APPENDIX I

EXTRACTION AND USE OF HUMAN BLOOD PRODUCTS

NOTE

This Appendix is included for completeness and reproduces relevant sections of Appendix I from the original February 1999 Final Report "Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products" Reference P:\C8288\word\report rev4\ finalreportrev4.doc, and should be viewed in this context.

The text has not been updated except:

- To add Factor II, IX & X, Factor IX and anti-thrombin to Figure I.5.1 and to remove the incorrect indication that Fraction IV paste was used in albumin production.
- Where indicated by ** with an accompanying note.

Contents

I. EXTRACTION AND USE OF HUMAN BLOOD PRODUCTS I.1
I.1 Introduction I.1
I.1.1 Outline of Appendix I.1
I.1.2 Nomenclature I.1
I.1.3 Biological Variation I.1
I.2 Constituents of Human Blood I.3
I.2.1 General Description I.3
I.2.2 Plasma I.3
I.2.3 Red Blood Cells I.4
I.2.4 White Blood Cells I.4
I.2.5 Platelets I.5
I.3 Blood Donations I.5
I.3.1 Whole Blood Donations I.5
I.3.2 Apheresis Donations I.6
I.3.3 Stem Cell Donations I.7
I.3.4 Autologous Transfusions I.7
I.3.5 Donor Screening I.7
I.4 Blood Components I.8
I.4.1 Data Sources I.8
I.4.2 Manufacture of Blood Components I.8
I.4.3 Whole Blood I.9
I.4.4 Component Segregation I.9
I.4.5 Red Cells I.10
I.4.6 Platelets I.12
I.4.7 Plasma I.13
I.4.8 Cryoprecipitate I.14
I.5 Blood Derivatives I.15
I.5.1 Time Period Described I.15
I.5.2 Fractionation of Pooled Plasma I.15
I.5.3 Factor VIII I.16
I.5.4 Factor IX I.17
I.5.5 Albumin I.17
I.5.6 Immunoglobulins I.18
I.6 Blood Transfusions I.19
I.6.1 Data Sources I.19
I.6.2 Blood Component Losses I.19
I.6.3 Whole Blood I.19
I.6.4 Red Cells I.20
I.6.5 Platelets I.21
I.6.6 Plasma I.21
I.6.7 Summary of Transfused Components I.22
I.7 References I.22

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I. EXTRACTION AND USE OF HUMAN BLOOD PRODUCTS

I.1 Introduction

I.1.1 Outline of Appendix

This appendix presents an outline of the processes that are analysed in the present study. Its purpose is to document the information that has been received and the assumptions that have been made by DNV. It describes the principal components of blood, the ways in which blood is donated, the blood products that are extracted from it, and the uses to which the blood products are put. It refers to current practice (1998) in England & Wales, as covered by the National Blood Service, although much of the information has more general validity.

I.1.2 Nomenclature

This appendix uses WHO nomenclature for the following key terms:

- **Blood products** - a term that covers all products derived from human blood, including blood components and blood derivatives (see below).
- **Blood components** - a term describing products derived from single donations, or pools of up to 6 donations, manufactured within Blood Centres and supplied direct to hospitals. These include red cells, platelets and plasma.
- **Blood derivatives** - a term describing products produced by fractionation of a pool of blood plasma comprising thousands of donations. These include Factor VIII and human albumin. The term **plasma derivatives** is also used.

I.1.3 Biological Variation

All numerical quantities and contents quoted in this appendix are subject to variations resulting from:

- Biological variation between individuals.
- Variations in the manufacturing processes for blood components.

Biological variations in blood, in the absence of disease, are represented by a "normal range", comprising the mean ± 2 standard deviations.

Specifications for manufacturing processes for blood components take account of both biological variation and manufacturing variation. In the UK these specifications are contained in "*The UKBTS/NIBSC Guidelines for the Blood Transfusion Services in the United Kingdom*" ("The Red Book"). The content of blood components can be specified in several ways:

- The mean (or range) of values identified during routine inspection of finished components.
- The value identified in the manufacturing specification. Normally, this must be met in at least 75% of components inspected.

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- In some cases, the manufacturing specification requires the value to be met in 100% of components. In effect, this is a maximum (or minimum) value. In order to achieve this, the majority of components will have values well within the specification.

For example, the manufacturing specification for leucodepleted red cells specifies that 100% of components will have less than 5×10^6 white cells. In practice, most components will have values of 1×10^6 or less.

In risk analysis, the mean values are suitable for best-estimates, if the range is used for uncertainty analysis. Use of manufacturing specifications for point-estimates will introduce an unknown level of conservatism.

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I.2 Constituents of Human Blood

I.2.1 General Description

Blood consists of solid elements (red cells, white cells and platelets) suspended in a liquid matrix (plasma). It has a density of approximately 1.05 kg/l. In adults, blood amounts to typically 8% of body weight, or approximately 5 litres.

I.2.2 Plasma

Plasma is the liquid part of blood, which provides the transport mechanism for the blood cells, and also includes proteins, nutrients, hormones, waste products and antibodies. It comprises 55% of blood by volume.

The components of plasma are:

- Water (90% of plasma by weight), which maintains hydration in the body.
- Plasma proteins (7% of plasma by weight). These are:
  - Albumin (60% of plasma proteins), which promotes water retention in the blood.
  - Fibrinogen (4% of plasma proteins), which is essential for blood clotting.
  - Globulins (36% of plasma proteins), which are:
    - Alpha & beta globulin, which transport fat-soluble vitamins in the blood.
    - Gamma globulin (or immunoglobulin, Ig), which are antibodies against diseases, divided into 5 classes designated IgG, IgA, IgM, IgD and IgE.
- Plasma electrolytes (inorganic molecules separated into ions).
- Nutrients, including glucose (an energy source), amino acids (building blocks for proteins) and lipids (a body fat component of nerve cells).
- Waste products, including lactic acid and nitrogenous wastes.
- Dissolved gases.

Plasma proteins involved in blood clotting have been categorised into 13 factors identified by Roman numerals, including:

- Factor I – fibrinogen.
- Factor VIII - antihaemophilic factor (AHF). Deficiency causes Haemophilia A.
- Factor IX. Deficiency causes Haemophilia B.
- Factor XI. Deficiency causes Haemophilia C.

Serum is a term for plasma when fibrinogen has been removed, as occurs when blood clots.

Note: This Appendix is included for completeness and reproduces relevant sections of Appendix 1 from the original February 1999 Final Report, and should be viewed in this context.

I.2.3 Red Blood Cells

Red blood cells (erythrocytes) comprise approximately 93% of the solid elements in the blood, and approximately 42% of blood volume. They transport oxygen from the lungs to the body tissues. They have no nucleus, and consist mainly of haemoglobin, an oxygen-carrying globular protein, contained in a bi-concave disc approximately 7 μm in diameter. Each red cell contains 2.8×10^8 haemoglobin molecules. The normal adult red cell count is approximately 5×10^{12} per litre.

Red cells are produced from stem cells in bone marrow. They have a life of approximately 100 days, and are eventually removed by the spleen.

I.2.4 White Blood Cells

White blood cells (leucocytes) comprise approximately 0.16% of the solid elements in the blood, and approximately 0.1% of blood volume. They absorb bacteria and foreign particles. They have a nucleus, and are able to move independently and pass through blood vessel walls into the tissues, and can also synthesise protein. The normal adult white cell count is in the range 4 to 12×10^9 per litre, but may increase to 25×10^9 per litre as a result of infection.

There are many different types, including neutrophils, eosinophils, basophils, lymphocytes and monocytes. They range from 6 to 20 μm in diameter, with life spans from days to years. Most are formed in the bone marrow, and flow through the blood. Most are phagocytes, engulfing and destroying bacteria and foreign bodies.

Lymphocytes comprise 20-40% of white cells. The normal adult lymphocyte count is in the range 1.5 to 4×10^9 per litre. Lymphocytes originate from the bone marrow, but reproduce in lymphoid tissues (lymph nodes, spleen, thymus, tonsils, adenoid). They move slowly through the lymph (the fluid of the lymphoid system), and are able to recirculate between the blood and lymphoid tissues. Their life span may be from days to years.

Unlike other white cells, lymphocytes are not phagocytes, but are part of the body's immune system. There are two distinct types of lymphocytes:

- B cells (25% of lymphocytes), which provide the antibody-mediated (humoral) response to antigens (foreign bodies). They are formed in the bone marrow and migrate through the blood to peripheral lymphoid tissue. There are approximately 2×10^9 B cells in the body. If activated by an antigen they differentiate into plasma cells that release antibodies (globulins) for the antigen. These antibodies are not capable of independent movement, and so are carried by the blood and lymph to the site of the infection or injury.
- T cells (75% of lymphocytes), which provide the cell-mediated response to antigens. They are formed in the bone marrow and thymus, migrating through the blood to peripheral lymphoid tissue. If activated by an antigen, they differentiate into cells with different functions for combating infection.

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I.2.5 Platelets

Platelets (thrombocytes) comprise approximately 7% of the solid elements in the blood, and approximately 3% of blood volume. They are fragments of precursor cells called megakaryocytes. Their purpose is to start the blood clotting process. They have no nucleus. The normal adult platelet cell count is in the range 1.5 to 4 x 10^{11} per litre. They are produced in the bone marrow and have a life of approximately 8 days.

I.3 Blood Donations

I.3.1 Whole Blood Donations

In the area of England and North Wales covered by the National Blood Service (NBS) during 1996/97, 1,907,000 donors donated 2,215,000 units of usable blood. A conventional whole-blood donation consists of 450 ±45 ml of blood.

Individual donors may donate up to 3 times per year, although the average is only 1.2 per year. In the NBS during 1996/97, 17% of whole blood donations were from new donors who had not given blood before. In the Scottish National Blood Transfusion Service (SNBTS) for 1996/97, 56% of donors donated once, 30% twice, 11% three times and 3% four times.

The average rate of blood donation, based on 2,215,000 donations among the England & Wales population of 51.8 million for 1995, is estimated as 0.043 donations per person year.

Donors are normally aged 18 to 65. While 65 is the normal age for retirement from donation, a significant proportion of donors are allowed to continue until their 70th birthday. The age distribution of donors for the NBS in December 1997 is given in Table I.3.1. In order to calculate an age-dependent donation rate, the England & Wales population in the corresponding age groups has been estimated for 1997 as given in Table I.3.1. The distribution has been corrected to give the average donation rate of 0.043 donations per person year. The resulting age-dependent donation rates are plotted in Figure I.3.1. They show a peak at age 40-50.

Table I.3.1 NBS Age-Dependent Blood Donations

Age Group (years)	Donors Dec 1997	Population 1997 (1000s)	Donation Rate (per person year)
18-24	9733	4338.3	0.039
25-29	12328	3921.9	0.055
30-34	15077	4281.2	0.061
35-39	17278	3890.3	0.077
40-44	17547	3401.8	0.090
45-49	17852	3492.4	0.089
50-54	17678	3347.1	0.092
55-60	10592	2651.1	0.070
60-64	6489	2455.3	0.046
65-69	2570	2330.8	0.019
Total	127144	34761.4	0.043

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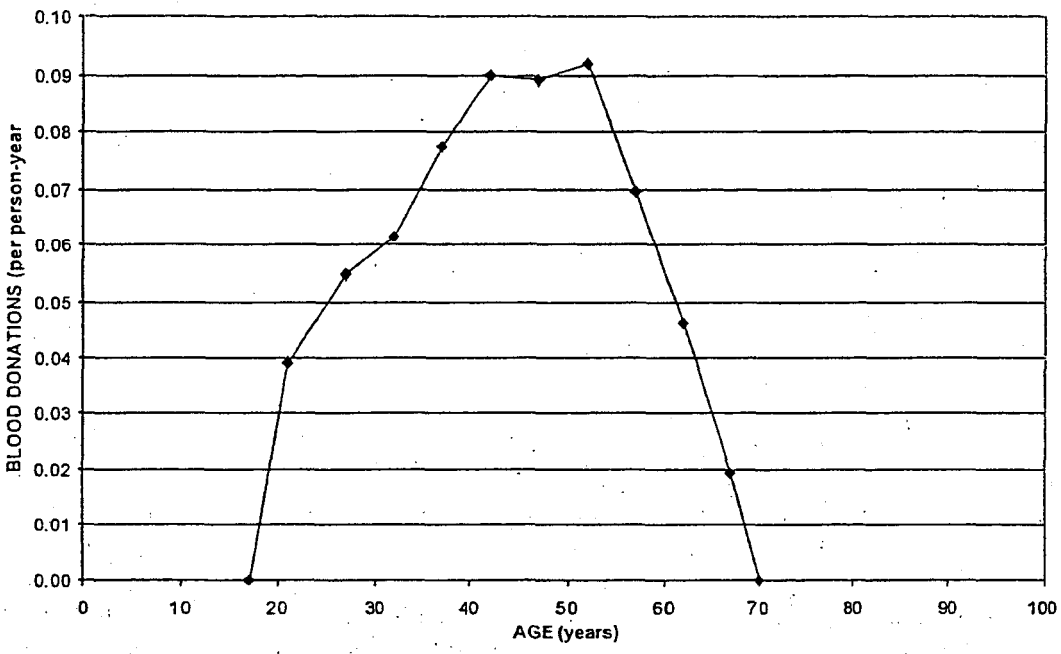
Figure I.3.1 Age-Dependent Blood Donation Rate



I.3.2 Apheresis Donations

Some donations are by apheresis, where specific products are removed from the blood and the remainder returned to the donor in a continuous process. This is used to collect platelets to match specific patients, or to collect plasma rich in specific antibodies. Types are:

- Plasmapheresis - up to 600 ml of plasma may be given up to 15 times/year.
- Cytapheresis - up to 600 ml of platelets and white cells may be given up to 24 times/year.

In the NBS approximately 82,000 apheresis procedures are undertaken each year. This amounts to approximately 4% of all blood donations. The breakdown of apheresis types estimated for NBS in 1998/9 is given in Table I.3.2.

Table I.3.2 NBS Apheresis Donations

Apheresis Type	Donations
Cobe LRS (leucodepleted) platelet donations	19,699
Haemonetics platelet donations	36,698
Total apheresis platelet donations	56,397
Apheresis plasma by-products from Haemonetics platelet donations	26,498
Apheresis plasma for clinical fresh frozen plasma (FFP)	18,443
Apheresis plasma for anti-D and other specific immunoglobulins	6,701
Total apheresis plasma donations	51,642
Total apheresis donations (eliminating double-counted by-products)	81,541

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Apheresis donor populations are relatively stable. Donor selection criteria ensure that most apheresis donors have already donated whole blood on at least one and usually two occasions. In the NBS during 1996/97, only 0.4% of apheresis donations were from new donors.

I.3.3 Stem Cell Donations

There were also 2000 donations of stem cells from the umbilical cords and placentas of new-born infants in the NBS during 1996/97.

I.3.4 Autologous Transfusions

Autologous transfusions involve collecting blood from patients in advance of a planned operation and returning it to them during or after the operation. Up to 4 pre-deposit autologous transfusions can be collected at weekly intervals pre-operatively. This blood is usually kept as whole blood.

The procedure may reduce the risk of incompatibility and infection from some agents, but its relatively unusual nature introduces other risks of procedural errors and bacterial contamination. Bacterial contamination may be just as common as with donor blood, since its main source is from the skin puncture at the time of collection.

Autologous transfusion is not widely used in the UK. In the NBS there are approximately 1000 pre-deposit autologous donations per year. In countries where this approach has been actively promoted, autologous transfusion accounts for approximately 5% of red cell usage.

I.3.5 Donor Screening

Donors undergo a health assessment and a simple check for anaemia. Approximately 7-10% of donors attending will not be bled on the basis of these measures. All donations are screened during processing for evidence of infection with HIV, hepatitis B and C, and syphilis. A small proportion of donations will be discarded on the results of this testing, and more donations will be lost during component production. Overall, about 98% of completed donations will result in usable blood components (based on experience at the Manchester Blood Centre).

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I.4 Blood Components

I.4.1 Data Sources

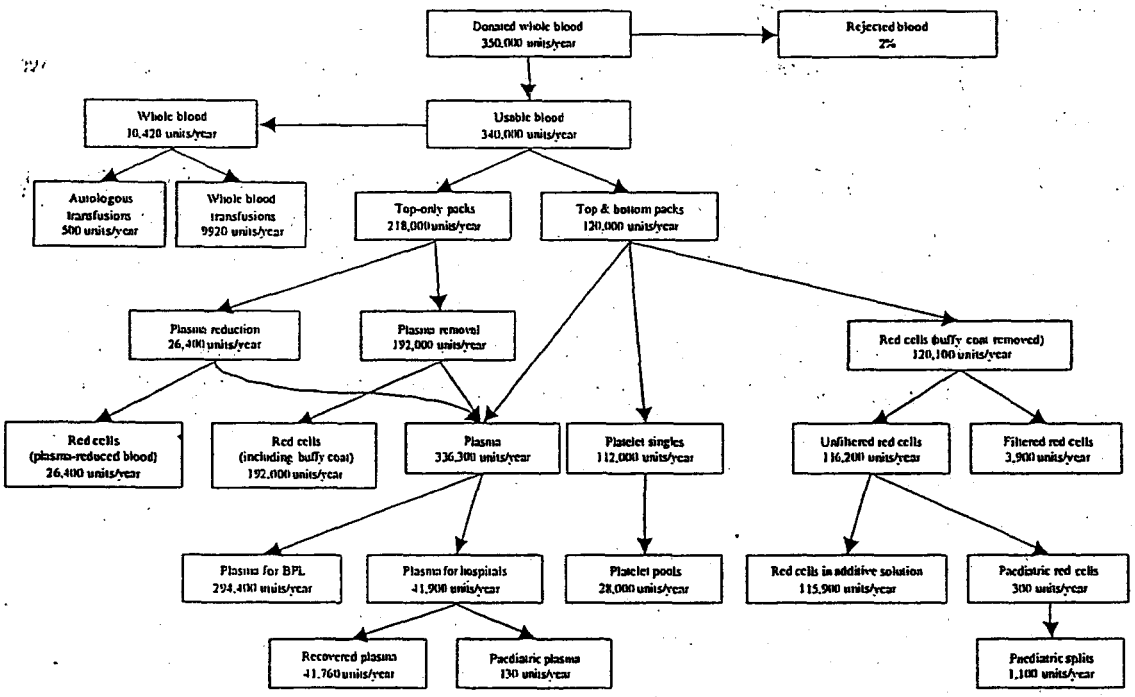
Data on production of blood components has been obtained from the following sources:

- National Blood Service (NBS) records for 1996/97.
- Manchester Blood Centre (MBC) anticipated production for 1998/99.
- Bio Products Laboratory (BPL) anticipated production for 1998.
- Handbook of Transfusion Medicine (HTM).
- Guidelines for Blood Transfusion Services in the UK, 3rd Edition, 1997.

I.4.2 Manufacture of Blood Components

The stages in processing blood donations and the principal blood component products are described below. Figure I.4.1 illustrates the process, based on planned production at the Manchester Blood Centre for 1998/99. The number of units produced varies from year to year and between the different blood centres, depending on local supply and demand for blood components.

Figure I.4.1 Processing of Whole Blood Donations at Manchester Blood Centre



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In general, blood donations are not pooled but are maintained as separate individually donated units throughout processing. Exceptions are:

- Platelets - 4 individual donations are combined to make one therapeutic unit of recovered platelets (Section I.4.6).
- Plasma - batches of typically 22,000 individual donations are combined to manufacture blood derivatives (Section I.5).

I.4.3 Whole Blood

Within the NBS about 5% of blood donations are used as whole blood. Modern medicine rarely requires whole blood transfusions, and processing into components allows blood donations to be used for more than one patient.

The specification for donated units of whole blood is 450 ±45 ml blood. This is mixed with 63 ml of anticoagulant, citrate phosphate dextrose adenine (CPDA), giving a total of approximately 510 ml.

Based on a normal range for white cell count of 4 to 12 x 10^9 per litre in adults, the white cell content of a unit of 450 ml of whole blood would be approximately 2 to 6 x 10^9, with a mean of 4 x 10^9 per unit.

I.4.4 Component Segregation

The majority of whole-blood donations are split into their main components by centrifugation. Two types of segregation are used:

- Two-component segregation, for which blood is donated into 2 linked packs ('top-only packs'). In this, the plasma is separated from the remainder, known as 'red cells' but also containing white cells and platelets ('buffy coat'). About 60% of the blood donations that are segregated are processed in this way (MBC).
- Three-component segregation, for which blood is donated into 3 linked packs ('top & bottom packs'). The plasma and red cells are separated from the remainder containing white cells and platelets ('buffy coat'). About 40% of the blood donations that are segregated are processed in this way (MBC).

If perfectly separated, the component quantities would be:

- Plasma - 50 to 55% of blood volume, i.e. about 200 to 270 ml per unit together with 60 ml anticoagulant.
- Red cells - 45 to 50% of blood volume, i.e. about 180 to 240 ml per unit.
- Buffy coat (platelets and white cells) - 3% of blood volume, i.e. about 13 ml per unit.

In practice, there is inevitably some loss of red cells (up to 50 ml) into the buffy coat.

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However, in order to produce a red cell component with suitable flow characteristics for transfusion, either some of the plasma is left on the red cells to produce a component simply known as 'red cells' or, after more complete plasma removal, an additive solution is added to the red cells (see below).

I.4.5 Red Cells

I.4.5.1 Types of Red Cell Product

The term 'red cells' refers to whole blood with most of the plasma has been removed. It is produced in several forms:

- Red cells (formerly known as plasma reduced blood).
- Red cells in additive solution.
- Red cells with buffy coat removed in additive solution.
- Red cells leucocyte depleted.
- Paediatric red cells.

These are described in turn below

I.4.5.2 Red Cells (Plasma Reduced Blood)

Blood with some of the plasma removed is known variously as 'plasma reduced blood', 'concentrated red cells' or simply 'red cells'. It is used in some cases instead of whole blood, as it reduces the risks associated with the large blood volume.

The volume specification for this component is 280 ± 60 ml. Hence it includes approximately 210 ml of red cells and 70 ml of plasma.

Most white cells would remain in the red cell component, and therefore the white cell content would be as for whole blood (Section I.4.3).

About 8% of blood donations are processed in this way (MBC).

I.4.5.3 Red Cells in Additive Solution

When all the plasma is removed, the red cells (usually including the buffy coat) may be re-suspended in additive saline solution (saline, adenine, glucose, mannitol, SAGM). This component is widely used, but the absence of plasma makes it unsuitable for exchange or large volume transfusion for neonates.

The volume specification for this component is 350 ± 70 ml. It includes approximately 240 ml of red cells, 13 ml of buffy coat and 100 ml of SAGM.

The white cell content would be approximately as for whole blood (Section I.4.3).

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About 60% of blood donations are processed in this way (MBC).

I.4.5.4 Red Cells with Buffy Coat Removed

Top and bottom processing of whole blood donations produces red cells with the buffy coat removed. These are usually suspended in additive solution. With the white cells removed, this reduces the risk of febrile transfusion reactions. This component may be used preferentially for patients who have reacted to previous transfusions.

The volume specification for this component is 280 ± 60 ml. The average volume of inspected components is 300 ml. This consists of 200 ml red cells and 100 ml SAGM.

The specification requires 75% of inspected units to have a white cell content $<1.2 \times 10^9$. The average content in inspected components in the SNBTS is 5×10^8. Compared to a typical white cell content in whole blood of 4×10^9, this implies that 88% of white cells are removed in the buffy coat. Routine production achieves 80 to 90% removal of white cells.

About 40% of blood donations are processed in this way (MBC), but this is very variable, depending on the demand for platelets and the production method used by individual centres.

I.4.5.5 Red Cells Leucocyte Depleted

Leucocyte depletion (leucodepletion) involves removing white cells by filtering. Approximately 50% of units selected for filtration have not had the buffy coat removed, to avoid double loss of red cells. Prior buffy coat removal does not result in lower final leucocyte counts.

Leucocyte depletion makes a negligible change in volume compared to red cells with buffy coat removed.

The UK standard for white cell content is $<5 \times 10^6$ in 100% of units. The Council of Europe standard is $<1 \times 10^6$ in 90% of units, which statistically is broadly similar. Current 4 log reduction filters will result in mean values of 1 to 2×10^5 per unit. Precise values depend on the type of filter, the conditions under which is filtration was performed, and the age of the product. Counting methods for leucocytes also vary, and inter-laboratory comparisons should be viewed with caution, as there is no national QC scheme for leucocyte counting at this level. A value of 5×10^5 per unit is assumed in this study. This implies 3 log depletion compared to red cells with buffy coat removed, or 4 log depletion compared to red cells with buffy coat. Hence current technology guarantees at least 3 log removal in all units, with 4 log being generally achievable.

Only a small proportion of blood donations is processed in this way - 1% (Manchester Blood Centre) to 10% (Brentwood Blood Centre). This might be increased, depending on the demand for the product.

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I.4.5.6 Paediatric Red Cells.

Premature infants often require multiple transfusions of small volumes of red cells. To achieve this, red cell units for paediatric use are split into 4 or 8, which can be allocated to a single infant to minimise donor exposure.

This gives a paediatric unit volume of 25 to 50 ml red cells. Since 1997, all units for infants under 1 year old are leucocyte depleted by filtration to $<1.25 \times 10^6$ white cells per split neonatal pack.

Only 0.1% of blood donations are processed in this way (MBC).

I.4.6 Platelets

I.4.6.1 Platelet Products

Platelets are produced in several forms:

- Recovered platelets from whole blood donations.
- Platelets from apheresis.
- Leucocyte depleted platelets, which may be from whole blood or apheresis.

I.4.6.2 Recovered Platelets

There are two ways of recovering platelets from whole blood donations:

- Production from platelet-rich plasma. In the NBS, use of this method will cease during 1998, and it is neglected here for simplicity.
- Production using 'top and bottom' processing from the buffy coat. This is described below.

For manufacture from the buffy coat in the NBS, the buffy coats from 4 individual donations are pooled. The resulting pool has a volume of approximately 250 ml. This consists of approximately 50 ml platelets** and 200 ml plasma. ***Note: this assumed volume has turned out to be factually incorrect since issue of the 1999 report.*

The UK specification requires that 75% of units contain $<2 \times 10^8$ white cells. In practice an adult platelet dose of 3×10^{11} platelets contains 10^7 to 10^8 white cells, with mean values of 2.5×10^7 on routine inspection of finished product. Filtration may be used to reduce the white cell content further.

Given that a platelet pool is derived from four individual donations the proportion of white cells remaining in the final product is 0.1% (3 log reduction) of that present in whole blood.

NBS production of platelets from buffy coat for 1998/9 is estimated to be 146,538 adult therapeutic doses. This is derived from approximately 586,000 individual whole blood donations, which is about 30% of donations. Production at individual blood centres varies widely depending on platelet demand.

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I.4.6.3 Apheresis Platelets

Apheresis platelet production provides approximately 35% of the platelets produced by the NBS. Two approaches are utilised, depending on the manufacturer, as follows.

Haemonetics machines are widely used to produce a single adult therapeutic dose plus 400 ml of plasma. The plasma can be utilised for direct clinical use or for plasma fractionation. The platelet product from such procedures has a volume of approximately 220 ml (range 150 to 300 ml). The specification requires that 75% of tested product should have a white cell count of less than 8×10^8. The mean white cell count is approximately 5×10^8.

Cobe machines offer an alternative approach to apheresis platelet production. An individual donation supplies up to 2 (occasionally 3) adult therapeutic doses of platelets. Current technology results in a leucodepleted product, without requiring further filtration.

The volume of an individual therapeutic dose is approximately 200 ml containing at least 2.4×10^{11} platelets.

NBS production of platelets from apheresis for 1998/9 is estimated to be 70,585 adult therapeutic doses. This is 32% of NBS platelet provision. These come from 56,397 donations (Table I.3.1), with many of the Cobe procedures yielding double doses.

I.4.6.4 Leucocyte Depleted Platelets

Standard platelet concentrates, from either buffy coat derived pools and apheresis donations (Haemonetics) can be leucodepleted by filtration. This results in a reduction in volume of between 5-10%. The specification for white cell count requires that 100% of units have a white cell content of less than 5×10^6 per adult therapeutic dose. Routine testing indicates an average white cell count of 5×10^5.

In the context of a filtered buffy coat derived platelet pool the proportion of white cells present in the final product is 0.01% (4 log reduction) of white cells present in the original donations.

The proportion of platelets issued as leucodepleted to hospitals varies considerably within England, ranging from over 30% in London and the Southeast to less than 5% in the north. Several factors probably contribute to the different practice. In part this reflects differences in opinion by haematologists on the value of leucodepletion as a means of reducing the risk of platelet refractoriness. In part it is due to the differences in case mix (in particular the number of patients undergoing bone marrow transplantation). Also, it is in part due to the use of bed side platelet filters.

I.4.7 Plasma

Until 1998, most UK plasma was collected for fractionation at BPL (see Section I.5). From Manchester Blood Centre, the plasma from 86% of whole blood donations was sent to BPL.

The remaining plasma from single donations, known as fresh frozen plasma (FFP), is produced for hospital use. FFP can be recovered in the following ways:

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- FFP recovered from whole blood donations. From the figures above, the unit size may be 190 ml (from plasma-reduced blood) or 250 to 300 ml (from component segregation).
- FFP from apheresis, either in conjunction with platelet collection or collected as a single component. The unit size is 500 to 600 ml, which can be split into 2 x 300 ml.

The white cell content in either form is 1 to 10×10^6. This implies that only about 0.1% of white cells from whole blood remain in the plasma. This could be reduced to 10^3 cells per unit by filtration.

I.4.8 Cryoprecipitate

Blood centres produce single unit cryoprecipitate by thawing FFP at 2 to 6°C, but the total such production is <10% of FFP production. The final product is rich in Factor VIII, fibrinogen and fibronectin. It was previously used for treatment of clotting disorders, but is now mainly used as a source of fibrinogen for liver patients and in massive transfusion/ disseminated intravascular coagulation.

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