Report on Notifications Pursuant to §21 German Transfusion Act for 2007

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Key Words

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

Summary

The present report contains the data collected in 2007, pursuant to Section 21 German Transfusion Act, and an analysis of the supply situation over the past 8 years. As in previous years, all blood donation centres located in Germany transmitted data on the collection, manufacture, import and export of blood components for transfusion. According to these data, a total of 6.7 million blood collections were performed in 2007. With 4.7 million, the portion of whole blood donations was at the level of previous years, whereas the number of apheresis donations rose again, to 1.9 million. The portion of autologous blood collections accounts for only 1.1% and thus continues to decline. Since 2003, the number of red blood cell concentrates prepared has been a constant 4.5 million transfusion units. The decay of red blood cell concentrates on the user side in 2000 accounted for 5% while in 2007 it was just above 3%, referred to the total quantity of data reported as transfused and decayed. The manufacture of platelet concentrates rose from 366,000 to 480,000 transfusion units between 2003 and 2007. The production of therapeutic single plasmas, too, markedly increased in 2007 (to 1.2 million transfusion units). In 2007, 2.2 million l of plasma for fractionation were collected in Germany. In addition, 1.0 million l were imported, and 1.8 million l were exported. The quantity available in Germany from a pure arithmetic point of view of 1.4 million l was almost entirely allocated to basic fractionation so that a sufficient plasma supply can be assumed. Due to the fact that manufacturing capacities are still lacking in Germany, recombinant factors need to be imported in their entirety. Since 2003, Germany has by far been the leader in Europe with more than 20 l of fractionation plasma collected per 1,000 inhabitants. Furthermore, regarding the manufacturing figures of red blood cell concentrates, platelet concentrates, and therapeutic single plasma, Germany is in the top third for all these products compared with other European countries. The manufacture of allogeneic stem cell products for haematopoietic reconstitution, obtained by apheresis, has continuously risen to 4,700. A large portion of this (1,810 transplants) could be exported while only a small number (179 preparations) had to be imported. The manufacture of autologous stem cell preparations from cord blood has risen drastically to more than 10,000 in 2007. The interest in the figures collected in compliance with Section 21, German Transfusion Act remains high both in Germany and at an international level. Meanwhile reliable data are available.

Schlüsselwörter

Blutspenden · Erythrozytenkonzentrate · Plasma zur Fraktionierung · Gerinnungsfaktoren · Versorgungslage

Zusammenfassung

Der vorliegende Bericht enthält die nach §21 Transfusionsgesetz (TFG) erhobenen Daten des Jahres 2007 und Auswertungen zur Versorgungssituation im Verlauf der vergangenen 8 Jahre. Wie in den Jahren zuvor haben alle in Deutschland ansässigen Blutspendedienste Angaben zu Gewinnung, Herstellung, Import und Export von Blutkomponenten zur Transfusion übermittelt. Danach wurden im Jahr 2007 insgesamt 6,7 Millionen Entnahmen durchgeführt. Der Anteil der Vollblutspenden lag mit 4,7 Millionen auf dem Niveau der Vorjahre, während die Zahl der Apheresespendsen sich erneut auf 1,9 Millionen erhöhte. Der Anteil der Eigenblutentnahmen liegt bei nur noch 1,1% und ist damit weiter rückläufig. Seit 2003 liegt die Zahl hergestellter Erythrozytenkonzentrate konstant bei 4,5 Millionen Transfusionseinheiten. Der Verfallsanteil von Erythrozytenkonzentraten auf der Anwenderseite ging, bezogen auf die insgesamt als transfundiert und verfallen gemeldete Menge, von über 5% im Jahr 2000 auf knapp über 3% in 2007 zurück. Die Herstellung von Thrombozytenkonzentraten stieg im Zeitraum zwischen 2003 und 2007 von 366 000 auf 480 000 Transfusionseinheiten an. Auch die Produktion von therapeutischem Einzelplasma wurde 2007 im Vergleich zu den Vorjahren deutlich auf über 1,2 Millionen Transfusionseinheiten gesteigert. In Deutschland wurden 2,2 Millionen l Plasma zur Fraktionierung gewonnen. Zusätzlich wurden 1,0 Millionen l eingeführt und 1,8 Millionen l exportiert. Die rein rechnerisch in Deutschland verfügbare Menge in Höhe von 1,4 Millionen l wurde fast vollständig der Basisfraktionierung zugeführt, so dass von einem ausreichenden Aufkommen an Plasma ausgegangen werden kann. Wegen nach wie vor fehlender Herstellungskapazitäten in Deutschland müssen sämtliche rekombinanten Faktoren eingeführt werden. Mit über 20 l gewonnenen Fraktionierungsplasmas pro 1000 Einwohner ist Deutschland seit 2003 europaweit führend. Auch bei Betrachtung der Herstellungszahlen von Erythrozytenkonzentraten, Thrombozytenkonzentraten und therapeutischem Einzelplasma liegt Deutschland im europäischen Vergleich durchweg im vorderen Drittel. Die Herstellung allogener Stammzellpräparate zur hämatopoetischen Rekonstitution aus Apherese steigt kontinuierlich auf nunmehr 4700. Ein großer Anteil davon (1810 Transplantate) konnte exportiert werden, während nur eine geringe Anzahl von 179 Präparaten importiert werden musste. Auch die Herstellung autologer Stammzellpräparate aus Nabelschnurblut ist im Vergleich zum Jahr 2006 enorm gestiegen, auf über 10 000 im Jahr 2007. Das Interesse an den nach §21 TFG erhobenen Zahlen ist in Deutschland und international unverändert hoch. Inzwischen sind auch belastbare Daten verfügbar.

Introduction

Can the population in Germany be supplied with a sufficient amount of medicinal products derived from blood? This is the question to be answered by the annual data collection pursuant to Section 21 German Transfusion Act (Transfusionsgesetz; TFG) on the collection of blood and blood components, the manufacture, imports and exports of blood products and genetically engineered plasma proteins for the treatment of haemostasis disorders, and the consumption and loss of blood products. Comparing the 'as is' with the 'target' side serves to provide an overview of the degree of self-sufficiency.

This also included the question concerning the number of patients with congenital haemostasis disorders requiring treatment, in particular haemophilia patients, and the amount of coagulation factors prescribed for these patients, broken down by patient group and degree of severity of the disease.

This report provides an overview of the data reported in 2007 and the development of selected aspects since 2000.

Methodology

Report Forms

Since 2007, report forms have been accessible only online for registered users on www.tfg.pei.de. Access is granted by the Paul-Ehrlich-Institut (PEI).

Collection

The data to be reported refer to the number of autologous and allogeneic blood donations, stem cell preparations from peripheral and cord blood as well as the amount of plasma as starting material for fractionation.

Manufacture and Consumption

The data recorded include the manufacture and consumption of blood components, stem cell products, medicinal products derived from human plasma, and coagulation factor products manufactured by genetic engineering. The package units recorded depend on the actual package sizes.

Patients with Congenital Haemostasis Disorders

The data recorded include the number of haemophilia A and B patients and of patients with von Willebrand's disease. The quantities of coagulation factors consumed for the therapy of these diseases are assigned to age and degree of severity of the disease.

As per reporting year 2008, these data are collected via the German Haemophilia Register (Deutsches Hämophilieregister; DHR; see www.pei.de/dhr).

Categorisation of the Reporting Organisations

In Germany, several organisations are involved in supplying blood products. Accordingly, each organisation is assigned to a group. Strictly speaking, the division between state, local authority-based and charitable organisations on the one hand and private ones on the other can no longer be maintained in its previous form because of the increasing privatisation of the former organisations. To compare the data with those of the previous years, however, it appeared to be useful to keep to the existing classification:

- Blood donor services of the Red Cross:

All blood donor services of the German and the Bavarian Red Cross

Organisations have comparable organisational structures. As a rule, the institutes of the Red Cross operate independently from hospitals and do organise not only blood donations on a large scale but also the provision of the blood components derived from these donations. They have the company structure of a non-commercial GmbH (limited liability company), i.e. they are not profit-orientated and have invested surpluses in medical research for many years.

- State/local authority/non-commercial blood donation services:

Even if these organisations have been privatised in their entirety or in part, their primary role has been maintained. Apart from local provision with blood and blood products (local authority blood donation services) and supplies for own hospitals (university hospitals, local authority and non-commercial hospitals), their responsibilities include research – above all at universities.

- Private donation centres:

These include blood donation and plasmapheresis centres with the corporate form of a GmbH or AG (joint stock company) not operating on a charitable basis: Only those organisations are included as private institutions, in addition to pharmaceutical companies, which operate on a purely private and profit-orientated basis.

- Plasma-processing companies:

This category contains pharmaceutical companies manufacturing, importing, and exporting coagulation factors or other blood plasma products as well as recombinant coagulation factor products, or selling these products in Germany.

- The separate categorisation of the German Army (Bundeswehr) remains unchanged.

Consuming organisations are classified in the following categories as in the past:

- Hospital

- Panel doctor/dialysis centre/out-patient clinic:

This includes all panel doctors, doctors at dialysis centres and at out-patient clinics that perform out-patient surgery.

- Other medical institutions:

This includes rheumatology centres, rehabilitation centres, geriatric institutions, psychiatric institutions, and blood donation centres which perform transfusions.

- Bundeswehr.

Results and Discussion

Response

Compared with the reporting year 2006, the number of those institutions which collect, manufacture import or export blood and blood products and are required to report these data decreased by 85 to 483. These institutions were predominantly health care institutes collecting autologous blood. On the other hand, the number of consuming institutions increased by 11 to 2,907.

As in previous years, the response for reports on the collection and manufacture of allogeneic blood components is complete. Missing data concern data on the manufacture and imports of some plasma manufacturing companies with offices outside Germany and reports from hospitals in which autologous blood is collected (table 1).

Compared with 2006, the response for institutions using blood and blood products increased slightly to 73% (table 2). Further exploration and direct enquiries at the registered institutions are planned for the years to come in order to update

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

Type of organisation	Number of manufacturers	Notifications	
		n	%
State-run or municipal hospitals / non-profit limited liability company	55	55	100
Red Cross	9	9	100
Plasma processing industry	17	14	82
Private donation centre	20	20	100
Bundeswehr	1	1	100
Facilities collecting autologous blood	381	328	86
<i>Total</i>	483	427	88

Table 2. Response from the users (consumption)

Type of organisation	Number of facilities	Notifications	
		n	%
Hospital	1,763	1,368	78
Panel doctors / dialysis centres / surgery	1,007	692	69
Bundeswehr	1	1	100
Other medical facilities	136	52	38
<i>Total</i>	2,907	2,113	73

Table 3. Response from haemophilia treaters

Type of organisation	Number of facilities	Notifications	
		n	%
Panel haemophilia treaters	69	47	68
Haemophilia treatment centre at hospital	52	51	98
<i>Total</i>	121	98	81

the list of institutions required to report and to complete the reports.

Up to 2006, only around 62% of the institutions registered treating haemophilia patients submitted their reports. In 2007, the response rate of the haemophilia treaters increased to 81% (table 3). It thus reached the highest rate ever.

Collection of Blood and Blood Products

Out of the past 8 years, the figure of 2007 for first and multiple allogeneic donations of 6.65 million was outnumbered only in the 'boom year' of 2003 (table 4). From 2000 to 2003, a tremendous rise in plasmapheresis donations could be observed, which can obviously be ascribed to government incentives. This rise even led to a decrease in whole blood donations in 2003. The portion of apheresis donations of the past 8

years fluctuated between 14% in 2000 and 35% in 2003. The number of allogeneic whole blood donations per year has been very stable, with roughly 4.7 million (fig. 1).

Compared to 2006, the portion of autologous blood collections within the total amount of donations continued to decrease and is only 1.1% now, accounting for 76,000 units. This downward trend has continued since the year 2000 (fig. 1). An ever decreasing number of hospitals offer their patients the opportunity of in-house autologous blood collection. In most cases, the collection is carried out by a nearby blood donation service. It was only in 2003 that nearly 500 hospitals reported the collection of autologous blood. This figure halved, i.e. it was only 245 in 2007.

Germany is clearly above the European median, accounting for 58 whole blood donations per 1,000 inhabitants. According to the draft report of the Council of Europe [1] from 2005, a median of 37 whole blood donations per 1,000 inhabitants were carried out in Europe; Germany thus ranked third in 2005, after Denmark and Greece. Rejman [2] postulated that 40–60 whole blood donations per 1,000 inhabitants yearly would provide optimum availability. It can therefore be concluded that a sufficient amount of blood components for therapeutic use should in principle be available in Germany and that bottlenecks in the availability of donations, e.g. during the holidays, need not necessarily lead to serious supply problems.

Red Blood Cell Concentrates

Red blood cell concentrates represent the most important medicinal products from whole blood donations – only 0.6% of the red blood cell concentrates originate from apheresis. Around 4.5 million transfusion units (TU) of red blood cell concentrates have been produced per year since 2004, with minor fluctuations (fig. 2). In 2007, 972 red blood cell concentrates were produced per 1,000 whole blood donations. This means a loss in the processing of donations of around 3.4%, similar to the mean of previous years.

Similarly to previous years, around 75% of the red blood cell concentrates were produced by the blood donation centres of the German and Bavarian Red Cross. The Red Cross therefore constitutes the most important supplier of this life-saving medicinal product. The group of government, local authority, and other non-profit institutions accounts for 20% of the red blood cell supplies. Private institutions, on the other hand, only provide a small portion of the red blood cell supplies with 5% (fig. 2).

Since the data have been recorded in conformity with Section 21 TFG, there has been a discrepancy between the red blood cells reported as sold, transfused and lost (table 4). The real consumption cannot be deduced directly from the data reported, due to this missing quantity which can either be ascribed to reporting errors or missing response. In order to indicate the 'consumption' of red blood cell concentrates in a plausible way despite this problem, the consumption was cal-

Table 4. Products from allogeneic blood (whole blood and apheresis donations)

	Number	Loss	Manufacture	Expiry (manufacturer)		Portion exports from Germany (EEA ^a)	Consumption	Expiry (user)		Calculated consumption ^b
				n	%			n	%	
Total number of whole blood donations	4,706,259									
Total number of apheresis donations	1,943,760									
RBC	13,905									
Thrombocyte concentrate	173,761									
Plasma	1,740,732									
Multi-component apheresis donations	15,362									
Total RBC, TU	73,013	4,572,587	74,293	1.62		805	3,931,152	125,445	3.17	4,355,867
From whole blood	72,311	4,544,742	74,200	1.63		805				
From apheresis	702	27,845	93	0.33		0				
Total thrombocyte concentrate, TU	8,528	480,189	31,428	6.54		0	396,327	19,050	4.59	428,180
Pooled	3,674	193,068	22,910	11.87		0				
From apheresis	4,854	287,121	8,518	2.97		0				
Total therapeutic plasma, TU	65,434	1,286,385	9,855	0.77		7,868	1,122,087	31,580	2.74	1,241,587
From whole blood ^c	56,101	908,824	8,815	0.97		0	1,045,588	30,699	2.85	
From apheresis ^d	9,333	377,561	1,040	0.28		7,868				
SD Plasma ^e							76,499	881	1.14	
Total plasma for fractionation, TU	29,768	2,231,828	1,683	0.08						
From whole blood	26,468	972,755	102	0.01		see table 6				
From apheresis	3,300	1,259,073	1,581	0.13		see table 6				
Total hyperimmune plasma, TU	162	17,895	7	0.04						
From whole blood	114	3,683	0	0.00		see table 6				
From apheresis	48	14,212	7	0.05		see table 6				

RBC = Red blood cell concentrate.

^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)].^ca 270 ml.^da 245 ml.^eSD plasma is manufactured by less than three pharmaceutical companies. Therefore it is not published.

Fig. 1. Development of donations. Table: Number of whole blood donations per 1,000 inhabitants in Germany and, for comparison, in the member states of the Council of Europe from 2001 to 2005 specified as (25% quartile) median (75% quartile).

Fig. 2. Production of red blood cell concentrates from allogeneic blood. Table: Red blood cell concentrates per 1,000 inhabitants and, for comparison, in the member states of the Council of Europe from 2001 to 2005 specified as (25% quartile) median (75% quartile).

Fig. 3. Consumption of red blood cell concentrates from allogeneic blood: The calculated consumption and loss decline are highlighted. The total of these figures corresponds to the red blood cell concentrates sold. The total height of the column corresponds to the red blood cell concentrates produced (see also table 4).

Fig. 4. Red blood cell concentrates from allogeneic blood: Reported amounts of lost red blood cell concentrates in % among manufacturers and users.

Table 5. Autologous blood and its components

	Number	Manufacture	Portion expiry (manufacturer)		Consumption	Expiry (user)	
			n	%		n	%
Total number of autologous blood collections	75,658						
From whole blood	72,241						
From apheresis	3,417						
Left as whole blood for transfusion, TU		17,612	1,170	6.64	8,371	8,683	50.91
Total RBC		52,761	3,825	7.25	27,193	20,333	42.78
From whole blood		49,305	2,978	6.04			
From apheresis		3,456	847	24.51			
Total thrombocyte concentrate, TU		162	1	0.62	323	3	0.92
From whole blood		135	1	0.74			
From apheresis		27	0	0.00			
Total plasma, TU		53,945	3,895	7.22	29,243	18,320	38.52
From whole blood		47,249	3,095	6.55			
From apheresis		6,696	800	11.95			

RBC = Red blood cell concentrate.

Fig. 5. Manufacture of platelet concentrates from allogeneic blood: Amounts of manufacture from whole blood and apheresis. Table: Platelet concentrates per 1,000 inhabitants and for comparison in the member states of the Council of Europe from 2001 to 2005 specified as (25% quartile) median (75% quartile).

culated as an approximate figure for the first time. For this purpose, it was assumed that i) all sold red blood cell concentrates were either transfused or lost at the consumer and that ii) the portion of red blood cell concentrates lost in the reporting institutions does not differ from the loss in the institutions which failed to report. The portion of lost red blood cell con-

centrates on the consumer side was calculated from the data reported. The consumption was then calculated from the quantity of red blood cell concentrates sold (4,498,294 for 2007) minus the percentage loss in the health care facilities (3.1% in 2007). The amount thus obtained for 2007 was 4.36 million red blood cell concentrates (table 4, fig. 3).

Fig. 6. Consumption of platelet concentrates from allogeneic blood: The calculated consumption and loss decline are highlighted. The total of these figures corresponds to the platelet concentrates sold. The total height of the column corresponds to the platelet concentrates produced (see also table 4).

Based on this calculation, the highest consumption of red blood cell concentrates since 2000 was recorded for 2007. This cannot only be ascribed to the number of red blood cell concentrates produced and sold, which has increased slightly, but also to the constant and significant decrease in the loss rate for the consumers ($p < 0.001$) since 2000 from more than 5 to currently 3.2% (fig. 4). It would be welcomed if the decrease in the loss rate actually did reflect an economical use of these valuable products. The decrease could however be due to reporting errors since some major 'consumers' did not indicate a loss in 2007.

The percentage loss at the manufacturers did not show a significant trend, with rates between 1.7 and 3.1% (fig. 4). Since the major portion of red blood cell concentrates is passed from the manufacturers to the consuming institutes after only few days, the logistic possibilities for minimising the loss at the manufacturer are already exploited.

In contrast to the declining loss of red blood cell concentrates from allogeneic blood donations at the consumer, the loss of autologous red blood cell concentrates is rising. The loss rate of 27.6% in 2000, which was high anyway, rose to 42.8% in 2007. During the same period, the portion of autologous products, compared with the total amount of red blood cell concentrates produced in Germany, fell from 4 to 1.1% (table 5).

In 2007, 55 red blood cell concentrates were available per

1,000 inhabitants in Germany. According to the latest unpublished report of the Council of Europe for 2005 [1], the median value is 37 red blood cell concentrates per 1,000 inhabitants throughout Europe, but with considerable fluctuations. If less than 20 red blood cell concentrates were manufactured per 1,000 inhabitants, this would indicate an insufficient availability of red blood cell concentrates. From this point of view, red blood cell concentrate supplies in Germany can be considered as assured. Considering the comparatively high per capita availability, it should be possible to bridge short-term gaps in the supplies by prioritising the use without running the risk of creating life-threatening situations for the patients – providing other factors such as an influenza pandemic will not lead to an acute extreme shortage.

Platelet Concentrates

Since 2003, the manufacture of platelet concentrates has increased by approximately 25,000 TU to more than 475,000 units in the reporting year. The increase of 5.6% compared with 2006 can almost exclusively be ascribed to the increased manufacture of apheresis platelet concentrates (table 4, fig. 5). In Europe, the mean portion of apheresis platelet concentrates is 35% [1]. Only in 7 of altogether 33 European countries do more than 50% of the platelet concentrates originate from apheresis, as is the case in Germany.

Fig. 7. Platelet concentrates from allogeneic blood: Portions reported of expired platelet concentrates in % among manufacturers and users.

The consumption of platelet concentrates reported for 2007 has increased by almost 33,000 TU compared with 2006. Similarly to red blood cell concentrates, however, there is also a discrepancy between platelet concentrates reported as sold and those reported by the consuming institutions (transfused plus lost), even though this 'gap' caused by missing reports has fortunately decreased considerably, with only 7% in 2007 compared with 10% in the previous year. To obtain more plausible figures for the real consumption, the latter was calculated as an approximate value, as was done for red blood cell concentrates. According to this calculation, 428,188 platelet concentrates were consumed in the reporting year (fig. 6). Approximately 5.5 platelet concentrates per 1,000 inhabitants were provided by the blood donation centres. For comparison while in European countries in median 2.75 [3] platelet concentrates were sold in 2005, in the same year this figure was 4.9 platelets per 1,000 inhabitants for. Since 2003, manufacturing figures and the consumption reported for platelet concentrates have increased steadily which can be interpreted to indicate that production rates have so far been able to keep up with the increased demand. From that point of view, availability of platelet concentrates can be regarded as good.

In the health care facilities, 3.7–5.5% of the platelet concentrates were lost between 2000 and 2007 (fig. 7). According

to reports from a total of 1,051 hospitals that transfused platelet concentrates, in 2007 a total of 4.7% were lost. Only apheresis platelet concentrates showed a loss rate at the manufacturer in the same order of magnitude. The loss rate for pool platelet concentrates, on the other hand, was markedly higher. This difference is not unexpected since apheresis platelet concentrates are predominantly produced by institutes at maximum care hospitals which can react to the current demand in a targeted manner. In addition, apheresis platelet concentrates are often produced for a particular purpose and occasion. Besides, the higher price, might affect the lower loss rate.

Plasma for Transfusion

From 2000 to 2003, the number of produced TU of plasma for transfusion decreased by 25%. During the same period, the plasma quantity assigned to fractionation increased by 39%, which is the highest value during the observation period (figs. 8 and 9).

Between 2003 and 2006, the amount of single units of therapeutic plasma showed a mean of slightly more than 1.1 million TU. In the reporting year, the number of units for this product was more than 1.2 million TU for the first time after a long period (fig. 8).

Fig. 8. Therapeutic single plasma sample from allergenic blood: Portions of manufacture accounted for by whole blood and apheresis. Table: TU per 1,000 inhabitants and for comparison in the member states of the Council of Europe from 2001 to 2005 specified as (25% quartile) median (75% quartile).

Fig. 9. Plasma for fractionation: Amounts from whole blood and apheresis donations. Table: 1 l/1,000 inhabitants in Germany and, for comparison, in the member states of the Council of Europe from 2001 to 2005 specified as (25% quartile) median (75% quartile).

Fig. 10. Plasma for fractionation: Portions of the manufacturers compared with the total amount.

Similarly to the red blood cell and platelet concentrates, the reported consumption and loss of plasma for transfusion is approximately 10% lower than the quantity sold by the manufacturers. The consumption reported fluctuated only slightly during the period from 2000 to 2007, i.e. between 1.05 and 1.17 million TU. Since 2007, SD plasma is no longer manufactured in Germany. The portion of SD plasma compared with the plasma consumption reported in total decreased from 9.7% in 2006 to 6.7% in 2007.

According to the figures reported, the loss rate for therapeutic single plasma and for SD plasma at the user has been a constant rate of 3.2% and 1.2% respectively since 2000. The difference may be affected by differences in prices, or else, by the fact that SD plasma is predominantly sold as universal plasma (AB plasma).

Plasma for Fractionation

No other country in Europe collects as much plasma for fractionation as Germany. Compared with 2006, the quantity rose by 4% to a total of 2.2 million l in 2007, the second highest value after the 'boom year' 2003. This is equivalent to 27 l plasma per 1,000 inhabitants (fig. 9). As a comparison, in Europe, in median 5 l were collected in 2005; in Germany, the figure was 21 l per 1,000 inhabitants. This constituted the highest per-capita quantity in Europe in 2005. Only Germany, Belgium, the Netherlands, Sweden, and Luxembourg of the

35 European countries recorded, showed a figure of more than 15 l per 1,000 inhabitants [1].

As in the past few years, private plasmapheresis centres, including plasmapheresis centres of the plasma processing industry, accounted for the highest portion of this type of plasma collection in 2007, with 53%. The institutes of the Red Cross provided 38.5% while the government and local authority institutions, and those classified as non-profit-making accounted for the remaining 8.1% (fig. 10). Fluctuations in the total volume for plasma for fractionation are solely caused by the amount of plasma produced by plasmapheresis during the observation period 2000–2007. During the same period, the portion of plasma for fractionation from whole blood was constantly at around 1 million l/year (fig. 9). Despite the fluctuations observed, plasma for fractionation in Germany today is derived mainly from plasmapheresis, contrary to the year 2000. The report by the Council of Europe for the years between 2001 and 2005, however, indicates a mean of 28% throughout Europe [1].

Plasma for fractionation is sold across countries, as required. Thus, 2.25 million l were produced in Germany in 2007; at the same time, however, 1.83 million l were exported and 1.01 million l imported. Referred to the amount produced in 2007, the remainder amounted to a net value of 1.41 million l (63%) in Germany. 1.29 million l were fractionated in Germany (table 6 and fig. 11).

Table 6. Plasma for fractionation

	Collection	Loss	Portion expiry (manufacturer)	Portion exports (EEA)	Portion ex- ports (non-EEA)	Total exports	Imports (non-EEA)	On the German market	Fractionation in Germany
Total plasma for fractionation, l	2,231,828	29,768	1,683	352,366	1,481,341	1,833,707	1,015,199	1,413,320	1,385,183
From whole blood	972,755	26,468	102	145,783	158,587	304,370	0	668,385	112,283
From apheresis	1,259,073	3,300	1,581	206,583	1,322,754	1,529,337	1,015,199	744,935	1,272,900
Total hyperimmune plasma, l	17,895	162	7	3,308	16,991	20,299	120,961	118,557	0

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

Fig. 11. Plasma for fractionation: Columns show the amounts collected in Germany annually. The continuous line shows a year's net production including import and export. In addition, the amount of plasma fractionated in Germany from 2004 to 2007 is highlighted in grey. The dashed line corresponds to the calculated amount available on the German market taking into account the imports, exports and the calculated residual amounts of previous years.

Since 2004, in addition to the collection, imports, and exports, the amount of plasma fractionated in Germany has been recorded. The evaluation of these figures shows that the amount of plasma available in Germany year by year by far exceeds the amount assigned to fractionation. This supposedly stored remainder is growing constantly. Whether or not reserves really are available in such amounts cannot be judged (fig. 11).

Plasma Proteins

In order to judge better the degree of self-sufficiency for plasma derivatives and recombinant medicinal products for the treatment of patients with haemostasis disorders, investigations were made on the amount of medicinal products sold and manufactured in Germany in 2004. The evaluation of the figures reported on the manufacture, sale, and consumption does not show a shortage of such products in Germany. Even

Table 7. Plasma derivatives: comparison of manufacture, amount sold on the German market and consumption in Germany

Product	Manufacture in Germany relating to consumption	Amount sold on the German market relating to consumption
α_1 -Proteinase inhibitor	–	↑
C1 inactivator	↑	↑
Antithrombin III	↑	±
Protein C	–	↑
Coagulation factor VIII from plasma	↑	↑
Coagulation factor VIII recombinant	–	↑
Coagulation factor IX from plasma	↓	↑
Coagulation factor IX recombinant	–	↑
Coagulation factor VII	–	±
Coagulation factor VIIa recombinant	–	–
Prothrombin complex (PPSB)	↓	↑
Coagulation factor VIII inhibitor bypass	–	↑
Coagulation factor XIII	↑	±
Fibrinogen	↑	↓
Fibrin sealants	↑	↑
Immunoglobulins, normal	↑	↑
Specific immunoglobulins (anti-D)	–	±
Specific immunoglobulins	↑	↓
Biseko	↑	↑
Human albumin	↑	↑

↑ = Manufacture /amount sold greater than consumption.
 ↓ = Manufacture / amount sold less than consumption.
 – = No manufacture / no data in Germany.
 ± = Amount sold equates ± consumption.

if a product was not manufactured in Germany, the demand could be met by imports.

The data on the products ‘fibrinogen’ and ‘specific immunoglobulins’ are not plausible. The quantity manufactured in Germany could have met the demand sufficiently without exports. According to the figures reported, however, a much higher quantity was consumed in Germany than was sold on the German market. Since this phenomenon persists throughout the years observed, it cannot be due to the sale of the stock from the previous year. The discrepancy referenced may be explained by re-imports not recorded in reports conforming to Section 21 TFG.

On the other hand, it is remarkable that only 4.7% of the quantity sold of the product ‘ α_1 -proteinase inhibitor’ was reported as consumed (tables 7, 8).

Peripheral Blood Stem Cells

The number of stem cell products manufactured from apheresis rose from just under 9,000 in 2000 to around 12,000 in 2007. The number of autologous products has been a mean of 6,800 per year ever since recording was started. The number of allogeneic transplantations increased from around 2,000 to roughly 4,700 in 2007 (fig. 12).

A total of 4,861 transplants from allogeneic donations were available in 2007. 4,682 of these transplants were manufactured in Germany and 179 were imported. At the same time,

1,810 transplants could be exported, which is almost the same amount as was used for transplantation in Germany (table 9). Stem cell donations are thus obviously so well organised in Germany that the demand can almost exclusively be met by donations from Germany.

Stem Cells from Cord Blood

Since 2000, the number of stored products per year has more than doubled to around 13,000 in 2007 – only around one sixth of these products are allogeneic transplants. There is no equivalent to the figure of more than 10,000 autologous products stored in the reporting year on the consumption side, but there were at least 15 transplantations per roughly 2600 allogeneic products (table 10).

Data on Patients with Congenital Haemostasis Disorders

The data on patients with haemophilia A and B requiring treatment were contradictory, particularly at the beginning of their collection. Thus, the strong decline in 2002 can hardly be ascribed to the fact that during this period a large part of patients did not need treatment (fig. 14). In 2007, too, the numbers of 2,782 patients reported with haemophilia A (table 11) and 526 with haemophilia B (table 12) are much lower than the total number of patients estimated in Germany, in spite of the increased response rate of 81% on the part of the known haemophilia treaters (table 3). For comparison, a report from

Table 8. Plasma derivatives

	Sold on the German market	Portion imports (EEA)	Portion imports (non-EEA)	Manufacture in Germany	Portion exports (EEA)	Portion exports (non-EEA)	Consumption	Expiry (user)
α_1 -Proteinase inhibitor ^a , kg							7	0
C1 inactivator ^a , IU							11,243,600	26,000
Antithrombin III, IU	98,433,500	11,596,500	34,676,000	137,123,500	65,386,500	68,614,500	92,860,385	518,630
Protein C ^a , IU							1,229,400	7,500
Coagulation factor VIII from plasma, IU	326,289,490	45,355,240	39,134,000	839,505,545	139,286,050	519,141,662	179,913,448	142,550
Coagulation factor VIII recombinant, IU	309,007,500	474,279,000	0	0	168,246,750	5,489,435	234,507,150	128,000
Coagulation factor IX from plasma	52,673,200	19,651,500	12,740,500	29,463,855	237,200	4,922,234	33,338,150	20,600
Coagulation factor IX recombinant ^a , IU							12,398,350	9,000
Coagulation factor VII ^b , IU							3,857,000	9,600
Coagulation factor VIIa recombinant ^a , IU							3,417,486,000	8,400,000
Prothrombin complex (PPSB) , IU	134,612,600	22,719,000	46,647,500	101,019,750	16,909,000	26,948,600	118,747,037	432,100
Coagulation factor VIII inhibitor bypass ^a , IU							14,321,750	11,000
Coagulation factor XIII ^a , IU							15,523,620	163,000
Fibrinogen ^a , IU							165	0
Fibrin sealants, pack	266,130	270,609	0	272,875	35,363	596,412	205,510	917
Immunoglobulins, normal, kg	6,492	3,856	1,931	4,618	1,874	2,067	2,486	3
Specific immunoglobulins (Anti-D) ^a , kg							36	0
Specific Immunoglobulins, kg	48	8	0	702	276	491	98	1
Biseko ^a , l							1,661	33
Human albumin, kg	5,665,297	4,810	5,658,876	47,620	10,203	41,539	9,921	25

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

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

Fig. 12. Blood stem cells from apheresis: Amounts from allogeneic donations and autologous collections. TXU = individual dose for a transplant which can consist of several apheresis donations/bags.

Table 9. Peripheral blood stem cells

	Peripheral blood stem cells	
	autologous	allogeneic
Number of separations	5,704	4,678
Number of donors	3,365	3,900
Manufacture, TXU	7,393	4,682
Portion expiry (manufacturer), TXU	189	19
Portion exports (EEA), TXU	0	1,034
Portion exports (non-EEA), TXU	1	776
Imports (EEA), TXU	0	112
Imports (Non-EEA), TXU	1	67
Loss (manufacturer), TXU	65	14
Number of grafts	3,072	2,027

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

the UK [4] can be used which refers to 6,500 patients with haemophilia A and 1,200 patients with haemophilia B. This discrepancy can be explained by still missing reports as well as by the fact that only patients requiring treatment are reported, but also by the fact that not all data on haemophilia treaters have been collected yet or the reports are incomplete.

Table 10. Stem cells from cord blood

	Stem cells from cord blood	
	autologous	allogeneic
Manufacture, TXU	10,313	2,657
Portion exports (EEA), TXU	0	65
Portion exports (Non-EEA), TXU	0	43
Imports (EEA), TXU	344	2
Imports (non-EEA), TXU	0	0
Loss (manufacturer), TXU	482	1,800
Number of grafts	0	15

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

Nevertheless, the numbers meanwhile show a clear trend towards consumption of recombinant factor VIII and IX concentrates in comparison to factor concentrates from human plasma.

The consumption of recombinant factor VIII was higher than the consumption of medicinal products from human plasma in 2007, accounting for 55%. On the other hand, factor VIII from human plasma was predominantly used for immune tolerance treatment in patients with inhibitors; the rate among

Table 11. Haemophilia A patients

	Number of patients	Consumption plasma-derived coagulation factor VIII, IU	Consumption recombinant coagulation factor VIII, IU	Consumption coagulation factor VIII inhibitor bypass, IU	Consumption recombinant coagulation factor VIIa, IU
Children and adolescents ^a without inhibitory bodies	799	39,673,900	70,445,750	0	13,980,000
Portion with mild ^b haemophilia A	160	4,020,400	2,694,500	0	0
Portion with haemophilia A of medium severity ^c	103	1,384,000	6,647,500	0	0
Portion with severe ^d haemophilia A	536	34,269,500	61,103,750	0	13,980,000
Children and adolescents ^a with inhibitory bodies	48	35,124,450	1,399,000	15,718,250	336,580,000
Portion low responder ^e	10	5,405,000	547,500	12,000	9,720,000
Portion high responder ^f	38	29,719,450	851,500	15,706,250	326,860,000
Adults without inhibitory bodies	1,885	119,150,050	181,069,550	20,000	42,128,000
Portion with mild ^b haemophilia A	326	4,877,050	8,838,722	0	0
Portion with haemophilia A of medium severity ^c	303	11,516,583	15,777,587	0	35,648,000
Portion with severe ^d haemophilia A	1,256	102,756,417	156,453,241	20,000	6,480,000
Adults with inhibitory bodies	50	12,788,500	2,813,000	8,114,000	807,160,000
Portion low responder ^e	13	387,500	1,080,000	542,000	29,640,000
Portion high responder ^f	37	12,401,000	1,733,000	7,572,000	777,520,000
Total children and adolescents ^a	847	74,798,350	71,844,750	15,718,250	350,560,000
Total adults	1,935	131,938,550	183,882,550	8,134,000	849,288,000
Grand total	2,782	206,736,900	255,727,300	23,852,250	1,199,848,000
^a Up to age 18 years. ^b >5% residual activity. ^c 2–5% residual activity. ^d <2% residual activity. ^e <5 Bethesda units/ml. ^f >5 Bethesda units/ml.					

Table 12. Haemophilia B patients

	Number of patients	Consumption plasma-derived coagulation factor IX, IU	Consumption recombinant coagulation factor IX, IU	Consumption coagulation factor VIII inhibitor bypass IU	Consumption recombinant coagulation factor VIIa, IU
Children and adolescents ^a without inhibitory bodies	180	15,408,900	6,654,500	0	0
Portion with mild ^b haemophilia A	22	244,500	216,250	0	0
Portion with haemophilia A of medium severity ^c	38	3,055,200	298,500	0	0
Portion with severe ^d haemophilia A	120	12,109,200	6,139,750	0	0
Children and adolescents ^a with inhibitory bodies	9	1,918,300	548,500	0	110,120,000
Portion low responder ^e	4	1,012,300	0	0	63,620,000
Portion high responder ^f	5	906,000	548,500	0	46,500,000
Adults without inhibitory bodies	332	22,694,800	6,842,000	0	0
Portion with mild ^b haemophilia A	69	706,769	731,428	0	0
Portion with haemophilia A of medium severity ^c	77	2,710,415	715,286	0	0
Portion with severe ^d haemophilia A	186	19,277,616	5,395,286	0	0
Adults with inhibitory bodies	5	1,962,000	504,000	530,000	605,080,000
Portion low responder ^e	1	1,122,600	0	0	0
Portion high responder ^f	4	839,400	504,000	530,000	605,080,000
Total children and adolescents ^a	189	17,327,200	7,203,000	0	110,120,000
Total adults	337	24,656,800	7,346,000	530,000	605,080,000
Grand total	526	41,984,000	14,549,000	530,000	715,200,000
^a Up to age 18 years. ^b >5% residual activity. ^c 2–5% residual activity. ^d <2% residual activity. ^e <5 Bethesda units/ml. ^f >5 Bethesda units/ml.

Fig. 13. Stem cells from umbilical cord blood. TXU = individual dose for a transplant which can consist of several apheresis donations/bags.

Fig. 14. Total number of haemophilia A and haemophilia B patients. Each column shows the respective amounts (bottom up) among adults, adults with inhibitors, children and children with inhibitors.

Fig. 15. Treatment of haemophilia A with recombinant and plasma-derived factor VIII concentrates among children and adults with or without immune tolerance therapy (ITT).

Fig. 16. Treatment of haemophilia B with recombinant and plasma-derived factor IX concentrates among children and adults with or without immune tolerance therapy (ITT).

children was approximately 96% and among adults still approximately 82%, based on the total amount of factor VIII prescribed in this patient group (fig. 15).

Both children and adult patients of haemophilia B have predominantly received factor IX from human plasma since 2003. In 2007 the figure was 74% regardless of availability of inhibitors (fig. 16).

As much as 672 patients with von Willebrand disease had been reported in 2007. These patients received 24,230,250 IU of von Willebrand factor-containing concentrates.

Statements with a higher informational value on the number of patients requiring treatment due to haemostasis disorder and their consumption of coagulation factors are expected in the near future by the data collection through the German Haemophilia Register.

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Disclosure

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