentrates rose from 30% in 2004 to 34% in 2009.

While, from 2002 to 2007, the expiry rate at the manufacturers has decreased steadily, it rose in 2008 slightly and increased in 2009 clearly. In this context, attention has to be paid to a major difference between pooled and apheresis

platelet concentrates. While the expiry rate for apheresis platelet concentrates moderately increased again after its low of 3% in 2007, with 1% per annum, it increased for pooled platelet concentrates from below 12 to 17%. The reason for the increase in the expiry rate – above all for pooled platelet concentrates – could be explained by the fact that a cut in the shelf life of 1 day was recommended in Opinion 38 in 2008

Table 5. Plasma for fractionation

	Unit	Collection	Loss	Portion expiry (manufacturer)	Portion exports (EEA ^a)	Portion exports (non-EEA ^a)	Total exports	Imports (non-EEA ^a)	On the German market	Fractionation in Germany
2008										
Plasma for fractionation from whole blood	1	15,267	1,014,818	879	202,712	171,336	374,048	0	639,892	165,407
Plasma for fractionation from apheresis	1	4,470	1,483,496	392	488,867	1,719,395	2,208,262	2,366,468	1,641,310	1,825,718
Total plasma for fractionation	1	19,737	2,498,314	1,271	691,579	1,890,731	2,582,310	2,366,468	2,281,201	1,991,125
Total hyperimmune plasma	1	45	29,609	15	2,842	14,867	17,709	191,601	203,486	
2009										
Plasma for fractionation from whole blood	1	16,614	1,207,605	216	370,411	176,854	547,265	0	660,124	229,052
Plasma for fractionation from apheresis	1	3,959	1,690,792	1,288	440,225	2,105,793	2,546,018	2,841,462	1,984,948	1,394,357
Total plasma for fractionation	1	20,573	2,898,397	1,504	810,636	2,282,647	3,093,283	2,841,462	2,645,072	1,623,409
Total hyperimmune plasma	1	41	35,947	46	2,296	15,118	17,414	115,623	134,110	

^aEEA = European Economic Area. (EU, Norway, Iceland, Liechtenstein). No imports from EEA were reported.

[13] together with a possibly stagnating demand for these products (table 3, fig. 6). Apheresis platelet concentrates are supplied in a highly demand-orientated manner so that accordingly, almost all these products are transfused. Compared with this, an increased quantity of pooled platelet concentrates has obviously been manufactured for stock-piling purposes to balance out any possible bottlenecks caused by the cut in the shelf-life, which, however, could not be transfused due to lack of demand and expired as a consequence. In 2009, for the first time after 6 years, fewer products were transfused compared with the previous year (table 3). Whether or not this high expiry rate will again decrease in the next few years, thanks to the change in manufacturing management and distribution logistics, remains to be seen.

Plasma for Transfusion

After 2007 when the largest therapeutic plasma quantity of the last 7 years was manufactured, the manufacture decreased again to 1.1 million units in 2009 (table 3, fig. 7). In 2009, a graduated plan came into force designed to reduce the risk of transfusion-related acute lung injury (TRALI). This graduated plan bans the marketing of untested plasma of women with a history of pregnancy [14]. There was no risk of a bottleneck, since, among other things, shortages can be mitigated by targeted plasmapheresis from male donors. Figures provide proof that no bottlenecks occurred after the graduated plan relating to TRALI was implemented. Amazingly enough, with 23%, the portion of plasma for transfusion manufactured from apheresis even dropped to its lowest level so far observed. The quantity of plasma produced from whole blood rose both for therapeutic plasma and for plasma for fractionation. At the same time, the quantity of plasma for fractionation produced from plasmapheresis also increased (fig 7 and 9).

Thanks to the long shelf-life of therapeutic plasma, the expiry rate is lower than for the more perishable cellular blood components. From 2000 to 2009, the mean expiry rate at the manufacturers was 1.6% with a markedly lower expiry rate reported for 2009 amounting to only 0.6%. The mean expiry rate at the users was 3.0% of the quantity distributed for transfusion purposes. Expiry of SD plasma at the users was clearly below that figure with a mean rate of 1.1%.

An indicator in the reports of the Council of Europe for the national use of blood component is the ratio of the plasma units transfused over the RBCs transfused (plasma/RBC ratio). According to these reports, between 2001 and 2006 the mean for Europe was one TU plasma per 2.5 RBC concentrates (plasma/RBC ratio = 0.39). In Germany, the ratio was below the mean for Europe throughout this period with values between 3.7 and 2.9 transfused RBC concentrates per plasma unit (plasma/RBC ratio 0.27–0.34). Whereas the ratio calculated for Germany has decreased markedly in the past 10 years, no general trend could be observed for Europe. This statement is based on the plasma/RBC ratio calculated from

Fig. 9. Plasma for fractionation: portions of whole blood and apheresis donations.

the total of all units reported as transfused in a given country (fig. 8).

If, however, the consumption by university and traumatology hospitals, which care for trauma patients with massive bleeding, is compared with that of ‘other’ health care facilities and hospitals in general, a dramatic difference is observed. Conforming to the recommendations of the cross section guidelines for the treatment with blood components and plasma derivatives [15], the pro rata plasma consumption has decreased in the major part of the ‘other’ facilities from one TU plasma per approximately 3.7 RBC concentrates in 2000 (plasma/RBC ratio = 0.27) to one TU plasma per 5.3 RBC concentrates in 2009 (plasma/RBC ratio = 0.19). The ratio at university and accident hospitals has remained nearly unchanged ever since 2001 with on average one TU plasma transfused per 1.8 RBC concentrates (plasma/RBC ratio = 0.55). This shows that a restrictive use of plasma in the treatment of excessive bleeding is obviously considered not to be appropriate. This phenomenon is also highlighted by studies of patients with massive transfusion requirements. Here, a lower mortality rate was observed if the plasma/RBC ratio for the transfusion was ≥ 0.6 [16]. Current recommendations from traumatologists on the portion of plasma in massive transfusions are in line with these observations [17]. The difference in plasma/RBC ratios between the group comprising university and traumatology hospitals and that comprising all other health care facilities performing transfusions is significant for all the years observed (Mann-Whitney U test $p < 0.05$). Here, it becomes apparent that an undifferentiated consideration of the plasma/RBC ratio disregards important facts (fig. 8).

Plasma for Fractionation

The collection of plasma as a starting material for the manufacture of plasma proteins continued to increase in Germany. For the first time in 2008, the 2.5 million l limit was reached – equivalent to an increase of 12% compared with the previous year. A further increase in the quantity of plasma for fractionation by 16% to 2.9 million l could be recorded in 2009; 58% of this quantity originates from plasmapheresis (table 5, fig. 9). The total quantity collected is equivalent to 35.5 l per 1,000 inhabitants. In the member states of the Council of Europe, the median collection in 2006 was 5 l (quartile distance 14–2) per 1,000 inhabitants; the figure for Germany was 26 l for the same year [5].

These increases are almost entirely brought about by private plasmapheresis centres. These facilities were able to more than double their production since 2005. In addition, the donation services of the Red Cross were able to step up their collection of plasma for fractionation by 17%, while the collection levels accounted for by state, local authority, and other non-profit-making donor services together with the facilities of private hospital operators and the German Army more or less remained at the level of 2007. Private plasmapheresis centres by now contribute 61% to the total quantity collected. 33% are contributed by the Red Cross and 6% by other donor services (fig. 10).

Germany is the number one supplier of plasma for fractionation in Europe. In 2006, around 50% of the stock reported from Europe was produced in Germany [5]. Reported figures from the past 2 years show the very complexity of international trade with this raw material, indicating

Fig. 10. Plasma for fractionation: portions of manufacturers compared with the total supply.

Fig. 11. Plasma for fractionation: collection as well as the quantity available and the quantity manufactured in Germany.

that the quantities of imported and exported plasma for fractionation produced in Germany were approximately equivalent. The net quantity available on the German market amounted to around 2.3 million l in 2008 and 2.6 million l in 2009 equivalent to around 91% of the quantity produced in Germany. In 2007, the net quantity available in Germany was almost entirely used for further processing in Germany.

In the subsequent years, the portion of plasma fractionated in Germany decreased to 61% (table 5, fig. 11). Arithmetically, there is a remainder of 1 million l for 2009 for which no explanation can be made. Such residual quantities could also be observed in previous years [11]. The quantity totalled as from 2004 suggests that there should be stocks in Germany of 2.5 million l.

Table 6. Plasma derivatives

	Unit	Sold on the German market	Portion imports (EEA ^a)	Portion imports (non-EEA ^a)	Manufacture in Germany	Portion exports (EEA ^a)	Portion exports (non-EEA ^a)	Consumption	Expiry (user)
2008									
α_1 -Proteinase inhibitor ^b	kg							8	0
C1-inactivator ^b	IU							11,624,550	25,000
Antithrombin III	IU	83,410,500	10,477,500	19,222,000	168,106,000	52,172,500	3,068,000	89,632,534	376,700
Protein C ^b	IU							1,584,540	11,000
Coagulation factor VIII from plasma	IU	331,071,200	49,390,500	32,725,950	744,620,250	132,600,500	388,456,063	199,390,650	75,650
Coagulation factor VIII recombinant	IU	230,968,638	427,155,138	0	0	158,099,250	1,236,000	225,986,710	27,500
Coagulation factor IX from plasma	IU	52,351,300	18,024,200	29,915,500	33,931,800	9,755,900	4,609,300	33,470,300	7,000
Coagulation factor IX recombinant ^b	IU							15,566,450	0
Coagulation factor VII ^b	IU							3,583,470	3,000
Coagulation factor VIIa recombinant ^b	IU							3,249,480,000	23,880,000
Prothrombin complex concentrate	IU	152,969,450	30,316,600	44,489,500	114,839,750	18,414,500	7,318,500	144,050,470	209,050
Coagulation factor VIII inhibitor bypass ^b	IU							14,751,300	3,000
Coagulation factor XIII ^b	IU							17,860,850	42,000
Fibrinogen ^b	kg							60	0
Fibrin sealants	pack	250,675	228,883	0	350,975	21,099	212,624	214,590	1,349
Immunoglobulins, normal	kg	3,429	529	2,136	5,183	1,873	1,313	2,755	3
Specific immunoglobulins (anti-D) ^b	kg							36	0
Specific immunoglobulins	kg	152	25	0	938	208	351	89	1
Biseko ^b	l							1,267	6
Human albumin	kg	12,353	3,445	4,724	47,819	9,943	49,068	10,628	18

Table 6 continued on next page

Table 6. *Continued*

	Unit	Sold on the German market	Portion imports (EEA ^a)	Portion imports (non-EEA ^a)	Manufacture in Germany	Portion exports (EEA ^a)	Portion exports (non-EEA ^a)	Consumption	Expiry (user)
2009									
α_1 -Proteinase inhibitor ^b	kg							22	1
C1-inactivator ^b	IU							13,049,207	29,500
Antithrombin III	IU	88,108,650	10,737,000	26,764,500	134,705,500	43,698,500	4,075,000	83,343,593	402,793
Protein C ^b	IU							552,500	8,500
Coagulation factor VIII from plasma	IU	347,452,650	52,018,750	34,905,650	868,114,604	167,158,000	411,916,500	c	c
Coagulation factor VIII recombinant	IU	241,704,513	494,062,513	0	0	227,361,250	1,815,500	c	c
Coagulation factor IX from plasma	IU	55,177,900	17,467,100	23,215,500	51,839,350	12,486,000	17,547,400	c	c
Coagulation factor IX recombinant ^b	IU							c	c
Coagulation factor VII ^b	IU							3,883,040	18,600
Coagulation factor VIIa recombinant ^b	IU							c	c
Prothrombin complex concentrate	IU	178,028,850	27,943,700	53,304,800	150,268,500	28,594,750	20,764,000	160,935,884	289,750
Coagulation factor VIII inhibitor-bypass ^b	IU							c	c
Coagulation factor XIII ^b	IU							17,096,280	92,000
Fibrinogen ^b	kg							97	0
Fibrin sealants	pack	265,242	250,902	0	415,957	20,891	186,315	223,291	920
Immunoglobulins, normal	kg	3,706	586	2,347	5,752	2,036	3,235	3,020	4
Specific immunoglobulins (anti-D)	kg	89	0	89	0	0	0	45	0
Specific immunoglobulins	kg	129	8	0	684	253	468	90	1
Biseko ^b	l							737	2
Human albumin	kg	12,354	3,801	2,906	56,946	13,493	40,992	10,666	20

^aEEA = European Economic Area. (EU, Norway, Iceland, Liechtenstein).

^bThe products are manufactured by less than three pharmaceutical companies. Therefore they are not published.

^cData is still incomplete. They will be published in the next report.

Table 7. Haematopoietic stem cells from peripheral blood

	Unit	2008		2009		
		autologous	allogeneic	autologous	allogeneic, related	allogeneic, unrelated
Total of separations	N	5,796	5,111	5,775	961	4,603
Donors	N	3,795	4,218	3,576	725	3,957
Manufacture	TXU	7,496	4,948	6,815	865	4,421
Portion expiry (manufacturer)	TXU	54	9	134	3	0
Portion exports (EEA)	TXU	0	1,162	0	1	1,766
Portion exports (non-EEA)	TXU	1	885	0	0	1,202
Imports (EEA)	TXU	0	396	3	0	78
Imports (non-EEA)	TXU	0	95	0	0	75
Loss (manufacturer)	TXU	24	3	63	1	0
Number of patients transplanted in Germany	N	2,584	1759	2,714	619	1,312
Number of transplants	N	3,272	1,918	3,177	686	1,410

EEA = European Economic Area. (EU, Norway, Iceland, Liechtenstein); TXU = individual dose for a transplant which can consist of several apheresis donations/bags.

Table 8. Haematopoietic stem cells from cord blood

	Unit	2008		2009		
		autologous	allogeneic	autologous	allogeneic, related	allogeneic, unrelated
Manufacture	TXU	8,793	2,528	9,575	17	3,289
Portion exports (EEA)	TXU	0	69	0	0	75
Portion exports (non-EEA)	TXU	0	56	0	0	55
Imports (EEA)	TXU	0	7	0	0	9
Imports (non-EEA)	TXU	0	6	0	0	6
Loss (manufacturer)	TXU	478	2,513	596	0	3,217
Number of patients transplanted in Germany	N	0	20	0	3	18
Number of transplants	N	0	24	0	3	24

EEA = European Economic Area. (EU, Norway, Iceland, Liechtenstein); TXU = individual dose for a transplant which can consist of several apheresis donations/bags.

Table 9. Haematopoietic stem cells from marrow

	Unit	2009		
		autologous	allogeneic, related	allogeneic, unrelated
Donations	N	17	100	822
Donors	N	17	88	820
Manufacture	TXU	19	97	843
Portion expiry (manufacturer)	TXU	0	0	0
Portion exports (EEA)	TXU	0	0	226
Portion exports (non-EEA)	TXU	0	0	187
Imports (EEA)	TXU	0	0	25
Imports (non-EEA)	TXU	0	0	9
Loss (manufacturer)	TXU	0	1	0
Number of patients transplanted in Germany	N	4	114	131
Number of transplants	N	4	117	134

EEA = European Economic Area. (EU, Norway, Iceland, Liechtenstein); TXU = individual dose for a transplant which can consist of several apheresis donations/bags.

Fig. 12. Haematopoietic stem cells: manufacture from peripheral blood, cord blood, and bone marrow. *Up to 2001, no distinction was made between autologous and allogeneic stem cell preparations from cord blood. Figures are given in transplantation units (TXU) = individual dose for one transplant, which may consist of several bags.

Fig. 13. Haematopoietic stem cells: transplantations. Black: Stem cells transplanted in Germany; Grey: Exported stem cells, i.e. stem cells transplanted outside Germany. Figures are given in transplantation units (TXU) = individual dose for one transplant, which may consist of several bags.

Plasma Proteins

In Germany, there is still no shortage of plasma proteins. Although plasma is available as starting material in large quantities, some products are not manufactured in Germany; however, the demand is satisfied thanks to the import of these products. In this context, the supply is rather greater than the demand for a major part of these products. The median per-

centage portion of the supply reported in relation to the quantity sold in Germany was 80% (quartile distance: 87–63%) in 2009 (table 6).

Haematopoietic Stem Cells

The number of stem cell preparations manufactured in Germany amounts to roughly 25,000 transplantation units (TXU).

Autologous stem cells from cord blood account for the largest portion with around 37% (table 8), followed by autologous stem cells from peripheral blood with 26% (table 7). Haematopoietic stem cells from bone marrow which have been notifiable preparations since 2007 pursuant to Section 8d, paragraph 3 German Transplantation Act (Transplantationsgesetz; TPG) [18] were recorded by means of online reporting pursuant to Section 21 TFG for the first time in 2009 because of the contextual relation to the Transfusion Act. Haematopoietic stem cells from bone marrow form the smallest group with a portion of roughly 4% (table 9, fig. 12).

The greatest increase can be recorded for autologous haematopoietic stem cells from cord blood. The number of TXU manufactured annually has risen by 77% compared with 2002. None of these preparations has been transplanted up to now. The manufacture of allogeneic haematopoietic stem cells from cord blood has risen sharply since 2002, and has nearly doubled in 2009. These products have been transplanted in relatively small numbers: 24 in 2008 and 27 in 2009 – just below 1% of the products manufactured (table 8).

On the other hand, in 2009, in relation to the total transplants manufactured from peripheral blood, the portion transplanted in Germany was 47% for autologous products and

40% for allogeneic products. More than 50% of the manufactured allogeneic stem cell products were exported. Based on the assumption that these products, too, were 100% transplanted, the transplantation rate has risen to even 96%. These figures show that the greatest significance is currently attached to the transplantation of haematopoietic stem cells from peripheral blood (table 7).

Germany is increasingly becoming an exporter for allogeneic stem cell transplants. In 2003, the portion exported was still 21%, while in 2009, 35% of the products manufactured were exported. The portion of imported transplants, on the other hand, is negligible (fig. 12, 13).

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