7.2.3 *Tests for infectious agents*

Syphilis. Each donation of whole blood shall, if required by the national control authority, be subjected to a serological test for syphilis. If so tested, only units giving negative results shall be used for transfusion or component preparation.

Viral hepatitis. Each unit of blood or plasma collected shall be tested for HBsAg and anti-HCV by a method approved by the national control authority and only those giving a negative result shall be used (*13*). Units giving a positive result shall be so marked, segregated and disposed of by a method approved by the national control authority, unless designated for the production of a reagent or experimental vaccine in an area designed and segregated for such production.

In some countries plasma pools are also tested.

The label on the container or the record accompanying the container should indicate the geographical source of the blood or plasma as well as whether and how the material has been tested for HBsAg and anti-HCV.

Liver function tests, such as serum transaminase determinations, are used in some countries to detect liver damage that may be associated with hepatitis.

Anti-HIV-1 and anti-HIV-2. Blood for transfusion and for use in the preparation of blood components must be tested by a method approved by the national control authority for antibodies to HIV-1 and HIV-2 and be found negative. However, when other important factors outweigh the benefits of such testing (e.g. in emergencies) formal arrangements, approved in advance by the national control authority, should be in place that enable the prescribing physician to have access to an untested product. In all such cases, retrospective testing of the pilot sample shall be performed.

Other infectious agents. It is important for the national control authority to reassess testing requirements from time to time in the light of current knowledge, the prevalence of infectious agents in different populations and the availability of tests for serological markers of infection. For example, human retroviruses other than HIV have been described (HTLV types 1 and 2) and more may be identified in the future.

7.3 *Blood-grouping*

Each unit of blood collected shall be classified according to its ABO blood group by testing the red blood cells with anti-A and anti-B sera and by testing the serum or plasma with pooled known group A (or single subtype A_1) cells and known group B cells. The unit shall not be labelled as to ABO group unless the results of the two tests (cell and serum grouping) are in agreement. Where discrepancies are found in the testing or the donor's records, they shall be resolved before the units are labelled.

In countries where polymorphism for the D (Rh_o) antigen is present, each unit of blood shall be classified according to Rh blood type on the basis of

the results of testing for the D (Rh_o) red cell antigen. The D (Rh_o) type shall be determined with anti-D (anti-Rh_o) reagents.

> With the high-strength antisera and sensitive techniques now available, it is usually considered unnecessary to use the D^u test if the cells are found to be D-negative in routine testing.

7.4 *Red cells*

Whole blood for the preparation of all components shall be collected as described in Part A, section 5, and tested as described in Part B, section 7.2.

Red cells shall be processed under aseptic conditions and whenever possible in a closed system. The sterility of all components shall be maintained during processing by the use of aseptic techniques and sterile pyrogen-free equipment. The methods shall be approved by the national control authority, and a written description of the procedures shall be prepared for each product, covering each step in production and testing. Proposals for any procedural modifications shall be submitted to the national control authority for approval before they are implemented.

The following may be prepared for therapeutic purposes (see pages 40–41 for definitions):

- red cells;
- red cells suspended in additive solution;
- modified red cells:
  - red cells, leukocyte-depleted;
  - red cells, leukocyte-poor;
  - red cells, washed;
  - red cells, frozen;
  - red cells, deglycerolized.

7.4.1 *Methods and timing of separation*

Red cells shall be prepared from whole blood collected in plastic bags or in glass bottles.

> Multiple-plastic-bag systems with sterile docking devices are preferable because they minimize the risk of microbial contamination by providing completely closed systems. They are easy to handle and are disposable. The use of glass bottles is cheaper but has the disadvantage that the system is then an open or vented one, so that separation must be carried out under strictly aseptic conditions in sterile rooms or laminar-flow cabinets and microbiological monitoring is necessary. The same conditions also apply to the separation procedure when plasma is transferred from disposable single plastic bags to separate containers.

All surfaces that come into contact with the blood cells shall be sterile, biocompatible and pyrogen-free. If an open plastic-bag system is used, i.e. the transfer container is not integrally attached to the blood container and the blood container is opened after blood collection, the plasma shall be separated from the cells under conditions such that the original container is kept under positive pressure until it has been sealed. If the separation

procedure involves a vented system, i.e. if an airway is inserted into the container for withdrawal of the plasma, the airway and vent shall be sterile and constructed so as to exclude microorganisms.

In some countries, the sterility of products prepared in open systems is monitored by testing a sample of at least 2% of the units. The national control authority should approve the system used.

The final containers for red cells (but not necessarily modified red cells) shall be the containers in which the blood was originally collected or satellite containers attached in an integral manner. If pilot samples are detached from the blood container during removal of any component, such samples shall be reattached to the container of red cells. The removal and reattachment of the pilot samples shall be recorded conspicuously (with a signature) on the label of the unit. The final containers for all other components shall meet the requirements for blood containers given in Part A, section 5.2. If the final container differs from the container in which the blood was originally collected, it shall be given a number or other symbol to identify the donor(s) of the source blood. Whenever appropriate, the secondary final container shall be similarly labelled while attached to the primary final container.

The timing and the method of separation (centrifugation, undisturbed sedimentation or a combination of the two) will depend on the components to be prepared from the donation. When platelets and coagulation factors are being prepared from the same donation, the components shall be separated as soon as possible after withdrawal of the blood from the donor.

Separation should preferably be effected within 8 h of blood donation.

When platelets and coagulation factors are to be prepared, it is especially important that the venepuncture be performed in such a way as to cause *minimal tissue damage so as to prevent the initiation of coagulation.* The blood should flow freely without interruption and as rapidly as possible, and be mixed thoroughly with the anticoagulant.

If platelets are to be prepared from a unit of whole blood, the blood shall be kept at a temperature of 20–24 °C for up to 8 h until the platelet-rich plasma has been separated from the red blood cells.

Red cells may be prepared either by centrifugation or by undisturbed sedimentation before the expiry date of the original whole blood. Blood cells shall be separated by centrifugation in a manner that will not increase the temperature of the blood.

Sedimentation is the least expensive method for separation of red blood cells and does not require special equipment.

Repeated washing with saline and centrifugation and filtration are used to reduce the number of leukocytes and platelets and the volume of trapped plasma in red cells. Frozen red cells after thawing are also repeatedly washed with special solutions to remove cryoprotective agents while also preventing haemolysis.

7.4.2 *Expiry date*

The expiry date of whole blood and red cells prepared in a closed system from blood collected in acid-citrate-glucose or citrate-phosphate-glucose is generally 21 days after collection. The time of removal of plasma is not relevant to the expiry date of the red cells when the integrity of the container is not compromised.

The shelf-life of stored blood has been extended to 35 days by collecting the blood in acid–citrate–glucose supplemented with 0.5 mmol/l adenine or in a mixture of 0.5 mmol/l adenine and 0.25 mmol/l guanosine with extra glucose, and to 42 days by adding a solution containing adenine, glucose and mannitol. Recent studies indicate that it may also be possible to extend the shelf-life of stored blood to 35 days by collecting it in citrate–phosphate–glucose supplemented with 0.25 mmol/l adenine and extra glucose.

When red cells are prepared with very high erythrocyte volume fractions, an expiry date 14 days after collection is recommended in some countries because the cells may become glucose-deficient after this time. The erythrocyte volume fraction of red cells collected in citrate–phosphate–glucose–adenine should not exceed 0.9 if the expiry date is more than 21 days after collection.

The usefulness of acid–citrate–glucose is limited by the significant reduction in cell viability when the volume of cells collected is small, which is unavoidable for some donations.

Provided that sterility is maintained, the shelf-life of red cells is not influenced by the method of separation used. However, if an open system is used that does not maintain sterility, the expiry date shall be 24 h after separation and the cells should be used as soon as possible. Red cells and whole blood should be stored at 5 ± 3 °C and transported with wet ice in insulated boxes at 5 ± 3 °C. Care should be taken not to place containers directly on ice.

Refrigerated whole blood and red cells will warm up rapidly when placed at room temperature. Every effort should be made to limit the periods during which the products are handled at ambient temperatures in order to prevent the temperature from rising above 10 °C until they are used.

7.4.3 *Modified red cells*

Red cells, leukocyte-depleted and red cells, leukocyte-poor.

Because of the possibility of reactions, some countries require that red cells contain less than 2% of the leukocytes of the original whole blood.

Leukocyte depletion may be achieved by buffy-coat removal, freezing and washing, or by washing alone.

Leukocyte-poor red-cell concentrates are prepared by filtration.

Red cells, washed. Red cells can be washed by means of interrupted or continuous-flow centrifugation. If the first of these methods is used, the washing procedure shall be repeated three times.

Centrifugation should be carried out in refrigerated centrifuges. If such

equipment is not available, the washing solution should have a temperature of 5 ± 3 °C.

Red cells can also be washed by means of reversible agglomeration and sedimentation using sugar solutions.

Washed red cells should be transfused as soon as possible and in any case not later than 24 h after processing if prepared in an open system that does not maintain sterility, unless the national control authority has specified a longer shelf-life. They should be stored at all times at 5 ± 3 °C.

Requirements for pilot samples, labels and storage and transport temperatures are the same as those for unmodified red cells.

Red cells, frozen and red cells, deglycerolized. Red cells less than six days old are usually selected for freezing in order to minimize loss of yield due to haemolysis during processing.

Frozen red cells are red cells that have been stored continuously at low temperatures (-65 °C or below) in the presence of a cryoprotective agent. The red cells must be washed to remove the cryoprotective agent before use for transfusion. The methods of preparation, storage, thawing and washing used should be such as to ensure that at least 70% of the transfused cells are viable 24 h after transfusion. Storage at temperatures below -65 °C is usually necessary to achieve 70% recovery.

The cryoprotective agent in most common use is glycerol. The temperature of storage should be between −65 °C and −160 °C, depending on the glycerol concentration used.

The shelf-life of frozen cells below −65 °C is at least three years and may be much longer under certain circumstances, but the reconstituted (thawed and washed) red cells should be used as soon as possible and not later than 24 h after thawing unless a closed system is used.

Frozen cells are usually shipped in solid carbon dioxide ("dry ice") or liquid nitrogen, depending upon the glycerol concentration used. Deglycerolized red cells should be stored at a temperature of 1–6 °C and shipped at 5 ± 3 °C.

Requirements for pilot samples and labels are the same as those for unmodified red cells.

7.5 *Plasma*

Single-donor plasma shall be obtained by plasmapheresis or from units of whole blood that comply with the requirements of Part A, section 5, and Part B, section 7.2.

Fresh-frozen plasma and frozen plasma should be stored in carefully monitored freezers equipped with recording thermometers and audio and visual alarms to give warning of mechanical or electrical failure. If refrigeration is interrupted for longer than 72 h and the temperature rises above -5 °C, the product may no longer be considered as fresh-frozen plasma, although testing may indicate that reasonable amounts of factor

VIII remain if the plasma has not become liquid. Repeated thawing and freezing may cause denaturation of plasma constituents and cause prekallikrein activation.

7.5.1 *Plasma, fresh-frozen*

Fresh-frozen plasma shall be prepared by separating plasma from whole blood and freezing it rapidly within 8 h of collection.

Ideally, fresh-frozen plasma should be prepared by rapid freezing using a combination of solid carbon dioxide and an organic solvent such as ethanol. If this procedure is used, it should have been shown that the container cannot be penetrated by the solvent or substances leached from the container into the contents. Fresh-frozen plasma should be stored at or below −20 °C, and below −30 °C if to be used for transfusion purposes.

Before use for infusion, fresh-frozen plasma should be thawed rapidly at 30–37 °C. Agitation of the container and/or circulation of water at a temperature of 37 °C during the thaw cycle will speed thawing. Once thawed, fresh-frozen plasma must not be refrozen. It can be stored at ambient temperature and should be used within 2 h of completion of thawing.

Fresh-frozen plasma shall have an expiry date one year from the date of collection.

Before its expiry date, fresh-frozen plasma may be used for preparing cryoprecipitated factor VIII. It may be used for the preparation of other pooled plasma fractions (e.g. factors I, II, VII, VIII, IX and X) at any time, even after its expiry date.

7.5.2 *Plasma, frozen*

Frozen plasma is, by definition, a plasma separated from whole blood more than 8 h after the latter has been collected, but the delay should be as short as possible. Frozen plasma may be used directly for transfusion or fractionation, or it may be freeze-dried as single-donor units. Plasma may be combined in small pools before freezing if it is to be used to prepare freeze-dried plasma.

The national control authority should determine the specific requirements for frozen plasma.

If frozen or freeze-dried plasma is intended to be used directly in patients without further processing, the blood shall be collected in such a manner and in containers of such a type as to allow aseptic handling, e.g. by means of closed systems.

In some countries, frozen plasma is given an expiry date five years from the date of collection.

Whenever the container of frozen plasma is opened in an open procedure, the method of handling shall avoid microbial contamination; as an additional precaution, sterile rooms or laminar-flow cabinets can be used. Delay in processing shall be avoided, and the ambient conditions shall be regulated so as to minimize the risk of contamination.

Plasma may be pooled at any time after collection.

7.5.3 *Plasma, freeze-dried*

Freeze-dried plasma shall be made from single units or small pools of fresh-frozen plasma or frozen plasma.

The storage conditions and expiry dates of different forms of freeze-dried plasma shall be approved by the national control authority. The product normally has a shelf-life of five years when stored at 5 ± 3 °C, but this will depend on the source material, storage conditions and residual moisture in the product. Pooled freeze-dried plasma has a significant potential for the transmission of infectious diseases. This is likely to be substantially diminished by the introduction of viral inactivation procedures applicable to plasma.

7.5.4 *Plasma, recovered*

Recovered plasma intended to be pooled for fractionation shall not be used directly for transfusion; a preservative shall not be added.

Plasma may be separated from whole blood at any time up to five days after the expiry date of the blood. The method used for separation shall avoid microbial contamination. As an additional precaution, sterile rooms or laminar-flow cabinets can be used.

If the plasma has been pooled, it shall be stored and transported frozen at or below -20 °C.

7.5.5 *Plasma, platelet-rich*

Platelet-rich plasma is a preparation containing at least 70% of the platelets of the original whole blood.

The preparation shall be separated by centrifugation, preferably within 8 h of collection of the whole blood. The temperature and time of processing and storage shall be consistent with platelet survival and maintenance of function.

To achieve the desired haemostatic effect, platelet-rich plasma shall be transfused as soon as possible after collection, and not later than 72 h afterwards, unless stored at 22 ± 2 °C in containers approved for a longer storage period.

7.6 *Platelets*

Platelets shall be obtained by cytapheresis or from whole blood, buffy coat or platelet-rich plasma that complies with the requirements of Part A, section 5, and Part B, section 7.2. Aspirin ingestion within the previous three days precludes a donor from serving as a source of platelets.

Whole blood or platelet-rich plasma from which platelets are derived shall be maintained at 22 ± 2 °C until the platelets have been separated.

The separation shall preferably be performed within 8 h of collection of the whole blood. Blood shall be obtained from the donor by means of a single venepuncture giving an uninterrupted flow of blood with minimum damage to the tissue. It must have been demonstrated that the time and speed of centrifugation used to separate the platelets will produce a suspension without visible aggregation or haemolysis.

The national control authority shall determine the minimum acceptable number of platelets that should be present in the products prepared (e.g. 5.5×10^{10}).

A pH of 6.5–7.4 shall be maintained throughout storage of platelets. The volume of plasma used to resuspend platelets will be governed by the required pH of the platelet suspension at the end of its shelf-life, but shall be no less than 50 ± 10 ml.

Licensed artificial suspension media may be used to replace plasma.

Platelets stored at 5 °C are inferior to the same product stored at 22 ± 2 °C. Cold storage should be avoided where possible.

When stored at 22 ± 2 °C, platelet products shall be gently agitated throughout the storage period.

Platelet products with high platelet counts that are stored at 22 ± 2 °C may need to contain as much as 70 ml of plasma or more if the pH is to be maintained above 6.5 throughout the storage period. This period may be as long as seven days for containers made of certain special plastics, but it is prudent to restrict platelet storage to five days because of the risk of bacterial contaminants.

The product should be ABO typed and, in countries where D (Rh_o) is polymorphic, D (Rh_o) typed; it may also be desirable to know the HLA type.

The material of which the final container used for platelets is made shall not interact with the contents under normal conditions of storage in such a manner as to have an adverse effect on the product.

The requirements for labelling the final container are given in section 7.9. In addition to the customary data, the label shall bear: (a) the recommended storage temperature; (b) the statement that, when stored at 22 ± 2 °C, the platelets should be gently agitated throughout storage to obtain maximum haemostatic effectiveness; and (c) a statement to the effect that the contents should be used as soon as possible, and preferably within 4 h once the containers have been opened for pooling.

7.6.1 *Monitoring the quality of platelets*

Units randomly selected at the end of their shelf-life shall be tested on a regular basis. They shall be shown to have: (a) plasma volumes appropriate to the storage temperature; and (b) a pH between 6.5 and 7.4.

The number of units and of platelets to be tested shall be specified by the national control authority.

Some countries require there to be no visible contamination by red cells.

7.6.2 *Expiry date*

The expiry date of platelets processed in a closed system shall be 72 h after the original whole blood was collected, unless they are stored in a plastic container approved by the national control authority for a longer storage period.

Platelets prepared in an open system should be used within 4 h of preparation if stored at 22 ± 2 °C, unless the procedure used has been shown to allow a longer storage period.

Single-donor platelet concentrates may be pooled for one recipient under aseptic conditions before issue. Such small pools should be used as soon as possible, and within 4 h of preparation if stored at room temperature.

7.7 *Leukocytes*

Leukocytes are obtained by the separation of whole blood or by apheresis, and may contain a large number of platelets and red blood cells, depending on the method of preparation. When leukocytes are obtained from units of whole blood, such units shall comply with the requirements of Part A, section 5, and Part B, section 7.2.

The methods used to process leukocytes shall comply with the requirements and recommendations given in section 7.4.1 for the separation of red cells.

The label on the final container shall bear, in addition to customary data, instructions to use the leukocytes as soon as possible and in any case not more than 4 h after the container has been opened for pooling. The temperature of storage and transport shall be 22 ± 2 °C.

Leukocytes can be separated from blood by centrifugation, sedimentation or leukapheresis. To obtain a sufficient number, the leukocytes from units obtained from several healthy donors may have to be pooled.

Leukapheresis by continuous-flow filtration or centrifugation is the most efficient way of obtaining leukocytes, since it gives large numbers of high-quality cells from a single donor.

If centrifugation of whole blood is used, 30–60% of the leukocytes present in the original whole blood may be recovered.

Approximately 90% of the leukocytes present in the original whole blood can be separated by sedimentation of the red cells, accelerated by the addition of suitable substances with high relative molecular mass.

Leukocytes should be negative for cytomegalovirus.

The product should be ABO typed and, in countries where D (Rh_o) is polymorphic, D (Rh_o) typed; it may also be desirable to determine the HLA type. If not HLA typed, leukocytes should be irradiated.

The large number of red cells present in products prepared by some methods makes compatibility testing before transfusion necessary.

7.7.1 *Testing of leukocytes*

The number of units to be tested and the leukocyte yield (number) required shall be specified by the national control authority.

7.7.2 *Expiry date*

The expiry date of leukocytes shall be 24 h after collection of the original whole blood.

7.8 *Cryoprecipitated factor VIII*

Cryoprecipitated factor VIII is a crude preparation of factor VIII. It shall be obtained from single units or small pools of plasma derived either from units of whole blood that comply with the requirements of Part A, section 5, and Part B, section 7.2, or by plasmapheresis.

> The product may be prepared as a pool from a small number of donations, usually four to six but not exceeding ten. It may be freeze-dried. However, preparations of cryoprecipitated factor VIII carry the risk of viral transmission unless they have undergone specific virucidal procedures during manufacture.

The method of thawing and harvesting the cryoprecipitate shall have been shown to yield a product containing an adequate activity of factor VIII (see section 7.8.1).

In procuring source material for coagulation factors, the following technical considerations should be borne in mind:

- In order to prevent coagulation, venepuncture should performed in such a way that tissue damage is minimal. The blood should flow freely without interruption, and be mixed thoroughly with anticoagulant during collection.
- Microbial contamination should be avoided during separation of the plasma by using multiple-plastic-bag closed systems or laminar-flow cabinets if an open procedure is used.
- The recovery of factor VIII depends on the interval between venepuncture and freezing of the plasma, the temperature at which the plasma is held and the freezing method. While a useful product may be obtained with plasma frozen as late as 18–24 h after phlebotomy, freezing the plasma as early and as rapidly as possible is strongly recommended.
- Ideally, fresh-frozen plasma should be prepared by rapid freezing using a combination of solid carbon dioxide and an organic solvent such as ethanol. Fresh-frozen plasma should be stored at or below −20 °C. Contamination of the plasma by the solvent or leaching of substances from the container into the plasma should be avoided.
- If the temperature of the thawed plasma exceeds 2 °C, a high proportion of the factor VIII is lost in the supernatant. During thawing or separation of the supernatant plasma, therefore, the temperature should not be allowed to exceed 2 °C. The plasma may be separated while there is still a small quantity of the ice present in the plasma

container. Increasing the speed of thawing by circulating air or water at a temperature of 0 °C is believed to increase the yield of factor VIII.

7.8.1 *Testing of cryoprecipitated factor VIII*

Randomly selected units shall be tested for potency and sterility on a regular basis. The number of units to be tested shall be specified by the national control authority. The freeze-dried preparation shall dissolve without any signs of precipitation in the solvent recommended by the manufacturer within 30 min when held at a temperature not exceeding 37 °C.

The potency of cryoprecipitated factor VIII shall be compared with that of an appropriate plasma or intermediate-purity standard, by measuring its ability to correct the prolonged activated partial thromboplastin time of haemophilia A plasma or by another suitable method.

When cryoprecipitated factor VIII is produced from fresh-frozen plasma (frozen within 8 h of donation), the yield should be greater than 400 IU/l of starting plasma. Plasma frozen after this time will yield less cryoprecipitated factor VIII.

> In many laboratories, the average yield of factor VIII is 400 IU/l of starting plasma. The average yield of factor VIII as freeze-dried cryoprecipitate is then at least 300 IU/l of starting plasma. Whether this yield can be obtained elsewhere will depend on local technical possibilities. In some countries, the yields will be much lower, and the national control authority should decide as to the yield that is acceptable.

7.8.2 *Expiry date*

The frozen product shall be stored at or below -20 °C (if possible below -30 °C) and shall have an expiry date one year from the date of collection. The freeze-dried product shall be stored at 5 ± 3 °C and shall also have an expiry date one year from the date of collection. After thawing or reconstitution, cryoprecipitated factor VIII should be kept at 20–24 °C. It shall be used as soon as possible and in any case not more than 4 h after its container has been opened for pooling or reconstitution.

7.9 *Labelling*

After having been tested and before being issued for transfusion, units of single-donor and small-pool products shall be identified by means of container labels that clearly state at least the following information:

- the proper name of the product;
- the unique number or symbol identifying the donor(s);
- the expiry date, and when appropriate, the expiry time after reconstitution;
- any special storage conditions or handling precautions that are necessary;
- a reference to a package insert containing instructions for use, warnings and precautions;

- the name and address of the blood donor centre and, where applicable, the manufacturer and distributor;
- the average content in International Units of activity, where appropriate.

The results of red cell grouping shall be stated on the label of whole blood, red cells, fresh-frozen plasma (for clinical use), platelets and leukocytes but not necessarily on that of cryoprecipitated factor VIII.

Part C. Requirements for large-pool products

8. Introduction

A number of requirements common to albumin, plasma protein fraction, immunoglobulin preparations and coagulation-factor concentrates are given in Parts A and B, sections 3-7. However, for clarity, it has proved convenient to bring together in Part C certain specific requirements applicable to these products when manufactured on a large scale.

The source material for the large-scale preparation of blood products should comply with the relevant provisions of Parts A and B.

9. Buildings

The buildings used for the fractionation of plasma shall be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance in accordance with the requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products. They shall comply with the Guidelines for National Authorities on Quality Assurance for Biological Products (*6*) and in addition provide adequate space, lighting and ventilation for the activities listed below.

> Each of listed activities is an important integral part of the production procedure, and countries wishing to start manufacturing large-pool blood products and related substances should not do so unless adequate provision can be made for all of them.

9.1 *Storage of whole blood and plasma*

Whole human blood and plasma shall be stored frozen or refrigerated in separate facilities that are used only for this purpose. The source materials shall remain in quarantine until the results of testing show that they are suitable for introduction into the fractionation premises.

9.2 *Separation of cells and fractionation of plasma*

Cells shall be separated and plasma fractionated in a building isolated from those where non-human proteins or microbiological materials, such as vaccines, are manufactured or processed and separate from the animal house.

> In some countries, cell constituents are separated in an area separate from that where plasma is fractionated.

9.3 *Supply and recovery of ancillary materials*

Adequate facilities shall be provided for the supply of ancillary materials, such as ethanol, water, salts and polyethylene glycol.

Facilities for the recovery of organic solvents used in fractionation may also be provided.

9.4 *Viral inactivation*

A separate area shall be provided for all processing subsequent to the completion of viral inactivation procedures when these are carried out at a stage in production before aseptic dispensing and filling (see section 9.5).

9.5 *Freeze-drying, filling, packaging, labelling and storage*

Separate facilities shall be used for the freeze-drying, filling, labelling and packaging of containers. A separate area shall be provided for the storage of labels, package inserts and packages. Another separate area shall be used for the storage of final containers before dispatch.

9.6 *Keeping of records*

Adequate provision shall be made for keeping records of all donors, materials, fractionation steps, quality-control procedures and results, of the distribution of the final products and of the disposal of potentially infectious materials. Records should be retained for at least two years beyond the expiry date of the products to which they relate.

Some manufacturers might wish to extend this period to cover any future legal disputes.

9.7 *Quality control*

Separate facilities shall be provided for quality control, including haematological, biochemical, physicochemical, microbiological, pyrogen and safety testing.

9.8 *Disposal of infective material*

Provision shall be made for the suitable disposal of potentially infectious materials by autoclaving or incineration according to good manufacturing practices.

The disposal of these materials should comply with local legislation.

10. Equipment

Equipment used for the collection, processing, storage and distribution of source materials and large-pool blood products shall comply with the requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products.

Particular attention shall be paid to:

- The maintenance, monitoring and recording of the operation of continuously operating equipment, the validation of its reliability and the provision of stand-by equipment.
- The suitability and compatibility of the surfaces of all materials (e.g. filter medium, glass, stainless steel, plastic and rubber) that come into contact with the products.

  Metal surfaces that come into contact with proteins should be resistant to scratching. The surfaces of some materials can denature certain proteins or activate certain coagulation factors.

- The ease and efficiency with which equipment can be cleaned and, where necessary, sterilized. Any bactericidal agent used shall be capable of being completely eliminated before the equipment is used.

  Caution should be exercised in the use of detergents because of their possible effects on the final product; tests should be made to ensure that they do not have any adverse effect on it.

- The provision of suitable facilities for decontamination and for the disposal of potentially infective materials and equipment.

11. Provision of support services

A number of support services are essential for the fractionation of source materials.

11.1 *Water supply*

An adequate supply of suitable pyrogen-free water shall be provided for use during the fractionation process and for the reconstitution and/or dilution of the plasma fractions before filling and freeze-drying.

The two most commonly used types of water are pyrogen-free distilled water and pyrogen-free deionized water, each of which should be maintained at 80°C. Water preparation and delivery systems should be tested at regular intervals for endotoxin content and conductance. The water system should be a continuously circulating one and should have no dead ends.

Water for injections is generally used for the preparation of final products (*14*).

11.2 *Steam supply*

An adequate supply of steam shall be provided for the operation of sterilizing and cleaning equipment. The steam shall be clean and have the quality of water for injections.

11.3 *Other support facilities*

Other support facilities required are:

- A supply of electrical and thermal energy.